IMW2013 KYOTO JAPAN
the XIVth international myeloma workshop

14th International Myeloma Workshop

April 3rd-7th, 2013 Kyoto, Japan
Venue : Kyoto International Conference Center

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Welcome Message

On behalf of the organizing committee it is my great pleasure and honor to invite you to attend the XIVth International Myeloma Workshop to be held in Kyoto, Japan, from Aiprl 3rd to 7th, 2013.
With the advent of novel drugs, thalidomide, bortezomib, and lenalidomide, as well as the integration of them into existing treatment approaches and the improved management of the complications, the outcome of patients with multiple myeloma has dramatically improved in the past decade.
Because of the unprecedented higher and deeper response to and the increasing treatment options of novel therapies, questions regarding existing treatment paradigm and optimal treatment have been raised.
To understand and share advanced knowledge and information of biology and treatment of myeloma, lively debate discussion within leading experts and with participants has been planned.
After the workshop please visit old temples and shrines to see serene gardens and relax by feeling a sense of peace. Kyoto is the right place to offer an extremely relaxing experience. Also around the time when the workshop is held, cherry blossoms will be in full bloom everywhere in Kyoto and you will be surrounded by the stunning beauty.
We are very much looking forward to welcoming you to Kyoto in April 2013.

Thank you.

Kazuyuki Shimizu, MD, PhD
President, XIVth International Myeloma Workshop

S1

PrIME Oncology Supported by Onyx Pharmaceuticals - sponsored symposium-

Relapsed/Refractory Myeloma: Impact Through Innovation

S1-1

Managing the Microenvironment Matters

A. J. JAKUBOWIAK

Section of Hematology/Oncology, University of Chicago Medical Center, United States

In recent years, bone marrow microenvironment (BMM) has emerged as an important factor in growth and progression of multiple myeloma (MM) and an important target for treatment (tx) interventions. BMM includes extracellular matrix and a number of BM cell types, including stromal cells, osteoclasts, osteoblasts, immune cells, hematopoietic cells, and vascular endothelial cells. Much has been learned about interactions between these cells and MM cells and their mediators, including adhesion molecules, cytokines, lymphokines, and receptors. Novel tx with immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) have made dramatic impact on tx outcome in MM, in part because of their abilities to target BMM. Initial rationale for the introduction of IMiDs to tx of MM, first thalidomide then lenalidomide and pomalidomide, was related to their anti-angiogenic properties. In addition, IMiDs affect MM via growth factor cytokine release, direct cytotoxicity, cell cycle arrest, and immunomodulation, all leading to MM-BMM disruption. PIs, bortezomib, carfilzomib, and more recently ixizomib, and oprozomib, exert their anti-MM effect in part via alteration of the cellular balance in BMM, including impact on effector T-cell plasticity, regulation of cytokine production, and regulation of IL-6-dependent signal transduction although specific effects could differ between different PIs. A new generation of anti-MM agents with different mechanisms of action, for example, elotuzumob and daratumomab, provide further support to the notion that BMM does matter in the treatment of MM.

S1-2

Recognizing and Responding to Resistance in Relapsed Multiple Myeloma

P. MOREAU

Department of Hematology, University Hospital of Nantes, France

Treatment of relapsed multiple myeloma continues to present a therapeutic challenge. Decisions regarding optimal therapy selection are often difficult, and need to take into account many criteria such as age, performans status and frailty, duration of first response, type of initial therapy, availability of stem cells, type of relapse (smoldering/biochemical or aggressive), cytogenetics, clonal evolution··· Immunomodulatory drugs (IMiDs) and proteasome inhibitors are the backbone of treatment at the time of relapse. Recent trials indicate that these 2 classes of agents may be combined to improve the response rates. When patients responded well and long to a previous high-dose therapy followed by autologous stem cell transplantation (ASCT), they may benefit from a salvage ASCT. Some authors also consider that in young patients in first chemosensitive relapse, allogeneic stem cell transplantation should systematically considered. Finally, many new drugs are or will soon be available, such as the proteasome inhibitors carfilzomib and MLN9708, the third-in-class IMiD pomalidomide or other classes of agents such as monoclonal antibodies anti-CS1 (elotuzumab) or anti-CD38 (daratumumab), heat shock protein (HSP) inhibitors, histone deacetylase inhibitors (HDACi), or inhibitors of the PI3K/AKT/mTOR. The best way to make progress is to enrol patients into clinical trials. The talk will focus on the most recent data regarding new drugs, combinations therapies, salvage transplantation and ongoing clinical trials in the relapse setting.

S1-3

Primary Refractory or Multiply-relapsed Multiple Myeloma: What are Our Options?

E. TERPOS

Department of Clinical Therapeutics, University of Athens School of Medicine, Greece

Patients with multiple myeloma (MM) who have received novel agents (thalidomide-, lenalidomide- and/or bortezomib-based regimens) and their disease has relapsed or has become refractory to these treatments present a particular challenge. These patients can be treated with carfilzomib or can be encouraged to participate in a clinical trial of novel experimental agents, such as pomalidomide, monoclonal antibodies (daratumumab, elotuzumab), bendamustine etc. Carfilzomib has been approved by FDA in July 2012 based on the results of a phase IIb trial, which enrolled 266 MM patients who had been exposed to both bortezomib and an IMiD and who were relapsed and refractory to their most recent line of therapy. Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of 28-day cycles (20 mg/m^2 in cycle 1; 27 mg/m^2 in cycles 2-12). The response rate was 23.7% (37% at least MR). The median time-to-response was <2 months and the response duration was 7.8 months. The median TTP was 3.9 months,

and the OS was 15.6 months. Carfilzomib showed very low rates of peripheral neuropathy. Pomalidomide is a novel IMiD which showed a response rate of 21% in 38 patients who had received both bortezomib and lenalidomide and 63% of them were refractory to both drugs. Median duration of response, PFS and OS were 4.6, 4.6, and 18.3 months, respectively. In a phase 3 study in 455 patients, PFS and OS was significantly longer with pomalidomide+low dose dexamethasone vs. high dose dexamethasone alone (median 15.7 vs. 8.0 weeks; p<0.001 and median not reached vs. 34 weeks; p<0.001, respectively).

S1-4

Tailoring Multiple Myeloma Therapy for Special Populations

A. PALUMBO

Myeloma Unit, Division of Hematology, University of Torino, Italy

Combination therapies with alkylating agents or corticosteroids plus either thalidomide, lenalidomide or bortezomib are suggested in patients with multiple myeloma (MM) ineligible for transplantation. Recently, maintenance therapy with lenalidomide or bortezomib-thalidomide improved progression-free survival of approximately one year, but longer follow-up is needed to assess the effect on overall survival. Second generation proteasome inhibitors, such as carfilzomib and MLN9708, and the monoclonal IgG1 antibody elotuzumab are currently under investigation and will soon increase the treatment options for MM.

In MM patients over 75 years of age, or in younger patients with heart, lung, liver, or renal dysfunctions, or in those needing help for household and personal care, lower doses of standard regimens or the use of two-drug regimens may prevent toxicities leading to treatment interruption. Specific therapeutic options associated with a good tolerability profile will be discussed for the treatment of MM patients with special conditions such as advanced age, renal insufficiency, peripheral neuropathy, or myelosuppression.

S2

Genomics

S2-1

Discovering the Underlying Genetics of Multiple Myeloma Through Whole Genome Sequencing Approaches

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Multiple Myeloma is a pathological description of a disease characterized by the accumulation of plasma cells in the bone marrow. Early genetic studies using metaphase cytogenetics identified two distinct groups of patients, hyperdiploid and non-hyperdiploid, defined by their modal chromosome counts. Subsequent studies using gene expression profiling microarrays have consistently identified 7-10 distinct biological subgroups, the majority of which are linked to specific immunoglogulin translocations. These results highlight that there are many distinct subtypes of multiple myeloma each with distinct genetic defects. The recent advances in next generation sequencing can now identify nearly all genetics events existing in an individual tumor. Initial studies have focused on whole genome sequencing or exome sequencing and identified both known mutations (TP53, NRAS, KRAS) but also novel mutations (FAM46C and DIS3). Moreover, the identification of recurrent BRAF mutations and the availability of targeted BRAF inhibitors provided an opportunity to translate research findings into clinical practice. We will present results from the multiple myeloma genomics initiative using paired whole genome and transcriptome sequencing on 84 patient samples and 68 cell lines. The combination of DNA and RNA based sequencing approaches has improved our ability to identify biologically relevant alterations within each sample.

S2-2

Copy Number Alteration

S. MINVIELLE

Cancer Research Center Nantes-Angers, INSERM U892/ CNRS 6299/ University of Nantes, France

Multiple myeloma (MM) is characterized by a wide variety of chromosomal abnormalities. As the technologies for DNA profiling based on high-resolution single nucleotide polymorphism arrays improve, the catalogue of chromosomal abnormalities grows and leads to an increase and non biased appreciation for the complexity of DNA rearrangements that

occur in MM cells and their prognostic impact . Recurrent copy number alterations (CNAs) range from narrow focal alterations, such as 14q32.32 homozygous deletion region targeting NF-kB pathway component, TRAF3 to chromosome arm and whole-chromosome alterations, including gain of 1q, loss of 12p, loss of 16p, gain of chromosomes 5, 9 and 15 and loss of chromosome 13. Low incidence of catastrophic event termed chromothripsis whereby tens of chromosomal abnormalities confined in one or two chromosomes are acquired in a single cellular crisis. CNAs including amplification of positive NF-kB regulator CD40 and biallelic deletions of negative NF-kB regulators: TRAF3, cIAP1/2, CYLD when combined dysregulate NF-kB signaling in more than 15% of the MM patients. Comparisons of CNAs at diagnosis and relapse indicate that intrinsic genomic instability of myeloma cells increases with progression and strongly support the concept of a Darwinian model of clonal evolution in the context of MM progression. Genome-wide compilation of CNAs at different stages of the disease reveals new and detailed facet of genomic landscape of MM cells and has implications in our understanding of relapse mechanisms and in the therapeutic strategies.

S2-3

Gene Expression Profiling - Arrival in Clinical Routine

D. HOSE,[1] A. SECKINGER,[1] T. MEISSNER,[1] U. BERTSCH,[1] B. KLEIN,[2] H. GOLDSCHMIDT[1]

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BACKGROUND. Gene expression profiling (GEP) using DNA-microarrays, performed on purified myeloma cells, allows simultaneously assessing the expression of (almost) all genes. QUESTIONS. 1) Should and 2) can GEP be used in the clinical routine? For the latter, GEP needs to be i) possible in the majority of pts. (~80%), ii) reported in a timely fashion to draw a clinical decision, iii) understandable by clinicians, iv) integrated with prognostic information from other sources (e.g. iFISH), at v) rational costs. RESULTS. ad 1) GEP allows: i) risk stratification by scores basically summing over genes associated with adverse prognosis or genes associated with survival (e.g. ARKA), ii) classification of myeloma into subentities, iii) assessing surrogates of biological variables with potential prognostic impact, and iv) therapeutic targets. ad 2) In our GMMG-MM5 trial (EudraCT 2010-019173-16) recruiting 504 pts. between Aug 2010 and Oct 2012, i) CD138-purification was performed for 471 pts. (93%). Of these, GEP could be done in 83% (78% of all pts.). GEP was not possible due to no (7%), or not enough material (7%), or quality issues (9%). ii) GEP data can be reported within 4-6 weeks using iii) our non-commercial GEP-R (http://code.google.com/p/gep-r), which iv) integrates prognostic information (metascore). v) In academia, GEP costs about 800USD, comparable to iFISH and 1/10 of monthly treatment cost with novel agents. CONCLUSION. GEP can and should be performed and reported in clinical routine in >80% of patients within 4-6 weeks.

S2-4

Alternate Splicing a Frequent Event with Clinical Impact Myeloma

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Alternate splicing is an important post translational change that alters specificity of gene function. Alternative splicing is observed in 92-94% of all human genes and it produces multiple protein isoforms. Eighty five % of genes have minor isoform frequency of 15% or more. Frequency of isoform vary between tissues providing specific function. The proteins translated from alternately spliced form may have related, distinct or even opposing functions thus providing a wider transcriptome profile from limited number of genes. Misregulation of alternative splicing has been implicated in number of disease processes including cancer. We have analyzed alternate splicing in myeloma using both massively parallel RNA sequencing and high throughput exon array analysis. These transcriptomic analyses not only provides information on expression levels for genes, but provides information on presence or absence of each exon and identify recurrent alternately spliced genes and proportion of each isoform relative to each other. Using these analysis we have identified 1) Baseline frequency of alternate splicing in myeloma; 2) Identified changes in splicing pattern following interaction of MM cells with growth stimulating cytokine; 3) Identified splicing factors and their implications; 4) Confirmed that splicing pattern may change over time associated with change in phenotype or growth characteristics of myeloma cells; and finally 5) Evaluated prognostic implication of splicing in myeloma. In regards to the last point we conducted a study in series of 170 newly-diagnosed patients with multiple myeloma treated homogeneously in tandem transplantation. RNA isolated from CD138 purified MM cells collected at the time of diagnosis were analyzed using the GeneChip Human Exon 1.0

ST Arrays. Following normalization by gene-level expression values across samples, differentially expressed exons between two sample groups were identified. These exons are candidates for alternatively splicing events. We observed over 100 genes with alternate splicing in myeloma with frequency in more than 20% patients. Eighty five alternately spliced genes were identified with influence on overall survival between groups divided by less than or more than 48 month survival. Forty-nine genes within this group had the most influence on overall survival. Number of spliced variants were shared between both survival groups and group of genes identified to drive response suggesting their biological and functional significance. Further validation of these alternate splicing is under investigation. These investigation highlights significant frequency of alternate splicing and points to the need for evaluation of not only the expression level of genes but also post translational modifications. The genes identified are important target for therapy as well as possible immune modulation.

S2-5

microRNA in the Biology of Multiple Myeloma

I. GHOBRIAL

Dana Farber Cancer Institute Boston, MA, United States

microRNAs (miRNAs) are non coding RNAs that lead to post-translational regulation of gene expression. They are increasingly recognized as significant players in oncogenesis and tumor biology impacting broad pathways of proliferation, differentiation, apoptosis, metastasis, and cell survival. Recent studies have found abnormal expression of miRNAs in multiple myeloma (MM). Currently, the precise role of these miRNAs in the biology of MM is continuously being elucidated. Several studies have shown their role in plasma cell proliferation, survival, homing, or in MM cell interactions with the bone marrow microenvironment. Studies focusing on subsets of MM including precursor disease (monoclonal gammopathy of undetermined significance (MGUS) have also identified differential expression of miRNAs in these patient populations suggesting a role in the progression of this disease. miRNA profiles can discriminate molecular subtypes of MM that are defined based on gene expression profiling (GEP) and cytogenetic abnormalities, demonstrating the potential diagnostic/prognostic utility of miRNA profiling for subclassification of MM. miRNAs are also differentially expressed in bone marrow stromal cells and their contribution to myeloma progression and dissemination has been recently elucidated through transfer of exosomes between microenvironmental cells and tumor cells. Circulating miRNAs have also been shown to play a critical role in the prognostic classification of patients as well as their potential role in modulating the distant microenvironment allowing further dissemination of tumor cells. Regulation of miRNAs, through methylation and histone methyltransferase (MMSET) has been suggested, although further studies into the mechanisms of regulation of miRNAs are needed. Finally, since miRNAs can act either as oncomiRs or tumor suppressors, the potential of targeting miRNAs as a novel therapeutic approach for myeloma is being examined. In summary, miRNA play a crucial role in the biology of MM and may prove to be promising factorsin the prognosis and future therapeutic interventions of patients with MM.

S3
Plasma Cell Biology 1

S3-1
Population(s) of Myeloma Cells with Stem Cell-Like Features: Pathophysiological and Therapeutic Implications

C. S. MITSIADES

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Cancer cells with stem cell-like features are viewed in many neoplasias as reservoirs of resistance to agents with potent activity against the bulk of the tumor. In multiple myeloma (MM), however, the precise molecular phenotype and clonotypic architecture of tumor cells with stem cell-like features remains to be fully elucidated. This presentation will review the molecular and functional characteristics of MM cell populations enriched in putative stem-cell like cells (e.g. clonotypic B or pre-plasma cells; side population (SP) cells). Emphasis will be placed on data indicating that cell surface markers (e.g. CD20, CD27 or CD138) may be insufficient to determine whether a given MM cell population exhibits stem cell features, because the intra-patient heterogeneity or plasticity over time in expression of these markers may significantly limit their correlation with the molecular networks which actually regulate "stemness"/self renewal properties of MM cells. The presentation will also address the impact of the bone marrow (BM) microenvironment on drug resistance of stem cell-like MM cells; the challenges associated with clinical development of candidate therapies targeting stem cell-like MM cells; the importance of targeting therapeutically both stem cell-like and bulk MM cell populations in the BM milieu; and how rational design of such dual targeting can be facilitated by recently developed preclinical in vitro (e.g. compartment specific bioluminescence imaging (CS-BLI)-based co-culture systems) and in vivo (humanized BM models in immunocompromised mice) models.

S3-2
Extramedullary Spread in Multiple Myeloma

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Although multiple myeloma (MM) typically remains confined to bone marrow (BM) due to the strong dependence of malignant plasma cells on the BM microenvironment, a number of patients develop extramedullary disease (EMD), However, little data on the biology of EMD is available. The incidence of EMD in newly diagnosed patients ranges from 7% to 18% and can have two origins: direct extension from skeletal tumors or hematogenous spread. Possible mechanisms of EM spread in MM are: 1) decreased expression of adhesion molecules, particularly VLA-4 and CD44 as well as loss of CD56, 2) low expression of chemokine receptors, such as CCR1, CCR2, or downregulation of CXCR4 and its ligand SDF-1alpha, that are critically linked to the bone marrow homing of myeloma cells, 3) downregulation of P-selectin or tetraspanin expression and 4) increased angiogenesis. Key questions for future research are: 1) what are the mechanisms involved in hematogenous myeloma spread?, 2) do these mechanisms differ from those involved in direct extension from bone?, 3) which are the mechanisms of myeloma cell growth and cell survival at extramedullary sites. 4) what is the molecular genetic status of the malignant clone, including GEP and epigenetics, and particularly, drugs sensitivity and resistance?, and finally, 5) could genomic studies identify MM with extramedullary potential?. In the regard, it has recently been shown that EMD is more prevalent in genomically defined high-risk myeloma and that GEP studies may identify EMD-unique genes potentially helpful for development of targeted agents.

S3-3
Single Nucleotide Variants; Insights into the Pathogenesis and Outcome of Myeloma

G. MORGAN

ICR London, United Kingdom

In this presentation I will focus on the insights into the pathogenesis and outcome of myeloma that have been gained by the study of both inherited and acquired sequence variants. We have focussed on the use of sequence analysis from cases of myeloma entered into large clinical studies, which can be used to understand what causes myeloma as well as what impacts clinical outcome.

Insights into the causes of myeloma come from two main approaches. The first of these approaches is the study of SNVs in large case control comparisons. The second is the characterisation of the chromosomal translocations that characterise myelomaat a sequence level. Using the first approach in collaboration with the GMMG we have described a number of genes in which inherited variation increases the risk of developing myeloma. Taken together these genes focus attention on the deregulation of specific pathways predisposing to myeloma. In the second approach we describe evidence for the involvement of VDJ recombination abnormalities as well as abnormal CSR events in myeloma aetiology that may sug-

gest that events at the B precursor cell level could impact the development of myeloma, prior to passing through a germinal centre reaction.

Insights into clinical outcome can come from studying inherited variation and their impact on both side effects and survival end points. Initial studies used candidate gene approaches but these are no longer tenable with global GWAS analysis being the most appropriate methodology. We have generated data with this approach looking at neuropathy, VTE, bone disease and PFS/OS. Further insights into clinical outcome come from the study of "tumour acquired" variants. We have used massively parallel sequencing to study presenting samples and paired SMM/MM samples with the aim of developing predictive diagnostics and personalised medicine. These analyses significantly add to prior FISH based analyses and can lead to the development of targeted treatment strategies. We have identified the mutation spectrum of presenting mutations in myeloma and have used this as a tool to study the impact of intraclonal heterogeneity on targeted and standard treatments.

S3-4

Clonal Dynamics in Multiple Myeloma

L. M. PILARSKI

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Multiple myeloma (MM) has recently been shown to consist of multiple clones with*intra*-clonal heterogeneity (sharing the same IgH VDJ gene rearrangement) or *inter*-clonal heterogeneity (clones with distinct IgH VDJ sequences). Clonal dominance occurs when a dominant clone dampens expansion of subservient clones. If/when clonal dominance weakens, subservient clones or subclonescan expand and perhaps achieve dominance of their own. Such dominance may be stable or transient. The dynamics of dominant and subservient clones has a potentially significant impact on the disease process and may contribute to second B lineage malignancies in MM. Inter-clonal heterogeneity arises in a significant subset of MM patients, defined as the presence of unrelated clones coexisting with the dominant MM clone, suggesting escape from clonal dominance. They are present in blood and BM at frequencies that considerably exceedthose of antigen-stimulated normal clones, persist during treatment and can be dormant in the repertoire long before extended clonal expansion occurs. Interpretations of clonal dynamic s must distinguish between inter- and intra-clonal heterogeneity through molecular signatures that definitively confirm clonal identities and relationships. Some genomic changes, e.g. mutations and copy number abnormalities, may arise prior toB-lineage commitment and transformation events that lead to MM. We speculate that MM biology or treatment may at some point in the disease weaken MM clonal dominance and allow extensive expansion of related or unrelated B cell clones.

S3-5

Ras Mutations and Multiple Myeloma

R. FONSECA

Mayo Clinic in Arizona, Scottsdale AZ.

Activating *RAS* mutations are the most common mutational event in myeloma. These mutations are thought to be key in the pathogenesis of the disease. Activating mutations of *RAS* are believed to originate at the time of progression from the monoclonal gammopathy of undetermined significance (MGUS, and perhaps smoldering myeloma) to active disease. While these mutations are likely clonal, recent reports using next generation sequencing suggest a subclonal nature of the mutations, with them being present in subpopulations of cells, thus raising the specter that mutations may increase in prevalence in later stages of the disease. *RAS*mutations are more frequently observed in patients with cyclin D1 upregulation, notably in patients with t(11;14)(q13;q32) and also in hyperdiploid disease. Traditionally *RAS*mutations were believed to be associated with a more adverse outcome, but only *KRAS*mutations are associated with inferior survival. Murine models have convincingly shown the combined effect of *RAS* mutants and other oncogenes in late B cell neoplasms. This may mean the *NRAS* mutations are more associated with disease pathogenesis, while *KRAS* mutations are more likely to be progression events. Notably *HRAS* mutations are not described in myeloma or related conditions. Very few studies have addressed the role of *RAS* mutations with disease progression salvo those that have compared MGUS to myeloma. Additional studies are needed to better understand ras mutations and disease progression into relapse and extramedullary disease, although a recent study of primary plasma cell leukemia did not identify in high frequency. Given the frequency of mutational events of *RAS*, targeting this elusive gene remains a viable target in the development of new therapies for the disease.

S4
Myeloma Bone Disease

S4-1
Overview of the Pathophysiology of MBD and Acquired Genetic Events.

G. D. ROODMAN

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Myeloma bone disease (MMBD) results in severe bone pain, pathologic fractures, hypercalcemia, and a markedly decreased quality of life. Osteoclast (OCL) activity is gretly increased in MM while osteoblast (OBL) activity is suppressed. MM cells produce or induce multiple osteoclastogenic factors in the bone marrow microenvironment that increase OCL activity including RANKL, MIP-1 α , TNF- α , IL-3, annexin II, and IL-6. Interestingly, several of these factors also suppress OBL formation and / or support MM cells directly, indicating that they play multiple roles in MMBD. In addition, adhesive interactions between MM cells and marrow stromal cells augment the bone destructive process. Further, MM cells and marrow stromal cells are hyper-responsive to Vitamin D, which increases bone destruction and tumor growth at very low levels of Vitamin D.

An important feature of myeloma bone disease is that the lytic lesions do not heal even when the patients are in prolonged remission, suggesting that bone repair does not occur at previous sites of bone destruction in MM patient. A number of inhibitors of OBL differentiation have been identified in MM that are produced by MM cells or cells in the marrow microenvironment and include TNF- α , MIP-1 α , IL-3, Activin A, DKK1, sclerostin, GFI-1, TGF β , HGF and IL-7. Current efforts targeting these OBL inhibitors could lead to development of several anabolic agents that may reverse the loss of skeletal integrity in MM patients. With the enhanced median survival of MM patients with the advent of new anti-MM therapies, managing MMBD and its complications will be evermore important for MM patients.

S4-2
Partnership between Multiple Myeloma Cells and Bone Marrow Stromal Cells in the Pathophysiology of Bone Destruction

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Multiple myeloma (MM) is a B-cell malignancy that selectively colonizes bone marrow (BM) and causes devastating bone destruction. BM is fertile for MM due to continuous supply of bone-stored growth factors by osteoclastic bone resorption. Moreover, BM stromal cells nourish MM to home, proliferate and survive in BM via cell-cell interactions that are mediated by cell adhesion molecules (CAMs) in the unique microenvironment called niche. Identification of CAM expressed in MM and BM stromal cells and determination of functional interactions between these CAMs are important to better understand the pathophysiology of MM bone disease. We established the mouse MM cell line 5TGM1 that expresses $\alpha 4\beta 1$ integrin. Co-culture of 5TGM1 and BM cells induced osteoclastogenesis, which was blocked by the antibody to $\alpha 4$ integrin or VCAM1. Mice inoculated with 5TGM1 cells developed MM accompanied with profound osteoclastic bone destruction. Anti- $\alpha 4$ integrin antibody significantly inhibited the development of MM and bone destruction, leading to improved survival of MM-bearing mice. Of note, combination of anti- $\alpha 4$ integrin antibody and suboptimal dose of melphalan significantly prolonged survival compared to each agent alone. In conclusion, our results suggest the cell-cell contact between MM and BM stromal cells via $\alpha 4$ integrin or VCAM1 is critical to the pathophysiology of MM and associated bone disease. The contact may be also involved in MM chemo-resistance. Disruption of the cell-cell contact in BM niche may represent a specific therapeutic strategy for MM.

S4-3
Bench Work for the Targeted Therapy to the Microenvironment of MBD

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Bone provides a unique microenvironment for myeloma cell growth and survival, including niches to foster clonogenic myeloma cells. Myeloma cells alter the microenvironment in bone where they colonize, which in turn favors tumor growth and survival, thereby forming a vicious cycle between tumor progression and bone destruction. Myeloma cells stimulate bone resorption by enhancing osteoclastogenesis, while suppressing bone formation. Multiple factors over-produced from myeloma cells and/or bone lesions act together to develop extensive bone destruction in myeloma. They include soluble Wnt inhibitors such as DKK1, sFRPs and sclerostin, the TGF family cytokines activin A and TGF-beta, TNF-alpha, IL-3, IL-7, and HGF to suppress osteoblastic differentiation from bone marrow stromal cells. The immature bone marrow stromal cells deflect and stimulate monocyte differentiation into mature osteoclasts. MIP-1alpha and RANK ligand play

a major role in the osteoclastogenesis enhanced in myeloma. In contrast to the numerousness of extracellular factors, relatively limited numbers of intracellular signalling mediators, including NF-kappaB, p38MAPK, Akt, the adaptor protein p62, and the serine/threonine kinase Pim-2, have been demonstrated to be activated in both myeloma cells and their surrounding environmental cells and predominantly regulate the pathological bone metabolism and tumor growth in myeloma. Further elucidation of the molecular mechanisms of tumor-bone interactions will provide us with new approaches that have a real impact on both bone disease and tumor progression.

S4-4

The Role of Imaging and Bone Markers in the Evaluation of Bone Disease in Multiple Myeloma

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Osteolytic disease is a major complication of multiple myeloma (MM) which may lead to devastating skeletal related events (SREs). Conventional radiography remains the gold standard for the evaluation of bone disease in MM. However, whole body MRI is recommended in patients with normal conventional radiography and should be performed as part of staging in all patients with a solitary plasmacytoma of bone. MRI is also of prognostic significance for patients with asymptomatic MM. Urgent MRI is the diagnostic procedure of choice to rule out cord compression. PET/CT can provide useful prognostic information and may be used for the better definition of complete response to treatment. The incorporation of abnormal MRI or PET/CT findings into the definition of symptomatic myeloma needs to be clarified. The alterations of bone metabolism in MM patients can be detected by measuring biochemical markers of bone turnover, such as the resorption markers N- or C-telopeptide of collagen type 1 (NTX and CTX or ICTP, respectively) and the formation markers bone-specific alkaline phosphatase and osteocalcin. Urinary NTX, serum CTX and serum ICTP are elevated in myeloma patients with osteolytic lesions and correlate with the extent of bone disease, advanced MM stage, increased risk for SREs and overall survival. Bone markers have also been used for the early detection of myeloma progression to bone. The value of the measurement of novel regulators of osteoclast or osteoblast function (sRANKL, osteoprotegerin, dickkopf-1, sclerostin, activin-A, periostin and others) is under investigation.

S4-5

Novel Agents to Treat Myeloma Bone Disease

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New insights into the biology of myeloma bone disease have provided important targets currently either in preclinical or clinical testing. The osteoclast (OC) compartment has always been an important target and to date bisphosphonates have remained the gold standard of myeloma bone disease treatment. Denosumab, a reversible inhibitor of RANKL is undergoing phase III clinical testing as an alternative strategy to bisphosphonates. More recently targets such as MIP 1 alpha and Bruton' s tyrosine kinase (BTK) have been identified to play a critical role in targeting the OC and their inhibitors have been tested in preclinical models. Targeting the osteoblast (OB) compartment is an alternative and exciting strategy. To this end, the identification of DKK1 as an inhibitor of OB formation has led to the development and testing of anti-DKK1 strategies such as BHQ880. Other targets such as Activin A are being studied in the clinic with the use of antibodies such as ACE011. Newer targets such as sclerostin are under investigation. All of these novel agents have the potential of not only treating myeloma bone disease but importantly indirectly impacting the tumor. Importantly, some of the newer anti-myeloma agents such as proteasome inhibitors like Carfilzomib and MLN 9708 and HDAC inhibitors such as ACY 1215 have profound bone effects. These exciting options will be discussed during this session.

S4-6

Updated Recommendation of Bisphosphonate Treatment Including Prevention and Management of Osteonecrosis of the Jaw (ONJ)

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Bisphosphonates (BPs) are recommended in all myeloma (MM) patients requiring frontline therapy, irrespective of the presence of bone disease at diagnosis, assessed by conventional radiography. Zoledronic acid (ZOL) is associated with improved survival of newly diagnosed patients and reduces SREs over clodronate (CLO). This advantage is sustained in patients who receive ZOL for >2 years. Therefore, ZOL should be given continuously with the possible exception of patients who have achieved CR, for whom there are no data regarding ZOL survival benefit. For pamidronate (PAM), there are no data for survival advantage in newly diagnosed patients and thus it can be given up to 2 years and then at the physician

discretion. PAM and ZOL are not recommended for patients with CrCl <30 mL/min, while CLO can be safely given in patients with a CrCl >12 ml/min. BPs should be discontinued in patients with renal problems until CrCl returns to within 10% of baseline values. ZOL is associated with a higher rate of ONJ than other BPs; the cumulative dose and the treatment duration are established risk factors for ONJ. The implementation of appropriate preventive measures greatly reduced the incidence of ONJ. BPs should be stopped if a patient develops ONJ. Clinical evidence supports restarting BP therapy after ONJ healing in patients with active bone disease. Furthermore, it appears that patients who developed ONJ after dental procedures are less likely to have recurrence or non-healing lesions after BP re-initiation following ONJ healing compared to patients who developed spontaneous ONJ.

S5

Plasma Cell Dyscrasias: POEMS, AL Amyloidosis, and Waldenstrom's Macroglobulinemia

S5-1

Designing, Monitoring, Modeling and Individualizing Myeloma Virotherapy Protocols II: MV-NIS.

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Oncolytic measles viruses are highly pleomorphic, approximately spherical particles with diameters of 100-300 nM. They extravasate from leaky tumor neovessels and propagate selectively in myeloma cells which express very high levels of CD46, the primary virus receptor. Infection spreads from infected cells to contacting cells. Based on its efficacy in myeloma xenograft models, MV-NIS, a recombinant oncolytic measles virus encoding the thyroidal sodium iodide symporter (NIS) was advanced to phase I clinical testing as intravenous therapy for patients with advanced treatment-refractory myeloma. The starting dose was 10^6 $TCID_{50}$ (with or without cyclophosphamide) with one log dose increments (3 patients per dose cohort) to 10^{11} $TCID_{50}$. 24 patients have been enrolled to date but the MTD has not yet been reached and evidence of antimyeloma activity was seen only at the 10^{10} $TCID_{50}$ dose level. Correlative studies show that the virus propagates in patient tissues and is shed in urine and/or saliva, maximally on day 8 post-administration. Antimeasles antibody titers are significantly boosted by day 28 post therapy, and in a few patients there is evidence from NIS imaging studies that the virus replicated selectively at sites of active tumor growth. We expect to see meaningful responses at the 10^{11} dose level, and have plans to further accentuate the response by co-administration of higher cyclophosphamide doses than we have used to date which will hopefully suppress the adaptive antiviral immune response, accelerate virus spread and pave the way for repeat virus dosing.

S5-2

Autologous Stem Cell Transplantation for POEMS Syndrome

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POEMS syndrome is a rare plasma cell disorder characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes associated with multiorgan involvement and extremely high level of serum VEGF. The prognosis of the syndrome had been poor with steroids or chemotherapy, however, in the past decade, high-dose melphalan followed by autologous stem cell transplantation (ASCT) dramatically improved the survival as well as patients' performance status with significant improvement of polyneuropathy and reduction of serum VEGF levels. However, patients with POEMS treated with ASCT experience higher rate of engraftment syndrome and regimen-related toxicity (RRT) than myeloma. Recently induction therapy with novel agents before ASCT has been introduced with successful reduction of RRT rate. In our institution, 23 POEMS syndrome cases with the median age of 52 (range, 34-64) have been treated with ASCT from 2004 to 2012. Fifteen patients (65.2%) received thalidomide before ASCT. Nine patients presented poor PS of 3 to 4 due to peripheral neuropathy. Improvement of clinical symptoms and reduction of VEGF were observed in 22 patients (95.6%). No transplant related death was observed. At median observational period of 51 months, 2y OS and PFS was 95.6% and 77.3%, and 5y OS and PFS was 64.6% and 59.8%, respectively. These data suggest that ASCT is an effective therapy for POEMS syndrome but certain number of patients experience late disease relapse. Therefore, all patients should be followed carefully, and effective salvage strategies are required.

S5-3

Management of AL amyloidosis in 2013

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AL amyloidosis has an incidence of approximately 10 per million person years and is caused by a usually small, indolent plasma cell clone synthesizing a misfolded monoclonal light chain that causes systemic proteotoxicity. The amyloidogenic clone represents a particularly early stage of monoclonal gammopathy possibly more susceptible to chemotherapy. Early, accurate diagnosis is the key to effective therapy, and early "red-flags" should trigger the appropriate diagnostic procedures. Unequivocal identification of the amyloidogenic protein may require mass spectrometry-based proteomic techniques that are now considered gold standard for amyloid typing. Prognosis is dominated by the extent of cardiac involvement, and cardiac biomarkers direct the choice of therapy. Treatment for AL amyloidosis is highly individualized and close monitoring of clonal response and of cardiac response guides regimen changes and duration of therapy. Novel criteria for hematological and organ response are now available. Alkylator-based chemotherapy is effective in almost two thirds of patients. Risk-adapted stem cell transplant and consolidation with novel agents should be considered in selected patients. The combinations of proteasome inhibitors with dexamethasone and alkylators (melphalan and cyclophosphamide) show promising results and controlled studies are warranted. The role of IMiDs in maintenance therapy and in refractory/relapsed patients is being explored. Novel therapeutic approaches targeting amyloid deposits will be integrated with chemotherapy in the future.

S5-4

Biology of Waldenström Macroglobulinemia

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WaldenströmMacroglobulinemia first described by Jan-Waldenström in 1944 is a lymphoplasmacytic lymphoma characterized by the presence of an immunoglobulin M (IgM) monoclonal gammopathy in the blood and monoclonal small lymphocytes and lymphoplasmacytoid cells in the bone marrow. WM is a rare and indolent disease but remains incurable. Here, I will discuss the pathogenesis of WaldenströmMacroglobulinemia and focus on novel treatment options that target pathways deregulated in this disease. Recent studies have helped us identify specific genetic mutations that are commonly seen in WM and may prove to be important therapeutic targets in the future. I will discuss the role of epigenetics and the changes in the bone marrow microenvironment that are important in the pathogenesis of WM. The commonly used drugs will also be discussed with a focus on novel agents that are currently being used as single agents or in combinations to treat WM. Finally, I will focus on some agents that may be promising in future clinical trials in WM.

S5-5

Current and Emerging Treatment Options for Waldenstrom's Macroglobulinemia

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Genetic factors play an important role in WM, with 25% of patients demonstrating familial predisposition. The presence of familial disease impacts treatment outcome, and patients with familial WM may benefit with proteasome inhibi-

tor based therapy. Asymptomatic patients should be observed. Patients with a disease related hemoglobin level <10g/L, platelet count<100x109/L, bulky adenopathy or organomegaly, symptomatic hyperviscosity, peripheral neuropathy, amyloidosis, cryoglobulinemia, cold-agglutinin disease or evidence of disease transformation should be considered for therapy. Patients with anemia often demonstrate a functional iron deficient state due to high levels of hepcidin, and may benefit with parenteral iron therapy. Among chemotherapy options, nucleoside analogues and oral alkylators should be avoided in younger patients due to increased risks of secondary malignancies. Plasmapheresis should be considered for symptomatic hyperviscosity, and as a prophylactic measure prior to rituximab administration in patients with high IgM levels since rituximab often induces an IgM flare. Cyclophosphamide, bendamustine or bortezomib based therapy in combination with steroids and rituximab can be considered as an appropriate first line treatment. Bortezomib in combination with steroids and rituximab may be particularly beneficial to patients with symptomatic hyperviscosity. Peripheral neuropathy is more prevalent in WM versus MM patients with bortezomib, and close monitoring and adoption of weekly administration can be considered. Carfilzomib represents a novel neuropathy sparing option for proteasome inhibitor based therapy in WM patients. In the salvage setting, the re-use or use of an alternative frontline regimen can be considered as well as everolimus, alemtuzumab and stem cell transplantation. Ibrutinib is a novel agent which blocks Bruton' s Tyrosine Kinase, which is triggered by the recently identified MYD88 L265P mutation in WM cells. High rates of responses, and improvements in anemia have been observed in an ongoing clinical trial in relapsed/refractory WM. Panobinostat is histone deacetylase inhibitor with activity in relapsed/refractory WM. Novel response criteria have recently been developed for WM, but remain challenged by novel agents which often show discordance between serum IgM levels and underlying disease burden.

S6

New Imaging Techniques

S6-1

Usefulness of Newer Imaging Techniques as Predictor of Outcomes in MM-Comparison between PET/CT and MRI in Different Settings

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Imaging plays an important role in the diagnosis and management of MM. Various techniques are currently available to assess bone disease, evaluate bone marrow plasma cell infiltration, detect spinal cord and/or nerve root compression and reveal the presence of soft tissue masses. Moreover, newer imaging tools, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) integrated with computed tomography (PET/CT), have shown to be predictors of clinical outcomes in different settings. In particular, whole body MRI appeared to predict the risk of early progression from asymptomatic or smouldering MM to symptomatic disease. Both PET/CT and MRI have proved reliable techniques for predicting the outcome at diagnosis in symptomatic MM, as well as at the early phases after treatment and at the end of the treatment program. In addition, PET/CT showed prognostic significance for the risk of progression or death even among patients achieving conventionally-defined CR, thus allowing one to identify subgroups of patients with different depth of response and to refine the definition of CR. Integrating these techniques into the work-up of newly diagnosed MM patients may improve disease management, contributing to the design of individualised patient therapies.

S6-2

Clinical Contribution of PET/CT in Myeloma: From a Point of View of Radiologist.

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Positron emission tomography / computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG) has been widely used in various cancers. It can yield much useful information for staging or restaging, since glucose metabolism is activated in many cancer cells. As for the plasma cell malignancy (PCM), including multiple myeloma, it has been reported that FDG-PET/CT is useful not only for detecting viable lesions, but for monitoring therapy response and pre-

dicting patients' prognosis. Therefore, it is gradually increasing to have an opportunity of PET/CT scanning before treatment of PCM. However, FDG is not a cancer-specific agent. It also accumulates in some benign tumors, inflammatory foci or normal organs, resulting in false positive or even negative findings. We need to familiarize ourselves with many pit-falls in interpreting PET/CT images.

The PCM is characterized by excessive production of monoclonal immunoglobulin, which in most cases can be detected in serum and/or urine, it is reasonable to suppose that an amino acid-based tracer might be useful in PCM. ^{11}C-labelled methionine (MET) is a radiolabelled PET tracer, which can image hyper-metabolism of amino acid, and has been used for research purposes. However, clinical value of MET-PET for PCM has not been fully investigated. According to our preliminary data, MET-PET identified more viable lesions of PCM than FDG-PET. We believe that MET-PET/CT might provide useful information for determining a therapeutic strategy especially when FDG-PET/CT results are equivocal or undeterminable.

S6-3

New PET/CT Imaging Techonology in Myelomology; Two Innovative PET/CTs to Detect Protein-synthesizing Cellular Aggregates (Amino Acid PET/CT) and DNA-synthesizing Cells (Thio-thymidine PET/CT)

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FDG/PET has been used to evaluate myeloma tumor burden, and its usefulness to detect extramedullary disease (EMD) or plasmacytoma has been established. However, in some cases, FDG/PET sometimes failed to visualize EMD or myeloma cell nests. Taken this occasional false negativity of FDG/PET into consideration, the introduction of more sensitive or myeloma-specific PET must be investigated. In this article, we present two new PET technologies; amino-acid PET and thio-thymidine PET. The amino-acid PET using radio-labelled methionine can detect protein-synthesizing cell nests, resulting in higher detection rate of myeloma cell nests or EMD due to high efficiency of incorporation of radio- labelled methionine into protein-synthesizing cells such as myeloma cells. Thio-thymidine PET is truly a new-comer which can detect the DNA-synthesizing cell nests because this compound can be incorporated into DNA synthesis. Formerly, a radio-labelled thymidine was used to visualize DNA-synthesizing cells. However, this method failed to visualize DNA-synthesizing cell nests due to rapid degradation by blood enzymes. On the contrary to naive thymidine, our manipulated thymidine, thio-thymidine cannot be rapidly degraded. When thio-thymidine PET was performed on the next day after methionine PET, we could measure SUVs of thio-thymidine PET in protein-synthesizing cell nests detected by methionine PET. Using this technology, DNA-synthesis in various EMDs could be calculated ('in vivo' labelling index?). In this session, we present findings of our PETs, especially higher visualizing efficiency of myeloma cell nests by amino-acid PET and visualization of DNA-synthesizing cell nests. In addition, positivity by methionine PET was detected in some cases with normal FLC patterns. The upstaging might be possible in PLUS staging when methionine PET will be used.

S7

Minimal Residual Disease and Evaluation of Response: Updated

S7-1

What is the Best Surrogate Marker for Long-Term Survival in Multiple Myeloma, sCR, ICR,MCR or PET/CT?

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Important changes have been made in the treatment of multiple myeloma (MM), after the introduction of high-dose therapy regimens (HDT) followed by autologous stem cell transplantation (ASCT), and an increasingly high number of combinations of new drugs. With these treatment strategies, CR rates have progressively increased. Currently, a large body of evidence exists in the ASCT setting which shows a clear association between optimal response (eg. CR) and long-term outcome of MM. This has fostered the search for a more stringent definition of CR (stringent CR; sCR), but also for new minimal residual disease (MRD) approaches. Such new MRD approaches have proven to be particularly informative in patients that attain conventional CR, in whom assessment of either PCR- or flow-based MRD levels strongly correlates with the quality of response to HDT/ASCT and survival (PFS and OS). This also holds true in the non-transplant setting among older (>65y) patients treated with novel agents. Flow-MRD is less time-consuming and it has a higher applicability than PCR-MRD; however, it displays a lower sensitivity at MRD levels <10(-4). Moreover, flow-based MRD provides additional prognostic information in cases that achieve CR and sCR, flow-based MRD levels emerging as the strongest independent prognostic factor for PFS and OS in the ASCT setting. Despite this, preliminary data indicates that disease recurrence at extramedullary sites may go undetected by bone marrow-based MRD testing, pointing out a clear role of imaging techniques for early detection of extramedullary disease recurrence.

S7-2

Experience from the MRC Myeloma IX Study

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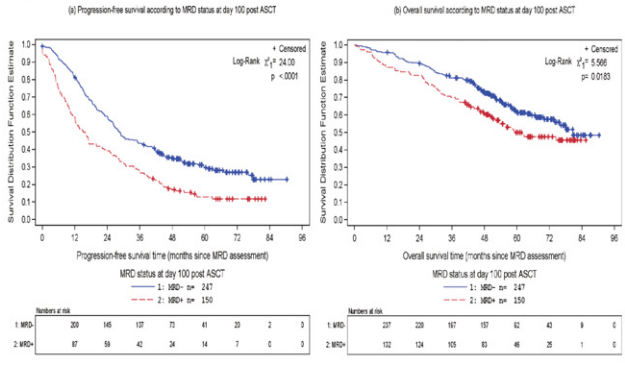
Patients were allocated to either an intensive pathway which included high dose melphalan (HDM) and autologous transplant (ASCT) or a non-intensive pathway. In both there were randomizations to thalidomide (thal) or non-thal containing induction regimens and to no maintenance or thal maintenance. Bone marrow samples were submitted centrally for multiparameter flow cytometry (MFC) at key time points to assess minimal residual disease (MRD). Post-induction, a significantly higher proportion of patients treated with thal-containing regimens achieved MRD negativity. In intensive pathway patients (n=397) MRD negativity at day 100 post-ASCT was highly predictive of superior outcome: overall p<0.0001 for PFS and p=0.0183 for OS; p=0.014 and p=0.0003 for PFS in favourable and unfavourable cytogenetic groups respectively; p=0.0068 for PFS in patients achieving conventional immunofixation negative CR. There was no statistically significant effect of MRD status after induction in the non-intensively treated group. Across all intensive pathway patients investigated by MFC in maintenance (n=292), the shortest PFS was observed in MRD-positive patients who did not receive thal, the longest PFS in those who were MRD-negative and had thal (p=0.0003); 28% of MRD-positive patients who were given thal became MRD-negative. With the introduction of intensive treatment it became clear that the achievement of CR was predictive of outcome. The more critical assessment of depth of responses, exemplified by MRD by MFC, should be of importance in evaluating new therapy in induction, consolidation and maintenance.

Figure 1.



S8

PrIME Oncology Supported by Millennium: The Takeda Oncology Company - Sponsored Symposium

Can Multiple Myeloma Become a Chronic Disease in the Short-Term Future?

S8-1

Functional Oncogenomics: A Tool for Identification and Validation of Targeted Therapies in MM.

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With the completion of the human genome project and advent of microarray and sequencing technologies, we can now identify mutated or deregulated genes and pathways in cancers (oncogenome) with unparalleled depth and throughput. However from identifying these deregulated genes and pathways to effective therapeutics still requires a process of differentiating what is functionally relevant to oncogenesis and identifying what are 'driver' and 'passenger' mutations. This is where functional oncogenomics, a process where the functional relevance of the oncogenome is elucidated, comes in. A logical approach incorporating functional genomics through targeted or unbiased approach would greatly facilitate this process to narrow down to the most promising candidates for therapeutic targeting. These experimental strategies have been successfully applied to the identification of new drug targets, new strategies to overcome resistance,rational new combinations and new strategies to target 'Achilles heels' that are not directly targetable in cells through synthetic lethality.For example, these approaches have already led to the discovery of (1) cyclin D kinase inhibitors as potential therapeutic options with some lead compounds already showing single agent activity in relapse / refractory myeloma; (2) the potential use of aurora kinase inhibitors in high-risk myeloma; (3) theidentification that malignant plasma cells are addicted to IRF4;and (4) the identification of potential modulators of bortezomib response. These discoveries are making important contributions in pushing the therapeutic frontiers in myeloma. This is particularly important as despite great therapeutic advances, myeloma is still generally incurable and new treatments are much needed.

S8-2

Targeting the Proteasome

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Treatment of multiple myeloma has undergone a paradigm change during the past decade leading to significantly improved survival for patients with myeloma. Proteasome inhibitors and immunomodulatory drugs represent the two classes of drugs that are primarily responsible for the treatment advancement in this disease. The ubiquitin proteasome system, which plays a major role in protein degradation in cellular systems have proven to be an attractive target for cancer therapy in general, and myeloma in particular. Bortezomib was the first proteasome inhibitor to reach the clinic and was found to be highly effective in the treatment of myeloma. Bortezomib specifically inhibits the 26S proteasome function through its reversible but strong covalent binding between its dipeptidyl boronic acid moiety and the threonine proteases of the 20S subunit. The anti-myeloma effect of bortezomib has been attributed to a variety of different actions, the most studied of which has been the effect on the NFkB pathway. Mutations of molecules along this pathway have been shown to correlate well with disease response following therapy with bortezomib. More recently, newer proteasome inhibitors have been developed including carfilzomib, a non-reversible, non-boronic acid containing inhibitor, as well as oral molecules such as MLN9708, another boronic acid containing molecule like bortezomib. Proteasome inhibitors have shown considerable activity in the newly diagnosed setting as well as relapsed disease, either alone or in combinations and particularly effective in high-risk myeloma.

S8-3

Targeting the Ubiquitin Proteasome Cascade (UPS) in Multiple Myeloma (MM)

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In multiple myeloma (MM) cells Bortezomib targets chymotrypsin-like (CTL) proteasome activity, inhibits growth and survival, induces apoptosis, upregulates heat shock proteins, inhibits DNA damage repair, and induces ER stress. Mutations in NF-κB signaling confer Bortezomib sensitivity; conversely, mutations in β 5 proteasome subunit confer in vitro, but not clinical, Bortezomib resistance. Preclinical studies provide the rationale for clinical trials targeting UPS: upstream of the proteasome with deubiquitinating (DUB)

inhibitors (USP7 or USP14/UCHL5 inhibitors); with more potent CTL inhibitors carfilzomib, ONX0912 (oprozamib), or MLN9708 (ixazomib); as well as with CTL, trypsin-like, and caspase-like inhibitor NPI-0052 (marizomib). Preclinical studies define their mechanisms of action and show that these agents can overcome Bortezomib resistance. Ubiquitinated protein can also bind to histone deacetylase-6 (HDAC6) and to the dynein motility complex, thereby facilitating its aggresomal degradation. Inhibition of the proteasome upregulates aggresomal degradation, and vice versa. Blockade of aggresomal degradation can be achieved either by genetic studies (HDAC6 knockdown) or pharmacologically with broad HDAC inhibitors (vorinostat, panobinostat) or HDAC6 selective inhibitors (tubacin, ACY1215). Combined aggresomal and proteasomal blockade triggers synergistic cytotoxicity, associated with increased ER stress and activation of extrinsic (caspase 10) apoptotic signaling. Targeting UPS and protein homeostasis therefore represents a promising therapeutic strategy in MM.

S8-4

Combination Targeted Strategies: Choosing Rational Designs

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Treatment in oncology, and specifically multiple myeloma, has recently shifted from the use of unspecific chemotherapeutic agents, towards an era of novel targeted therapy in which drugs target specific mechanisms within tumor cells. Nevertheless, only second and third generation IMIDs (pomalidomide) and proteasome inhibitors (carfilzomib) have some clear activity, which is even higher to that of their parental compounds. Combinations of targeted agents with high scientific rational include: 1. Elotuzumab (Anti-CS1 MoAb) + lenalidomide. 2. Combination of agents targeting different steps within the unfolded protein response; this is the case of the simultaneous inhibition of the aggresome formation by DACi + proteasome inhibition. HSP-90 + proteasome inhibitors is another combination directed against the UPR, that has shown advantage in a phase 3 trial. 3. The combination of agents inhibiting the AKT/mTOR pathway with proteasome inhibitors (to block the indirect AKT up-regulation induced by bortezomib) or with IMIDs have also shown activity in very refractory patients. Less advanced combinations includes: 4. agents inducing DNA damage with proteasome inhibitors that block the DNA repair pathways; 5. The combination of CDK5 inhibitors with proteasome inhibitors (this was based on a RNAi screening that identified CDK5 as one of the top bortezomib-sensitizing molecules in MM); or 6. agents blocking the cell cycle progression (such as Arry-520 or the CDK 4/6 inhibitors) together with proteasome inhibitors.

S-9
Initial Therapy -Transplant Eligible-

S9-1
Risk Assessment

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For now almost 20 years, therapeutic intensification with high-dose melphalan is the gold standard for patients under 65 years of age. Even though this approach is currently discussed by some investigators in the novel drug era, and is the main question of some large phase 3 trials, it is still the standard approach. Even with the significant improvement observed with this strategy, most of the patients relapse. However, some patients encounter very long progression free survival, and some might be cured from myeloma. Thus, it is of major importance to evaluate this risk of relapse at diagnosis. Apart from the ISS, most of the outcome variability is related to the genetic abnormalities observed in the myeloma clone. Several techniques can be used: karyotype, FISH, gene expression profiling (GEP), CGH/SNParray, sequencing. At the chromosomal level, an abnormal karyotype (reflecting proliferation), and the presence of the t(4;14) or the del(17p) are the main factors associated with poor outcome. GEP is more problematic since many gene models have been published, with different performances in risk assessment depending on the therapeutic strategies. CGH/SNParray is probably more accurate at the individual level since it evaluates copy number rather than relative expression level. Large studies based on this technique are still lacking. Finally, sequencing is just at the beginning of its life, and cannot be yet utilized in large series because of cost. But no doubt that we are on the way to be able to really assess the risk at the patient level.

S9-2
Debate: Induction Therapy: Risk-Adapted, Response-Adapted, or One Size Fits All Strategy

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Numerous trials have been conducted in myeloma in the last 10 years since the arrival of thalidomide and other newer agents, but few are randomized trials. Few have shown survival improvement with new regimens compared with older regimens, but very little data are available from randomized trials comparing two modern regimens with each other. These regimens differ from each other in terms of cost, toxicity and ease of administration. In the absence of clear survival or quality of life advantage of one regimen versus the other, therapy needs to be risk-adapted because the choice of a patient will vary depending on anticipated prognosis. Patients with standard risk myeloma have a median overall survival (OS) of 6-7 years while those with high risk disease have a median OS of less than 2-3 years despite tandem autologous stem cell transplantation (ASCT). Patients with intermediate risk myeloma have a survival similar to high risk in the absence of bortezomib, while in the presence of bortezomib-based induction, high dose therapy, and bortezomib based consolidation/maintenance, have an outcome similar to that of standard risk patients. It is hard to ignore these factors when deciding on initial therapy. Clearly the choice of therapies varies across countries based on availability. More importantly, as much as possible patients are best served by enrollment in prospective clinical trials than by following the suggestions listed above.

S9-3
Debate: Induction Therapy: Risk-Adapted, Response-Adapted, or One Fits All Strategy

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Introduction: We evaluated efficacy of bortezomib (B)-based versus non-B-based induction regimens in various risk groups in phase 3 studies of newly diagnosed transplant-eligible patients with myeloma. Methods: Data from IFM 2005-01 (BD vs VAD induction), HOVON-65/GMMG-HD4 (PAD vs VAD) and PETHEMA GEM05MENOS65 (VTD vs TD) studies were pooled in an integrated analysis. Study-level data from the GIMEMA MM-BO2005 study (VTD vs TD) supplemented the analysis. Key efficacy endpoints were post-transplant CR+nCR rate and progression-free survival (PFS). Results: Patient-level data for 1572 patients (787 B, 785 non-B induction) were included. Post-transplant CR+nCR rate was higher after B-based induction (38% vs. 24%, OR 2.05, P < .0001); benefit remained (pooled OR 1.96) upon inclusion of GIMEMA data. Median PFS was 35.9 vs 28.6 months (HR 0.75, P <.0001) with B vs non-B induction; 3-year overall survival (OS) rates were 79.7% and 74.7%, respectively (HR for OS: 0.81, P = .0402). The benefit of B-based induction was higher in ISS stage 2 or 3 and poor risk FISH. Achieving CR+nCR was a significant risk factor for PFS (HR 0.65 [95% CI: 0.53, 0.79], P < .0001). In addition we performed Gene Expression Profiling in HOVON-65/GMMG-HD4 and we were able to identify 20% high-risk vs 80% standard risk patients for PFS and OS across B-based or non-B-based induction (p<0.001). Conclusions:

B-based induction especially benefits patients with high ISS and poor-risk FISH. Further assessment of risk subgroups is needed before risk adapted treatment choices can be made.

S9-4

Debate: Early or Delayed Transplantation for Multiple Myeloma in the Era of Novel Therapies: Does One Size Fit All?

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High-dose therapy with autologous stem-cell transplantation (ASCT) for multiple myeloma (MM) has been considered the standard frontline treatment for younger patients with adequate organ function. The introduction of novel agents, specifically thalidomide, bortezomib, and lenalidomide has changed the ASCT scenario in several ways. Novel agents are being incorporated as a part of induction with the objective of increasing the response rate prior to ASCT, and then as consolidation followed by maintenance. The goal of applying treatments in the post-ASCT setting is the extension of progression-free survival (PFS) and overall survival (OS). Combination approaches have shown promise with significant improvements of PFS and OS, and investigators are now even considering whether MM has become a functionally curable disease in a subset of patients. The efficacy of the novel therapeutics has also led to the investigation of these agents upfront without ASCT, and compelling preliminary results have been reported. Specifically, high quality, depth and duration of responses are being seen with three-drug induction regimens, with the result that the role and positioning of ASCT has become a matter of debate: should it be used early in all eligible patients, or as a salvage treatment at the time of progression for selected patients achieving a high quality response, with ASCT kept in reserve? Our discussion will focus on these important issues and derive a consensus that will hopefully be useful for clinicians considering both protocol-directed and non-protocol options for their patients.

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S9-5

Predictive Factors of Outcome

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High-dose therapy followed by autologues stem cell transplantation is the standard of care for younger patients with multiple myeloma since the last two decades. The incorporation of new drugs, i.e. Thalidomide, Bortezomib and Lenalidomide, has further improved the prognosis concerning overall survival. At the begin of treatment host and tumor characteristics predict the prognosis. Age, Karnofsky-Index, kidney- and other organ function are major predictive host factors. Furthermore, tumor burden and disease biologiy are associated are of prognostic significance. Extramedullary disease, plasma cell leukaemia, classical cytogenetic, iFISH results (Del 17p, t(14;16), t(4;14), t(14;20), Ampl 1q) and high-risk signature on gene expression profiling (GEP) are established prognostic factors based on genetic investigations. The combination of the ISS-Staging-System with iFISH improves the prognostic prediction. In a metascore system different GEP-risks are included and added to the ISS-/iFISH score. This score is used in daily praxis at our myeloma center. Further factors during and after treatment were defined: depth of remission with the aim of a molecular remission, imaging-based remission analysis with PET/CT and MRI as well as duration of remission. To analyze the immunreconstitution as a result of treatment is under investigation. Results of array comparative genomic hybridisation and genome sequencing will give new insights in the pathogenesis of multiple myeloma and will generate new prognostic factors.

S9-6

Search for the Cure: Special Commentary

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In considering best initial therapies, the role of risk and predictive factors in the setting of ASCT have been discussed. The key question is "What practical steps are needed to achieve success in finding a cure?" The first key step is to have accurate and practical ways to document the presence or absence of minimal residual disease. Immunophenotypic cell sorting as well as molecular testing and imaging techniques are available, but need to be studied in a systematic fashion and correlated with outcomes. Stratification and/or randomization by risk group are essential. It is likely that some good-risk patients are already curable with currently available thera-

pies. It is already known that 15-20% of patients can have conventional CR for ≥ 5-10 years with induction plus ASCT ± maintenance. Identification of this subset is under way through an IMWG analysis of collective data sets. The best chance of true cure is to optimize treatment for this type of good-risk patient by modifying therapy based upon presence or absence of residual disease. There must be a focus on creative ways to identify and study minimal residual disease using sorting/collection and/or imaging plus biopsy techniques, for example. Based upon results of such studies, new therapies can be directed against residual poorer-risk subclones that must be eliminated to achieve cure. Of course, new agents targeting novel pathways will undoubtedly be needed to cure multiple types of myeloma. And finally, early intervention will likely be crucial in achieving cures.

S10

Janssen Pharmaceutical Companies-sponsored Symposium

Should High Risk Myeloma be Managed Differently? -Experience from Center of Excellence-

S10-1

Risk Stratification in Myeloma: Current Perspectives

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Over the last decade, several prognostic factors have been identified at the time of diagnosis for patients with multiple myeloma, such as stage according to the International Staging System (ISS), chromosomal and genetic abnormalities detected through conventional cytogenetics, fluorescence in situ hybridization (FISH) or gene expression profiling, the combination of ISS and FISH, or other biological parameters. The development of a risk-adapted strategy, based on these initial prognostic criteria, is undoubtedly one of the most important goals in the 2010's. Nevertheless, our therapeutic choices should also be adapted according to other criteria such as disease response to therapy, that has been unambiguously shown to be a major prognostic factor, and its evaluation, within the bone marrow but also outside the bone marrow by new imaging techniques. In the future, an important new concept will also guide our therapeutic strategies both at the time of diagnosis and at relapse. Several groups in the US and Europe have clearly demonstrated that there is substantial genetic heterogeneity not only between myeloma patients but also within individual cases. The intrinsic genetic instability of aggressive myeloma subclones in addition to the selective pressures introduced by therapies during the course of the disease are the two driving forces of the dynamics of clonal evolution and diversification observed in MM. These new findings will probably modify our treatment algorithms in the future.

S10-2

Managing Transplant Myeloma Patients: High Risk vs. Standard Risk

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Autologous stem cell transplantation (ASCT) is considered

the standard of care in multiple myeloma patients without significant comorbidities. The incorporation of the novel agents into the different phases of the transplant procedure, including induction, consolidation and maintenance, has improved outcomes substantially. Nevertheless, the presence of high-risk cytogenetic abnormalities continues to present a substantial challenge and one of the open questions surrounds the appropriate management of these patient subgroups. Recent analyses of phase 3 studies comparing ASCT(s) incorporating bortezomib versus autologous transplantation not including bortezomib have shown that the use of bortezomib during induction and consolidation/maintenance is associated with a progression-free survival benefit that is retained both across patients with and without high-risk cytogenetics. Bortezomib is active in patients with high-risk genetic features, but is not able to overcome the adverse prognosis completely, suggesting that different strategies are needed. An intensified treatment approach appears to be appropriate for such patients and the role of double ASCT requires further investigation in this respect. Currently, there are no data to support a risk-stratified treatment approach, but instead, data indicate that all patients should receive the optimal treatment available, which for young patients consists of novel agents administered before and after ASCT.

S10-3

Managing Elderly Myeloma Patients: High Risk vs. Standard Risk

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The population of elderly patientsis highly heterogeneous, encompassing fit elderly patients, as well as those who are frail elderly. Age is therefore an important parameter for risk stratification as the tolerability of treatment will differ substantially between the various subpopulations. A geriatric assessment is valuable to enable an adaptation of treatment goals and strategies according to biological age, taking into consideration comorbidities and overall function.

Novel agents, including thalidomide, bortezomib, lenalidomide and also bendamustine, now form an integral part of treatment strategies in the non-transplant setting in combination with alkylating agents and/or steroids. In addition, recent results suggest that maintenance therapy incorporating novel agents is a valuable strategy in this setting. Importantly, the inclusion of novel agents has resulted intangible improvements in survival outcomes in a population that typically presents many challenges.

Important learnings in the management of novel agents in the elderly population have been made. A dose-adapted strategy according to biological age, as well as close monitoring to initiate prompt dose or schedule modifications in case of adverse events will contribute to patients being able to undergo the planned duration of treatment.

Taken together, the treatment of elderly patients requires a careful balance of efficacy and tolerability to enable the delivery of therapy for an optimal duration. Importantly, advanced age should not preclude the application of effective novel therapies.

S10-4

Managing High Risk (Severe) Kidney and Bone Disease in Myeloma

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The analysis of host characteristics, tumor burden, biological tumor subgroups of multiple myeloma and response as well duration of response allow to define high-risk myeloma patients. For younger patients we apply high-dose therapy followed by autologous stem cell transplantation as back-bone of the treatment. The incorporation of new drugs like Thalidomide, Bortezomib and Lenalidomide are associated with an improvement of response, event-free - (EFS) and overall survival (OS). In the HOVON-65/GMMG-HD4-Study we were able to show a better outcome for patients with poor cytogenetic features and severe kidney damage. The translation of these study results in daily praxis in Germany is ongoing. For cytogenetic high-risk patients we investigate the impact of allogeneic stem cell transplantation in prospective trials. For older high-risk patients we use Thalidomide, Bortezomib or Lenalidomide based approaches and have included as many patients as possible in prospective trials to investigate new substance classes. Focus of research to improve and predict the outcome are new drug combination, the role of depth and duration of remission. Minimal residual disease analyzed by FACS-, PCR- and imaging techniques are under investigation to develop better prognostic scores.

S11
Smoldering MM/MGUS

S11-1
The Molecular Pathway to Myeloma

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The risk of progression from smoldering multiple myeloma (SMM) to multiple myeloma varies considerably among individual patients. Reliable markers for progression to multiple myeloma are vital to advance the understanding of myeloma precursor disease (SMM and monoclonal gammopathy of undetermined significance, MGUS) and for the development of intervention trials designed to delay/prevent multiple myeloma. Clinically available risk models are significantly ($p<0.0001$) discordant in overall risk-classification (28.6% concordance). Indeed, we need prospectively validated models to characterize individual patient's risk of transformation.

The past few years, our insights regarding biological changes present in multiple precursor disease have increased significantly. Molecular lesions detectable in abnormal plasma cells, alterations in subsets of cells in the bone marrow microenvironment, and evidence of minimal bone disease are hallmarks of early myeloma pathogenesis. Functional imaging and advanced molecular profiling techniques reveal evidence of complex, multistep processes underlying the transformation from precursor disease to symptomatic multiple myeloma.

Recently, a large whole-body MRI imaging study found ~30% of patients diagnosed with SMM have bone marrow abnormalities similar to those found in multiple myeloma patients. Furthermore, epidemiological and clinical studies have found MGUS and smoldering myeloma patients to have an increased risk of bone fractures.

RNA-seq is an effective platform to discover somatic mutations and chromosomal translocations as well as to provide digital gene expression. Using RNA-Seq, one may conjecture that somatic mutations could be acquired as SMM progresses to multiple myeloma, some of which may represent "driver" mutations that alter proliferation or survival of the malignant cells. Furthermore, it is possible that other genetic or epigenetic events will alter gene expression upon transformation, which can be discovered using digital gene expression.

This presentation will summarize our current knowledge regarding the molecular pathway to myeloma. It will shed light on insights based on functional imaging and molecular profiling, and discuss these aspects in the context of clinical outcomes in early myeloma.

S11-2
What are the Most Relevant Biomarkers to Identify High Risk Patients with Smoldering Myeloma (SMM)?

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Recent data indicate that most, if not all, myeloma patients evolve from pre-existing MGUS or SMM. Standard biomarkers allow prediction of development of active myeloma with CRAB criteria within 2 years for 50% of SMM patients. Key markers are: bone marrow plasma cells (BMPCs) ≥ 10%, type of Ig protein (G versus A), M-component level (≥ 3 g/dl), serum freelite chain (FLC) level and immune features of the bone marrow. There is an urgent need to improve prediction for high risk SMM to ≥ 90% and identify patients at the "pre-CRAB" stage of disease. Using higher cutoff levels for bone marrow plasma cells (≥ 60%) and serum freelite levels (FLC ≥ 100 gives 98% prediction at 52 months), better prediction is achieved. Using more refined immune cell sorting in the peripheral blood and bone marrow, it is hoped that the currently used "Spanish immunophenotyping methodology" can be further enhanced. In addition, PET/CT, whole-body MRI, and other sensitive imaging techniques are being investigated to better identify early bone and/or extramedullary disease. More sensitive assessment of renal function is also being conducted to detect any renal impairment at a pre-clinical stage. Molecular testing including standard FISH and cytogenetic assessment of bone marrow plasma cells can also provide more refined predictive capability. These current and future perspectives will be presented and discussed.

S11-3
Should we Treat Smoldering Multiple Myeloma?

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The standard of care of Smoldering Multiple Myeloma (SMM) patients is observation until progression to symptomatic disease occurs. However, SMM is a heterogeneous disease and although there are SMM patients at low or standard risk of progression who won't obtain any benefit from an early treatment, there is a high-risk subgroup of patients in whom the median time to progression to active disease is of approximately 2 years and these should really be the target for an early intervention. All attempts to early treat SMM patients, including alkylators agents, thalidomide, or bisphosphonates, failed to obtain a benefit but no discrimination according

to the risk of progression was done. Currently, several trials are ongoing in high risk SMM patients with different drugs (lenalidomide, siltuximab, elotuzumab, MLN9708) and we have already consolidated results from a trial conducted by the Spanish Myeloma Group in this selected patient population comparing lenalidomide-based therapy vs. observation. The early treatment with lenalidomide-dexamethasone followed by lenalidomide maintenance significantly delayed the time to progression to symptomatic disease, and resulted into a benefit in overall survival. In addition, the oral administration of this regimen was convenient for the patients with a good toxicity profile. In summary, at the present time, we are in the optimal way to change the paradigm of treatment of SMM patients.

S11-4

Smoldering MM in 2013: "To Treat or not to Treat"?

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Approximately 15% of patients with myeloma (MM) have an asymptomatic "smoldering" MM (SMM) and are recognized incidentally. Until recently, it was recommended that these patients should not be treated until unequivocal signs of progression appear. Regular monitoring including serum protein electrophoresis to measure the level of the tumor marker, the monoclonal immunoglobulin (MIg) characteristic of the disease, was sufficient. Since the introduction of the so-called novel anti-myeloma agents has dramatically improved our capabilities for reducing myeloma tumor mass, a new issue recently emerges: should we treat SMM?

The definition of SMM is important to consider. Indeed, in some patients, the underlying B cell clone has deleterious consequences that are not related to cellular proliferation but to other mechanisms, such as deposition of the secreted MIg or a fragment thereof. These patients have a SMM (and even sometimes a monoclonal gammopathy of undetermined significance (MGUS)), which generates a high risk of tissue damage. The kidney is the most often involved organ and this situation has recently being individualized as "Monoclonal gammopathy of renal significance (MGRS)", the spectrum of which include AL amyloidosis, monoclonal immunoglobulin deposition disease (MIDD) and several other renal diseases. To date, targeting the underlying clonal B cell proliferation, although it is not toxic *per se*, is the only available therapeutic option for MGRS.

The general prevailing opinion of most of the investigators is still to not treat SMM arguing that 1) No chemotherapy combination has been demonstrated yet to be curative even in a small number of patients with low burden MM 2) Although data suggest that some regimens may delay the disease progression, no chemotherapy strategy has yet been shown to improve overall survival. Alternatively, the goal for early therapy may be to pre-emptively avoid deleterious effects of progressive plasma cell proliferation, particularly bone complications and neurological compressions. From this point of view, early use of magnetic resonance imaging (MRI) or PET/CT is recommended to detect bone changes otherwise not seen on routine skeletal survey. If no abnormal signal is detected by one of these imaging methods, then patient truly has SMM and risk of vertebral fractures and spinal cord compression may be lower. In contrast, if hyperintense lesions are detected, then the disease may be considered as symptomatic and MM therapy might be proposed. A recent consensus recommends treating patients with 3 or more hyperintense lesions or one large macrofocal lesion on MRI.

Curability and improvement in OS are crucial issues since early therapeutic intervention may cause toxicity that can complicate further therapy at the time of progression. In addition and may be more importantly, early therapy can produce differential responses within the myeloma clone that can lead to the selection and expansion of resistant sub-clones. This risk is likely to vary within subtypes of MM: it may be particularly high in the multi-clonal, unstable and prone to clonal divergence forms of the disease but may also be of concern in genetically stable and linearly evolving diseases, at least when using some of the agents. Current therapeutic strategies for SMM are based on clinical correlates that were identified as risk factors for progression (serum monoclonal immunoglobulin levels > 1.5 mg%, non IgG paraprotein and abnormal serum free light chain ratio). Identification and validation of biologically relevant genomic markers predicting high-risk disease and the impact of different classes of drugs are needed to solve the issue of when to treat which form of SMM.

S12
Myeloma-Related Renal Impairment

S12-1
Nephrotoxicity of Monoclonal Light Chains

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Monoclonal gammopathy (MG) is increasingly linked to kidney disease. While multiple myeloma is sine qua non for myeloma cast nephropathy (MCN), not all MG related kidney diseases require a high tumor burden. Even a few dangerous B cell clones can produce progressive kidney disease as denoted by monoclonal gammopathy of renal significance (MGRS). Every component of the immunoglobulin (Ig) can cause kidney injury. Examples include MCN (Ig light chain), heavy chain deposition disease (Ig heavy chain) and proliferative glomerulonephritis (GN) with monoclonal Ig deposits (entire Ig). These components injure the kidney via a number of mechanisms. Precipitation and tubular obstruction is characteristic of MCN. Deposition of the monoclonal protein is another method. Fibrillar deposits suggest Ig amyloidosis or immunotactoid GN while amorphous deposits are found in monoclonal Ig deposition disease (MIDD) and membranoproliferative GN. Fanconi syndrome, crystal storage histiocytosis and cryocrystalglobulinemia have crystalline deposits. Intracapillary obstruction with cryoglobulins is seen with cryoglobulinemia. C3 nephropathy is unique in that the deposits are composed of C3 instead of a monoclonal protein which acts as a C3 nephritic factor. Treatment of these diseases must be tailored to the clone responsible. It is therefore crucial to establish the link between the kidney disease and the B cell/plasma cell proliferative disorder before treatment. Successful treatment results in preservation of kidney function and prevention of recurrence after transplantation.

S12-2
Markers of Renal Injury in Multiple Myeloma

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Serum creatinine (sCr) >2 mg/dl is defined by CRAB as a criterion for symptomatic multiple myeloma (MM). However, the measurement of sCr for the evaluation of renal impairment (RI) has several limitations, while the estimation of GFR by the MDRD equation has not great value in patients with acute RI. For this reason, markers of renal injury have been recently measured in MM, such as cystatin-C (Cys-C; a sensitive endogenous marker of GFR), neutrophil gelatinase-associated lipocalin (NGAL; a protein which is overproduced by proximal tubular cells in response to kidney injury) and kidney injury molecule-1 (KIM-1, which is overexpressed in dedifferentiated proximal tubule epithelial cells after ischemic or toxic injury). In a large series of MM patients (n=203), sCys-C was found to be a sensitive marker of RI, correlated with advanced ISS and had an independent prognostic value for survival. In a recent study of our group, we found that approximately all patients at diagnosis (93% of 48 patients) have elevated urinary NGAL (uNGAL), while only 19% have elevated sCr and 10% elevated uKIM-1, suggesting that tubular damage is present very early in the disease course. This suggestion is further supported by the finding that asymptomatic MM and MGUS patents had also elevated uNGAL, while uNGAL correlated with the involved serum free light chain. These observations suggest that uNGAL and sCys-C offer valuable information for the kidney function of MM patients and their measurement may help in the identification of patients with high risk for the development of acute renal failure.

S12-3
Diagnostic Procedures and Management of Myeloma-Related Renal Impairment

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Renal impairment is a common complication of multiple myeloma (MM). Serum creatinine, urea, sodium, potassium, eGFR by MDRD, electrophoresis and immunofixation of a sample from a 24h urine collection should be measured in all MM patients at diagnosis and at follow-up visits. If the patient has proteinuria that consists mainly of light chains, a renal biopsy may not be necessary. The presence of nonselective proteinuria or significant albuminuria supports the suspicion of amyloidosis or MIDD; thus, a biopsy of the subcutaneous fat or a rectal biopsy is needed for the confirmation of amyloidosis. If amyloidosis is not demonstrated, a kidney biopsy is needed to search for amyloid, monoclonal immunoglobulin deposition disease, or an unrelated glomerulopathy such as glomerulonephritis or diabetes nephropathy. Bortezomib plus dexamethasone is the recommended treatment for MM patients with renal impairment of any grade. Bortezomib should be started at the standard dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 3-week cycle, and dexamethasone at a dose of 20 mg on the day of and the day after bortezomib administration. In fit patients, the addition of a third agent such as thalidomide, cyclophospha-

mide or doxorubicin should be considered. For patients who are not eligible for bortezomib-based regimens, lenalidomide is a feasible and effective option for mild and moderate renal impairment. Finally, there may be a role for plasma exchange and high cut-off hemodialysis filters in myeloma patients who present with acute renal failure.

S12-4

Avoidance of renal impairment

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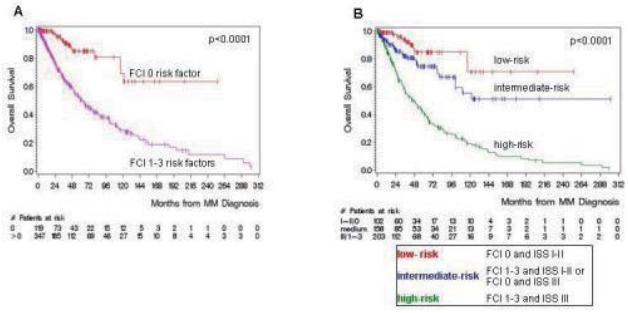
Renal impairment (RI) is a frequent complication in multiple myeloma (MM) and correlates with increased risk of treatment-related toxicity. The estimation of glomerular filtration rates is based on different equations, currently being pursued. Besides supportives, the management of RI requires immediate antimyeloma therapy to achieve early renal recovery (RR). In the era of novel agents, RR occurs more often. Bortezomib-based regimes induce favourable results in terms of RR, MM response and comparable survival in patients with and w/o RI. Compared with thalidomide, bortezomib induces more rapid responses. Albeit well tolerable and quickly acting combinations are important to reduce MM-burden, VMPT-VT vs. VMP in elderly patients had no advantage in terms of RR. Len/Dex can also be effective, but careful monitoring of renal function and appropriate dose adjustments are mandatory. Antimyeloma agents and high cut-off dialysis for extracorporeal FLC-removal can also be advantageous. Corticosteroids are particularly useful, initially at full doses. Bisphosphonates must be used cautiously and dose-adjusted. Older age and other comorbidities increase the risk with ASCT and are important to assess to define appropriate treatment and therapy tolerance. We have demonstrated the relevance of comorbidities and validated an easily assessable comorbidity score (FCI, Fig. 1). The management of MM with RI remains to be challenging and early diagnosis and highly effective treatment are crucial. The development of newer agents should address our need to further improve the outcome with RI.

Figure 1



S13

The Binding Site Group Ltd - Sponsored Symposium

Unstable Clones: MGUS to Myeloma Progression and Clonal Evolution

S13-1

Markers of Monoclonal and Polyclonal B Cells

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To date, work on free light-chains (FLCs) has focused almost entirely on their role for diagnosis and monitoring of patients with plasma cell dyscrasias, and these assays have been incorporated into a number of international clinical guidelines.

In addition to the assessment of monoclonal FLCs in plasma cell diseases, the potential utility of measuring serial polyclonal FLC concentrations as a biomarker of activation of the B-cell lineage has raised interest in several clinical settings. For example, recent studies have demonstrated that concentrations of polyclonal FLCs correlate with disease activity in patients with rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus.

Another possible context in which the measurement of chronic immune stimulation with polyclonal FLCs might be informative is the identification and stratification of future risk for malignancy. The relationship between chronic inflammation and cancer is well established, although not fully understood. Recently, in a cohort of patients with HIV, we found a polyclonal increase in FLCs to be predictive of the future risk of developing non-Hodgkin lymphoma. When serum κ and λ FLC concentrations were 2-fold higher than normal, the risk of non-Hodgkin lymphoma was increased by 4-fold and 8-fold, respectively. Similarly, based in a large prospective cancer screening trial, we found a polyclonal increase in the serum FLC concentration (both monoclonal and polyclonal elevations) was associated with an increased risk of chronic lymphocytic lymphoma (CLL). This association was present up to 9 years prior to the diagnosis of CLL but became stronger closer to the time of diagnosis.

Posttransplant lymphoproliferative disorder (PTLD) is a major complication of solid-organ transplantation. To expand on our observations from HIV patients to an analogous immunosuppressive state, we recently assessed the role of B-cell dysfunction in PTLD. We found strong FLC-PTLD associations. Among recipients with Epstein-Barr virus (EBV) DNA measured in blood, EBV DNAemia was associated with FLC

abnormalities (ORs 6.2 and 3.2 for monoclonal and polyclonal elevations). Thus, similar to HIV patients, FLC elevations are common in transplant recipients. Elevated FLCs are associated with heightened PTLD risk. FLCs likely reflect B-cell dysfunction, perhaps related to EBV-driven lymphoproliferation

This presentation will summarize our current knowledge regarding markers of monoclonal and polyclonal B cells. It will shed light on insights based on accomplished research studies and discuss clinical applications and future directions.

S13-2

Clonal Evolution

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Monoclonal gammopathies represent a spectrum of disorders ranging form asymptomatic monoclonal gammopathy of undetermined significance (MGUS) to relapsed refractory myeloma and plasma cell leukemia. The evolution from MGUS to myeloma is driven by a variety of alterations in the tumor cell as well as in the tumor microenvironment. It still remains a matter of debate as to which alterations are primary drivers of disease progression and which are accompanying secondary changes. Based on genetic studies of the monoclonal plasma cell using a variety of techniques ranging from conventional cytogenetic studies, FISH, gene expression profiling and most recently, whole genome sequencing, it is clear that significant genetic heterogeneity exists in myeloma. Some of the earliest abnormalities include translocations involving the immunoglobulin heavy chain locus on chromosome 14, trisomies of several odd numbered chromosomes, and monosomies or deletions involving different chromosomes. Many of these changes can be observed in MGUS while those involving chromosome 1 and loss of chromosome 17p become more common as disease evolves. While limited studies of whole genome sequencing have been performed in MGUS, studies of serial samples of patients with myeloma point towards a continuous process of clonal selection and clonal evolution. The continued efforts to characterize the genetic evolution will allow us both to develop treatment strategies at preventing the progression form MGUS to MM as well as prevention of relapsed refractory disease after being initiated on specific therapies.

S14

Celgene Corporation-sponsored Symposium

Current and Future Treatment Paradigms in Multiple Myeloma

S14-1

Cereblon is a Target of Thalidomide, Lenalidomide and Pomalidomide, Predicts Clinical Outcomes and is Mutated in Some Drug Resistant Multiple Myeloma Patients

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Immunomodulator drugs (IMiDs) are key components of myeloma (MM) therapy. Recently, we demonstrated that Cereblon (CRBN) is the major mediator of IMiD action in MM, operating in part via interferon regulatory factor 4 (IRF4). Both IRF4 and MYC are down regulated by lenalidomide (Len) treatment or CRBN knockdown. Conversely, over expression of IRF4 can rescue MM cells from Len exposure or CRBN deletion. Introduced mutations in the CRBN - thalidomide or DDB1 binding domains result in loss of Len-induced cytotoxicity.

CRBN mutations are uncommon in newly diagnosed patients although CRBN expression levels drop in relapsed MM. However, sequencing of a highly drug resistant MM revealed a Q99* truncating mutation as well as a R283K point mutation in CRBN. Additional sequencing in an expanded cohort of 25 patients with low CRBN levels revealed a synonymous mutation in only one sample.

We analyzed CRBN gene expression in 53 relapsed/refractory patients treated homogeneously with pomalidomide 2-4mg daily and weekly dexamethasone 40mg. The percent of patients that demonstrated at least a partial response was 0% for CRBN low expressors, 19% for intermediate expression, and 33% for higher CRBN expression. Significant differences in PFS (3.0 months vs. 8.9 months, $p = 0.0006$) and in OS (9.1 months vs. 27.2 months, $p = 0.01$) were observed when the lowest quartile of CRBN expression was compared to the top three quartiles. An important caveat with respect to PFS and OS is that CRBN mRNA level is primarily a reflection of the number of copies of CRBN on chromosome 3p and thus low risk hyperdiploid disease will have high levels of the protein.

In summary, CRBN is the major target of the IMiDs (now better named cereblon inhibitors) is mutated in some drug resistant patients, expression of CRBN predicts response to IMiD based therapy and survival outcomes. Inhibition of

CRBN and its associated complex results in alterations in the IRF4 pathway and blocks E3ligase function..

S14-2

Exploring the Biology of Multiple Myeloma to Determine Continuous Treatment Strategies

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Progression of multiple myeloma through distinct clinical phases from monoclonal gammopathy of unknown significance (MGUS) to symptomatic disease is driven by multiple mutations that deregulate normal plasma cell function and generate the features of myeloma.[1,2] Primary genetic events, such as chromosomal translocations and hyperdiploidy, are myeloma-initiating steps that lead to the immortalization of myeloma-propagating cells. Subsequent genetic events can affect various pathways and occur in a non-linear fashion, increasing clonal heterogeneity. There is, therefore, no single underlying genetic event responsible for disease development that could be targeted therapeutically.[2] Treatment itself can select for clones with a more aggressive phenotype, and the clinical course of the disease is currently characterized by increasingly shorter periods of remission followed by relapse.[3-6] A better understanding of the timing and impact of different genetic events may lead not only to new therapies but also to improved use of existing therapies through enhanced treatment schedules, rationally designed combination regimens, and optimal sequencing of therapy. Continuous therapy strategies have been evaluated that may improve the depth and duration of response to treatment thereby improving outcomes for patients. Early treatment of high-risk patients with MGUS or smouldering multiple myeloma is also being explored, and may help prevent or delay progression to symptomatic disease.

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S14-3

Treatment of Elderly Patients – Selecting the Right Therapy and Schedule for Each Patient

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Recent improvements in treatment outcomes in multiple myeloma have been confined mainly to younger patients, [1,2] underscoring the need for new and effective treatment options for elderly, non-transplant eligible patients.

Treatment of elderly patients with MM is a complex system in which not only the myeloma has to be considered. Decisions should be tailored to the individual patient and many factors, such as comorbidities and performance status, are important. The choice of therapy, the optimal dose, and the treatment schedule are strongly impacted by these factors, as the degree of frailty and comorbidity can vary considerably within this group. When selecting an appropriate treatment, consideration should be given to the treatment' s adverse event profile and the patient' s relevant comorbidities (e.g. renal impairment, neuropathy). In many cases, dose adjustments may be necessary for elderly patients to allow treatment to continue at therapeutically effective levels.[3]

For elderly patients with newly diagnosed disease, the addition of novel agents such as thalidomide[4] or bortezomib[5] to MP have improved treatment options in recent years. In addition combinations with lenalidomide have been evaluated.[6,7]

Upon relapse, the complex decision-making process continues and is further complicated by the type of prior treatment and the way it was tolerated.[8,9]

Several clinical trials are underway that may help further refine the current approach to the management of elderly patients with MM at every stage of their disease.

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S14-4

Extending treatment options for patients with advanced MM and optimizing the management of relapsed and refractory disease

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Patients with multiple myeloma (MM) refractory to lenalidomide and bortezomib have few effective treatment options available, and prognosis for these patients is poor.[1]Pomalidomide, a next-generation immunomodulatory compound (IMiD®), has shown encouraging activity in this setting, with favorable tolerability.[2-5]Recent data from a phase III trial indicated that, compared with Dex alone, pomalidomide plus low-dose dexamethasone (POM+LoDEX) improves survival outcomes (HR for PFS 0.45; p < 0.001; HR for OS 0.53; p < 0.001) in patients with advanced MM.[5] Furthermore, data from sub-analyses of a phase II trial (221 patients) showed that renal impairment did not influence the safety profile of POM+LoDEX and indicated that patients were able to obtain benefit from POM+LoDEX regardless of high-risk cytogenetics.[6,7] The potent second generation proteasome inhibitor carfilzomib (CFZ) was recently FDA approved for patients who have received at least two prior therapies, including bortezomib and anIMiD. A phase II trial of single agent CFZ demonstrated a 24% ORR and 16 months OS in advanced MM patients, and manageable toxicity.[8] Other novel agent combination approaches (including monoclonal antibodies and various small molecule inhibitors), as well as the proteasome inhibitors ixazomib (MLN9708) and marizomib (NPI0052), also show considerable promise in this area of exquisite unmet medical need.[9-12]

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S14-5

Future Treatment Combinations for Multiple Myeloma

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Doublet and triplet combinations are frequently used in the treatment of multiple myeloma, and immunomodulatory drugs (IMiDs®) and proteasome inhibitors have become established components of these regimens. In patients with relapsed and/or refractory multiple myeloma (RRMM), the combination of lenalidomide and dexamethasone (RD) was shown to improve time to progression and overall survival compared with dexamethasone alone in two randomized trials.[1] This regimen showed a well characterized safety profile, and data on long-term RD treatment suggest that continuous therapy strategies are feasible.[2–4] The RD regimen is, therefore, an attractive "backbone" to which other therapies may be added in attempts to further improve efficacy. Preliminary studies have evaluated RD in combination with conventional chemotherapeutic agents with known activity in RRMM, such as cyclophosphamide[5] and bendamustine,[6] as well as newer agents such as bortezomib,[7] carfilzomib,[8] and the histone deacetylase inhibitor vorinostat.[9] In a recent phase II trial, the combination of RD and the anti-CS1 monoclonal antibody elotuzumab elicited an impressive response rate of >90% and a median progression-free survival of 26.9 months.[10] The next-generation IMiD®, pomalidomide, has also been evaluated in combination with low-dose dexamethasone plus carfilzomib[11] or clarithromycin[12] and has shown promising results. Ongoing studies continue to evaluate novel treatment strategies using immunomodulatory drugs as the backbone of treatment for RRMM.

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S15
Consolidation / Maintenance

S15-1
What is the Role of Post-Transplant Consolidation Therapy?

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When discussing treatment strategies in multiple myeloma (MM), the terms consolidation and maintenance are often used synonymously, although they identify two treatment phases with different goals. Consolidation therapy is, by definition, short-term and intended to further enhance the frequency and quality of response obtained with the previous treatment phase(s). Traditionally, the most important consolidation therapy for transplant-eligible MM patients has been considered to be autologous stem-cell transplantation (ASCT), based upon the demonstrated ability of high-dose melphalan to overcome resistance to conventional chemotherapy. Over the last years, the choice of induction treatment before ASCT has moved from conventional chemotherapy to newer regimens incorporating the immunomodulatory derivatives (IMiDs) thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. Up-front use of novel-agent-based induction treatments has affected unprecedented rates of complete response (CR) that rival those previously seen with conventional chemotherapy and subsequent ASCT. Recent studies have demonstrated that ASCT is complementary with novel agents and further enhances the degree of tumor reduction. High activity shown by IMiDs and bortezomib before ASCT has subsequently led to their investigational use as part of consolidation therapy after ASCT. In these phase 2 and 3 studies, the novel agents have been given either alone or combined with one another for a (relatively) short time period, in the range between 2 and 5 months. Results from these reports have consistently shown the ability of novel-agent-based consolidation therapy to increase the rate of CR, even to the molecular or immunophenotypic level, in comparison with that seen after single or double ASCT. In several studies, enhanced rates of high-quality responses resulted in prolonged PFS and OS from start of consolidation therapy, suggesting that this latter treatment phase contributed to improved clinical outcomes observed with the entire treatment program. These data collectively support the benefits of post-ASCT consolidation therapy for MM. Randomized clinical trials designed to compare consolidation versus no consolidation therapy are currently ongoing and will definitely assess the role of consolidation therapy for MM.

S15-2
Is Maintenance Therapy Necessary for Every Patient?

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Maintenance therapy has been investigated extensively in multiple myeloma. Several agents including prednisone, interferon, and thalidomide were investigated in the past. However, until recently, data were often contradictory, and the benefits did not appear to outweigh the risks and costs associated with maintenance. More recently, we have made considerable progress. Three randomized trials found lenalidomide maintenance to prolong progression free survival in myeloma; one of them has also found a survival benefit. Therapy was tolerated well. Two other randomized trials using bortezomib maintenance have also reported improvements in progression free survival and overall survival, although in both of these trials, it is difficult to separate the value of maintenance from the variations in induction therapy between the two arms being tested. Questions remain. Should all patients receive maintenance therapy? If so, should it be bortezomib or lenalidomide? What is the required duration of maintenance for maximal clinical benefit? These questions will be discussed. Optimal selection of maintenance based on underlying risk categories also requires discussion and additional data. Maintenance therapy does carry some risks, such as second cancers with lenalidomide therapy. The cost and availability of maintenance are additional considerations to be discussed.

S15-4
What is the optimal duration of maintenance therapy?

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Thalidomide (THAL) when compared to prednisolone (PRED) maintenance or observation post-ASCT prolongs progression free (PFS) and overall survival (OS). Similarly, lenalidomide (LEN) when compared to observation significantly improves PFS with an emergent OS advantage. What remains unresolved is the optimal duration of post-ASCT therapy with IMIDS, taking into consideration toxicity, SPM and cost versus survival advantage obtained. Re-analysis of the ALLG MM6 trial of THAL-PRED consolidation (THAL Arm - TA) versus PRED (Control Arm - CA) now with a median follow-up of 5.4 years shows estimated 5 year OS rates of 66% and 47% (p=0.007; HR 0.12; 95% CI 0.028 to 0.558) in TA and CA, respectively. The TA cohort showed ongoing

disease response for up to 8 months on therapy, furthermore, the 80% of TA patients remaining on consolidation for at least 8 of the planned 12 months demonstrated improved OS when compared to either CA (p<0.001) or <8 months of THAL (p<0.032). Interim analysis of 30 patients receiving LEN and alternate day PRED post-ASCT with MRD monitoring (LEOPARD Trial) demonstrated a similar consolidative effect with 16 patients achieving maximal response after a median of 109 days on therapy (range, 28 – 287 days). In conclusion, these data would support a minimum of 8 to 12 months of post-ASCT IMID therapy with 12 months maximum being a realistic target for THAL, based predominantly on tolerability. The optimal maximum duration of LEN maintenance remains uncertain with emergent issues related to both cost-effectiveness and SPM associated with prolonged usage.

S15-5

Analysis of OVERALL Survival (OS) in the Context of Cross-Over from Placebo to Lenalidomide and the Incidence of Second Primary Malignancies (SPM) in the Phase III Study of Lenalidomide Versus Placebo Maintenance Therapy Following Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM) CALGB (ALLIANCE) ECOG BMT-CTN 100104

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CALGB 100104 demonstrated improved time to progression (TTP) and OS for MM patients treated with lenalidomide when compared to placebo maintenance starting at day 100 after ASCT (McCarthy et al, NEJM,2012,366:1770). The study was un-blinded at 18 months median follow-up and cross-over to lenalidomide occurred in 86/120 placebo patients without disease progression.

As the primary endpoint (TTP) was met, all subsequent analyses are conducted approximately yearly and this is a preliminary, updated OS, cross-over and SPM analysis at 48 months median follow-up.

As of Jan 2013, [29/231 (12.6%)] lenalidomide patients and [15/229 placebo patients (6.6%)] have developed SPMs. Updated OS demonstrates that deaths are less for lenalidomide [47/231 (20%)] versus placebo [69/229 (30%)] (P=0.008 HR: 0.61). After randomization, median cross-over time from placebo to lenalidomide was 11 months (range 3-50). Including placebo patients crossing-over within 6 months of randomization in the lenalidomide arm, deaths are lower for lenalidomide [48/250 (19%)] versus placebo [68/210 (32%)] (P=0.007, HR: 0.57). Including placebo patients crossing-over from placebo to lenalidomide within 12 months of randomization in the lenalidomide arm, deaths are lower for lenalidomide [53/277 (19%)] versus placebo [63/183 (34%)] (P=0.003, HR: 0.57). The cumulative incidence risk (CIR) of developing a SPM is higher for the lenalidomide arm when compared to placebo (P=0.03) and the CIR of progression (P=0.001) or death (P=0.002) is higher for placebo.

There is an increased incidence of SPM for lenalidomide compared to placebo. However, despite cross-over of 71% of placebo patients, lenalidomide maintenance continues to demonstrate an improved OS.

S16
Myeloma in Asia

S16-1
Report from Asian Myeloma Network (AMN)

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The incidence of MM shows ethnic difference evidenced by US SEER and IARC data. Asians show lower incidence compared to Caucasian. However, there are growing evidences that MM is increasing in Asia. We collected 3,405 patient data from 22 centers of 7countries to build an Asian myeloma data base. Retrospective analyses were done to elucidate the presence of clinical and cytogenetic characteristics of MM in Asia. Median age was 62 years, 56% were male, bone lesion, severe anemia, thrombocytopenia, extramedullary plasmacytoma, hypercalcemia, hypoalbuminemia, renal dysfunction, increased LDH was observed in 80/39/8/16/19/52/23/28% respectively. IgG/A/LC was 55/22/17%. ISS was 20/36/44%. Abnormal cytogenetics were observed in 33%, hypodiploid 15%, 13q deletion 12%, FISH analysis shows t (4; 14), t (11; 14), t (14; 16), del 17p, 11/17/4/13% respectively. OS was 47 months. Age, Hemoglobin, platelet, plasmacytoma, BMPC, calcium, albumin, creatinine, beta-2 MG, LDH, ISS, abnormal cytogenetics, 13q- by conventional cytogenetics, t(4;14) by FISH, ASCT, response to treatment, achievement of VGPR were prognostic variables for OS. Among them, azotemia, ISS, heavy chain, plasmacytoma, abnormal cytogenetics, ASCT, response to treatment remain as prognostic variables by multivariate analysis. In conclusion, there are no unique clinical or cytogenetic characteristics identifies in Asian population. However, some unique findings, such as high incidence of del 17p in China, need to be explored in future study.

S16-2
Toxic profiles of novel agents in Japanese patients

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The introduction of novel molecular targeted anti-myeloma agents, such as thalidomide (Thal), lenalidomide (Len) and bortezomib (Bort) has a great impact on the improvement of survival of patients with multiple myeloma. Since these novel drugs may have different and specific toxicity profiles in different races and countries, and should be analyzed in large patients cohort, the results of post-marketing surveillance on relapsed /refractory myeloma patients treated with these agents in Japan were summarized. The number of cases analyzed were Thal=1,548, Len=2,310, Bort=1,048, respectively.

The most common AEs associated with Thal are peripheral neuropathy(PN) (14.6%, grade3/4:0.5%), constipation (11.4%, G3/4:0.3%), leukocyotopenia (9.4%, G3/4:0.5%). Venous thromboembolism (VTE) was less common (1.1%) compared with previous reports from several western countries. The primary AEs associated with Len are myelosuppression, neutropenia:30.9%,G3/4:15.1%), thrombocytopenia: 32.6%,G3/4:9.5%), but again, less VTE (0.3%). The most relevant AEs reported in patients treated with Bort were PN (9.1%, G3/4:2.1%), thrombocytopenia (37.5%,G3/4:15.2%), and neutropenia (14.5%,G3/4:7.3%). The incidence of acute lung disorder/interstitial pneumonia was 3.1%. Overall, the toxic profiles of 3 drugs in Japan appeared to be similar with that reported in western countries except lower incidence of VTE in iMIDs, but the frequency of AEs is variable in the different clinical situations, depending on the administration of these drugs as single-agent or in combination with other agents. Finally, the management of these adverse events with a view to delivering optimal therapeutic effect in patients with newly diagnosed and relapsed and/or refractory multiple myeloma in Japan will be reviewed.

S16-3
MGUS Prevalence among Nagasaki Atomic Bomb Survivors

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Exposure to ionizing radiation is a known environmental risk factor for a variety of malignancies, including leukemia, myelodysplatic syndromes, and multiple myeloma. Therefore, for Hiroshima and Nagasaki atomic bomb survivors (surviving victims who were exposed to ionizing radiation emitted from the nuclear weapons), several cancer screening tests have been provided annually to detect the early stage of malignancies based on government support. An M-protein screening test is one of such cancer screenings to detect the early stage of multiple myeloma. For Nagasaki atomic bomb survivors, the screening test have been provided since 1988. In the screening process, a number of patients with MGUS, instead of multiple myeloma, have been identified. In 2009, we for the first time reported the age- and sex-specific prevalence of MGUS between 1988 and 2004 and the possible role of radiation exposure on the development of MGUS using the screening data of 1,082 patients of MGUS among approximately

52,000 Nagasaki atomic bomb survivors (Iwanaga et al, 2009, Blood). The findings include the following: (1) the overall prevalence was 2.1%, which was significantly lower than that of whites or blacks, (2) the prevalence was significantly higher in men than women (2.8% vs. 1.6%), (3) there was an age-related increase in the prevalence, and (4) the prevalence was significantly higher in people exposed to higher radiation doses only among those exposed at age 20 years or younger. The updated data on the survival and cause of death in patients with MGUS will be present as well.

S16-4

Showcase Japan-Histories and Trials

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Advances in the treatment of multiple myeloma (MM) in Japan are being accomplished through the joint efforts of the Japan Myeloma Society and Myeloma Patients Society. The Japan Myeloma Society was inaugurated in 1980 as the Myeloma Therapy Study Group with Dr. Yukio Imamura as the chairman. The Japanese Myeloma Patients' Society (JMPS), which became the Japanese branch of the International Myeloma Foundation (IMF), whose slogan is "Until there is a cure, there is the IMF", was inaugurated in 1997 with the slogan "Information can save your life" and has been working closely ever since with the Japanese myeloma study group.

In 2004, Dr. Nagura and Dr. Takagi of the study group became the lead authors of the first edition of the "Treatment Guidelines for Multiple Myeloma in Japan". The third version of the guidelines was published in 2012. These guidelines have been making an important contribution towards myeloma therapy in Japan.

In 2009, Dr. Kazuyuki Shimizu, who will also the chairperson of the IMW2013, was appointed as the Director, while in 2011 the 36th annual general meeting was held and attended by approximately 400 active members under the theme of the globalization of MM research in Japan. In 2011, the Asian Myeloma Network (AMN) was formed by 8 member countries and began functioning as an academic society.

However, in some respects, clinical research on MM in Japan is still in its infancy, and results for early phase treatments using new drugs are especially scarce. In the future it is important to conduct research within a larger framework in order to contribute our findings to the world, and through this myeloma therapy in Japan will surely develop and progress.

S16-5

Current Status of Multiple Myeloma in Taiwan: Paradigm Shift in the Front-Line Treatment

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Recently, the improvement on the survival of multiple myeloma (MM) has been reported in some western countries. In Taiwan, we also reviewed our epidemiology of MM update to year 2009. From the National Taiwan Cancer Registry, the age-adjusted incidence of MM increased from 0.2 per 10000 persons in 1979 to 1.6 per 10000 persons in 2009. Intriguingly, the age-adjusted mortality decreased from the peak at year 2007 (1.18 per 10000 persons), down to 0.95 per 10000 persons at year 2009. One explanation for the improved survival of MM here is the introduction of novel agents into MM treatment, like thalidomide (THA), bortezomib (BTZ) and lenalidomide (LEN). Except for LEN, the THA and BTZ have been reimbursed as the front-line treatment in transplant-eligible and transplant-ineligible MM patients. We retrospectively reviewed 400 newly diagnosed MM patients in our hospital since 2004 and we found that there was a treatment paradigm shift that the induction regimen for transplant-eligible MM patients becomes nearly all BTZ+THA+Dexa (VTD) regimen. This regimen was able to induce 95% response rate (RR), terms of PR or better, including 24% CR, which was significantly higher than the previous induction regimens ever used, like VAD (RR, 65%), VAD+THA (RR, 75%), and TD (RR, 71%); p=0.006. For transplant-ineligible MM patients, MPT or MPV are both now recommended as the front-line regimen. We also retrospectively analyze our MM patients who had received MPT (n=66) and MPV (n=23) as their front-line treatment and the comparison between these two regimens will be done and presented.

S16-6

Current State of Myeloma Treatment and Research in Singapore

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Singapore is a small City State in Asia with a population of about 4.5 million. We have a complex healthcare system with both private and public components. We have access to all FDA approved drugs, so compared to many other countries, we have the advantage of havingaccess to novel agents such as Bortezomib, Lenalidomide, and Thalidomide early on.As a

result, we have seen a significant improvement in the survival of our patients treated in the last 5 years.The drawback is that the patients have to pay for these treatments, which can be very expensive. We have a well-established clinical trial set-up and are also part of the Mayo P2C consortium. Over the last few years, myeloma patients in Singapore have managed to get access to novel drugs such as panobinostat, CDK inibitors, Carfilzomib, Denusomab, through clinical trials. The main public hospital treating myeloma patients have developed a strong collaboration through the Singapore Myeloma Study Group. Our focus is on developing patient registry, a myeloma cell bank, and clinical trials. Building on this platform, we have managed to contribute data for several international studies from the International Myeloma Working Group as well as the Asian Myeloma Network. Our research focuses on a few areas. One is through the use of genomics, to identify new therapeutic target via a biological understanding of the disease with a particular focus on high-risk myeloma with t(4;14) or 17p13 deletion. Another is using a variety of platform to identify targets for immunotherapy either through antibody-based therapies or cellular therapy using NK cells expressing chimeric antigen receptors. Another area is the development of new imaging techniques such as PET-MRI for myeloma.

S16-7

Aberrant DNA Methylation of Tumor Suppressive MicroRNAs in Myeloma

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DNA methylation refers to the catalytic addition of a methyl group to carbon 5 position of a cytosine ring in a CpG dinucleotide. Methylation of promoter-associated CpG islands leads to gene silencing. During cancer development, apart from global DNA hypomethylation, locus-specific hypermethylation and hence silencing of multiple tumor suppressor genes is frequently observed. MicroRNA (miRNA) is a novel class of short non-coding RNA molecules regulating a wide range of cellular functions through translational repression of their target genes. Methylation of promoter-associated CpG islands leads to repressed gene expressions and hence phenotypic alterations. Recently, promoter DNA methylation of tumor suppressor miRNA genes has been implicated in cancers including multiple myeloma (MM). Herein, we summarize the role of DNA methylation of tumor suppressive miRNAs in MM . First, miRNA methylation occurs in a tumor-specific manner, resulting in miRNA silencing. Secondly, tumor suppressive miRNAs were inactivated by promoter hypermethylation. Thirdly, miRNAs repress gene translation by binding to the 3' untranslated region of the target gene. Moreover, based on a candidate gene approach, methylation of miR-203 and -224 has been shown to be an early event in myelomagenesis starting at MGUS. Besides, mir-129-2 methylation is associated with progression from MGUS to symptomatic myeloma, miR-34b/c methylation is acquired at myeloma relapse/progression, and miR-124-1 methylation is acquired in-vitro during cell passaging, and hence unimportant in myelomagenesis.

S16-8

Clinical Trials for Myeloma in Japan; Japan Myeloma Network (JMN)

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In Japan, academic society for hematology/oncology was established over 70 years. Japan Society of Hematology was established in 1938, Japan Myeloma Society in 1980. For practical medicine, Japan established medical insurance system covered the all Japanese in 1961. Medical expenditure of Japan is over 320 billion USD per year now. On the other hand, approval of new drug has tendency to be delayed, caused by complex of factors, but one of major barriers should be the revised pharmaceutical affairs law. Japanese hematologists/oncologists has made their effort to research the mechanism of disease and have tendency to setting aside from clinical trials. But, mega-pharma and drug providers push the new and effective drug into practical medicine, Japanese hematologists/oncologists has made effort to establish their fundamentals for clinical trials by themiselves. Japanese hematologists/oncologists have established JALSG (Japan Adult Leukemia Study Group) for leukemia, JCOG (Japan Clinical Oncology Group) for lymphoma, and we have established JMN (Japan Myeloma Network) for myeloma. JMN is planning and conducting eight clinical trials and one of them, J-MEN 03 STUDY, is collaborated with Asian Myeloma Network (IMF/AMN). JMN is supported by fund/data management organization, ECRIN, legislative non-profit organization in the context of Japanese law and it leads us for time-cost saving. I would like to introduce several clinical study conducted by JMN and consider to strengthen the fundamentals of clinical trials (domestic and international) for myeloma in Japan.

S16-9

Multiple Myeloma in Korea: Past, Present, and Future. Experience of the Korean Multiple Myeloma Working Party

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The incidence of multiple myeloma in Korea is increasing steadily (figure). The most updated incidence rate of multiple myeloma in Korea is 1.5/100,000, and ranked as the third most common among the hematologic malignancies. This unprecedented increase is mainly due to environmental pollution and the aging. The Korean Multiple Myeloma Working Party (KMMWP) was launched under the auspices of the Korean Society of Hematology (KSH) in 2005. Main members are both diagnostic and clinical hematologists. KMMWP immediately began a multiinstitutional studies, including translational research projects such as cytogenetic study performed in the central laboratory. Next, we constructed the Korean Myeloma Registry (KMR), a web-based patient registry system. Currently, more than 4,000 patients diagnosed after Jan., 2,000 are registered from more than 41 institutes. This serves as an excellent platform to conduct high-quality multicenter studies. Based on these efforts, we presented dozens of abstracts at international meetings. Now, we are participating actively in several important global projects. In addition, we have a number of ongoing prospective and retrospective studies of our own. We also support patient seminars with collaboration with International Myeloma Foundation (IMF) since our first seminar in 2006. Also KMMWP is seeking for regional and international collaborations such as Japan and IFM. By this joined efforts, research activities on multiple myeloma in Asian regions will escalate to higher levels and eventually, treatment outcome will be improved considerably.

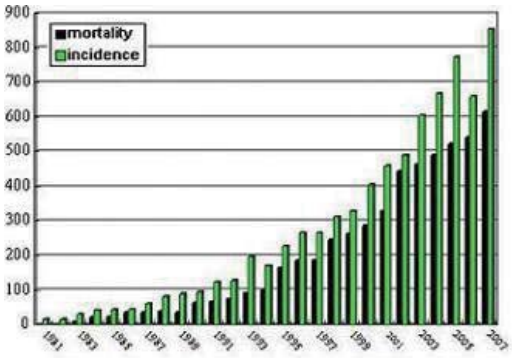

Fig. Changes of incidence and mortality of multiple myeloma over 30 years in Korea

S16-10

Clinical Trials for Multiple Myeloma in China: A Preliminary Review

J. HOU

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Multiple myeloma (MM) is still an incurable disease. China is becoming the new frontier in search for cure. As one of major myeloma centers in China, we perform many global and domestic clinical trials for MM. Some of them are summarized below. In a multicenter, open-label phase II study (MM021), we proved that lenalidomide plus low-dose dexamethasone (Rd) is efficient and safe in Chinese subjects with relapsed/ refractory MM. Among the enrolled 199 patients, the overall response rate (ORR) is 46%, overall disease control rate (including SD,PR/VGPR,CR) is 94.7%. Another multicenter, open-label phase IV study tested the efficacy of PAD vs. TAD in the newly diagnosed MM. Preliminary results demonstrated that the ORR is similar in two groups, but the CR rate in PAD group is much higher (35.9% vs. 0%). Recombinant Circularly Permuted TRAIL (CPT) is a recombinant mutant of human Apo2L/TRAIL developed by Sunbio Biotech Co. Ltd. CPT was well tolerated up to 15mg/kg.d with promising efficacy in patients with R & R MM in phase I study. In phase II study, the ORR of CPT alone has reached 33.3%. The drug related adverse events (>10%) included fever, AST/ALT elevation, leucopenia, neutropenia, rash, thrombocytopenia, and LDH elevation. In conclusion, a wide range of clinical trials in our center not only offer an opportunity for R & R patients, but also help to obtain progresses in the treatment of MM.

S17
Plasma Cell Biology 2

S17-1
Molecular Pathogenesis of Multiple Myeloma

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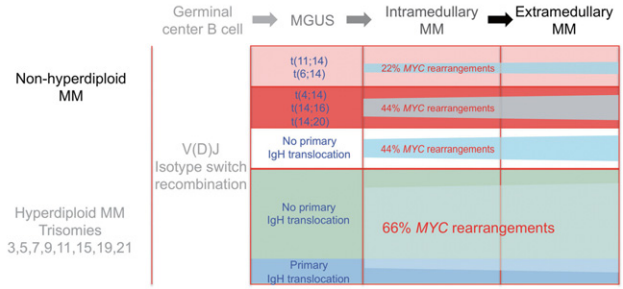
Chromosome content identifies two pathogenic pathways, each occurring in about half of patients with MGUS and multiple myeloma (MM). Hyperdiploid MM (HRD) has 48-75 chromosomes with multiple trisomies selectively involving chromosomes 3, 5, 7, 9, 11, 15, 19 and 21; only 10% of these HRD tumors have primary IgH translocations and no frequent focal genetic mutations have been identified. In contrast primary IgH translocations are identified in over 70% of non-hyperdiploid MM (NHRD). Rearrangements of MYC have been detected by FISH in only 16% of untreated MM, but over 90% of MM cell lines, identifying a late role for MYC in the progression of MM. The introduction of a MYC transgene into a mouse strain predisposed to MGUS results in mice that uniformly develop MM, suggesting a distinct early role of MYC in the progression of MGUS to MM. We have found that rearrangements in a 4Mb region surrounding MYC are present in 70% of HRD, representing the most frequent focal genetic mutation in this genetic subtype of MM. While only one third involve an immunglobulin locus, they are associated with cis-dysregulated expression of MYC, and may be one mechanism responsible for the progression of MGUS to MM. Tumors lacking MYC rearrangements biallelically over-express MYC by a trans mechanism including potentially inactivating mutations of BLIMP1/PRDM1, or activating mutations of IRF4. We propose two largely non-overlapping pathogenic pathways in MM: HRD associated with frequent MYC rearrangements, and NHRD associated with frequent primary IgH translocations.



S17-2
Cytokines

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Normal bone marrow plasma cells (BMPC) live up to decades, but immediately apoptose when aspirated and thus deprived from their interaction with the bone marrow microenvironment (BMME). This thus provides crucial survival signals.Likewise, myeloma cells from most untreated patients cannot be grown for days ex vivo, despite ubiquitous presence of genetic alterations impacting on signaling chains or one of their ultimatetargets, D-type cyclins. Cytokine signaling is thus crucial for the maintenance of normal as well as malignant plasma cells.

Almost all of these factors (but for Inteleukin-6) are heparin binding; in perfect agreement with expression of syndecan-1 (CD138) beingthe hallmark of normal and malignant plasma cells. Thisheparan-sulfate proteoglycan has no signal transduction capability, but acts as "sponge" locally concentratingheparin-binding growth (GF) and survival factors (SF) for receptors in its vicinity. These factors are either i) aberrantly produced by myeloma cells (e.g. HGF, IL-6) orii) their expression is "inherited" from normal BMPC (e.g. VEGFA). Indeed, BMPC share abilities of myeloma cells, likeexpression of pro-angiogeneic (e.g. VEGFA) or bone remodeling modifying factors (e.g. BMP6). iii) Factors are produced by normal or myelomatous BMME (e.g. IL-6), or are iv) present in the serum (e.g. IGF-1).

Thus, part of the myelomatous nature of the BMME can be caused by factors normally present but appearing in higher abundance due to an increasing number of "producers". This in turn marks themas targets - as those aberrantly expressed.

S17-3
Interactions of Plasmacytoid Dendritic Cells with Myeloma Cells: Therapeutic Implications

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The bone marrow (BM) microenvironment confers growth, survival, and drug resistance in multiple myeloma (MM) cells. Our prior studies delineated the functions of various cellular

components of the BM milieu including endothelial cells, fibroblasts, osteoclasts, and osteoblasts. Here we characterized the role of plasmacytoid dendritic cells (pDCs) in the BM milieu. We show increased numbers and more frequent localization of pDCs in MM patient BM than normal BM. pDCs are dysfunctional in MM, since they fail to stimulate T cell proliferation. Both in vitro and in vivo models of human MM show that pDCs confer growth, survival, chemotaxis, and drug resistance in MM cells. We observed that pDCs protect MM cells against the cytotoxicity triggered by novel and conventional anti-MM agents. Our studies have also identified a role of cell surface receptor-ligand interactions (e.g. BAFF-RANKL, Toll-like receptor-9, or IL-3R) in mediating pDC-MM interactions. Importantly, targeting Toll-like receptor-9 with CpG ODNs (SD101) both improves immune function of pDCs and abrogates pDC-induced MM cell growth. The anti-MM activity of SD101 is observed only in the pDC-MM co-cultures, with minimal cytotoxic effect on either cell type when cultured alone. Moreover, combinations of SD101 with bortezomib, HDAC inhibitors, lenalidomide, pomalidomide, or Dex trigger synergistic anti-MM activity. Our study exemplifies a treatment paradigm targeting MM cell-host BM interactions and their tumor-protective functional sequelae to overcome drug resistance and improve patient outcome.

S17-4

Importance of T Cells in Multiple Myeloma

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Multiple myeloma (MM) is still a fatal disease. Even with advances in high-dose chemotherapy and autologous stem-cell support, relapses of the underlying disease remain the primary cause of treatment failure. Novel therapeutic approaches that have a mode of action different from and non-cross-resistant with cytotoxic chemotherapy are required to eradicate tumor cells that have become multidrug resistant. To this end, immunotherapy aimed at inducing or enhancing myeloma-specific T-cell immunity in tumor-bearing patients may be desirable. Indeed, in the post-allograft relapse setting of MM (in which patients are chemotherapy refractory), long-lasting disease remission has been achieved after infusion of donor lymphocytes, suggesting that chemotherapy and T-cell-mediated cytolysis kill myeloma cells by different modes of action that are non-cross-resistant. In this presentation, I will discuss potential myeloma antigens, antigen-specific T cells and their function on myeloma tumor cells, and T-cell-based immunotherapies for myeloma. Furthermore, clinical studies of T-cell-based immunotherapy in the form of vaccination, allogeneic stem cell transplantation and donor lymphocyte infusions, with or without donor vaccination using patient-derived idiotype, and future application of donor-derived or patient-derived, antigen-specific T-cell infusion in this disease are also discussed. Based on the specificity of the immune effector molecules and cells, immunotherapies with specific T cells may represent novel strategies for the treatment of MM in the near future.

S17-5

Histone Deacetylase 6 (HDAC6) Inhibition in Combination with Carfilzomib Demonstrated Significant Cytotoxicity in Multiple Myeloma (MM) Cells

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HDAC6 selective inhibitors (tubacin, ACY-1215) with bortezomib (BTZ) show synergistic cytotoxicity in MM cells. In this study, we examined the cytotoxic effect of HDAC6 inhibition by knockdown or small molecule inhibitors (tubastatin A, ACY-1215, ACY-775) with BTZ versus carfilzomib (CFZ). Both BTZ and CFZ showed significant growth inhibition in HDAC6 knockdown RPMI8266 cells; however, more prominent combination effect was observed by CFZ treatment, assessed by MTT assay.Moreover, CFZ demonstrated more enhanced cytotoxicity than BTZ combined with ACY-1215 in MM.1S and RPMI8226 cells. Similar results were observed in cells treated with tubastatin A and ACY-775 with CFZ. Taken together, these results confirm the essential role of HDAC6 in this combination treatment. Since we also observed synergistic cytotoxicity with combination class-I HDAC inhibitor MS-275 and CFZ, we further delineated molecular mechanisms inducing cytotoxicity induced by class-I HDAC inhibition vs HDAC6 inhibitioncombined with CFZ. Surprisingly, we observed that ACY-1215, but not MS-275, triggered accumulation of lysine (K)48-linked polyubiquitinated proteins, followed by induction of endoplasmic reticulum stress, evidenced by induction of phosphorylation of IRE1 α , XBP-1 splicing, CHOP, and JNK activation. Importantly, ACY-1215 triggered intrinsic apoptosis (caspase-9 cleavage) whereas MS-275 triggered extrinsic (caspase-10 cleavage) apoptotic pathways in combination with CFZ. These results provide the preclinical framework for clinical evaluation of ACY-1215 with CFZ to improve patient outcome in MM.

S17-6

Aberrant Histone Methylation in Multiple Myeloma

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Aberrant regulation of histone methylation is a recurrent theme in multiple myeloma, lymphoma and other B-cell malignancies. MMSET (Multiple Myeloma SET domain) is a histone methyltransferase (HMT) overexpressed as a result of the translocation t(4;14), present in about 15% of multiple myeloma patients. MMSET encodes a histone methyltransferase, and protein overexpression of MMSET induces a global increase in H3K36 methylation with concomitant loss of global H3K27 methylation. The HMT activity of MMSET is essential for growth stimulation by MMSET as re-expression of MMSET in a t(4;14) myeloma cell line which the rearranged MMSET allele was disrupted by homologous recombination (KMS11-TKO), rescued growth only when the HMT activity of the protein was intact. The complete H3K36/H3K27 switch mediated by MMSET requires all PHD finger domains of the protein, the second PWWP domain and the functional SET domain. Despite the global change in histone methylation in response to MMSET, microarray and RNA-Seq analysis showed that only ~1000 genes are appreciably changed in response to MMSET. Many genes activated by MMSET display a peak of H3K27me3 near the transcription start site in MMSET low cells, which is absent in MMSET overexpressing cells, displaced by a broad pattern of H3K36me2 modification. We also found a subset of genes repressed in response to MMSET overexpression, displaying increased H3K27me3 levels were increased in association with increased occupancy by EZH2. Collectively, these data indicate that aberrant histone methylation, generally affecting H3K27 is a common theme in multiple myeloma. Oncogenic lesions in histone modifying enzymes in myeloma and other lymphoid neoplasms need to be understood on their own terms, as the lessons learned from normal function of these enzymes may not predict their activity in malignancy.

S18

Relapsed MM

S18-1

Cereblon is a Target of Thalidomide, Lenalidomide and Pomalidomide, Predicts Clinical Outcomes and is Mutated in Some Drug Resistant Multiple Myeloma Patients

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Immunomodulator drugs (IMiDs) are key components of myeloma (MM) therapy. Recently, we demonstrated that Cereblon (CRBN) is the major mediator of IMiD action in MM, operating in part via interferon regulatory factor 4 (IRF4). Both IRF4 and MYC are down regulated by lenalidomide (Len) treatment or CRBN knockdown. Conversely, over expression of IRF4 can rescue MM cells from Len exposure or CRBN deletion. Introduced mutations in the CRBN - thalidomide or DDB1 binding domains result in loss of Len-induced cytotoxicity.

CRBN mutations are uncommon in newly diagnosed patients although CRBN expression levels drop in relapsed MM. However, sequencing of a highly drug resistant MM revealed a Q99* truncating mutation as well as a R283K point mutation in CRBN. Additional sequencing in an expanded cohort of 25 patients with low CRBN levels revealed a synonymous mutation in only one sample.

We analyzed CRBN gene expression in 53 relapsed/refractory patients treated homogeneously with pomalidomide 2-4mg daily and weekly dexamethasone 40mg. The percent of patients that demonstrated at least a partial response was 0% for CRBN low expressors, 19% for intermediate expression, and 33% for higher CRBN expression. Significant differences in PFS (3.0 months vs. 8.9 months, $p = 0.0006$) and in OS (9.1 months vs. 27.2 months, $p = 0.01$) were observed when the lowest quartile of CRBN expression was compared to the top three quartiles. An important caveat with respect to PFS and OS is that CRBN mRNA level is primarily a reflection of the number of copies of CRBN on chromosome 3p and thus low risk hyperdiploid disease will have high levels of the protein.

In summary, CRBN is the major target of the IMiDs (now better named cereblon inhibitors) is mutated in some drug resistant patients, expression of CRBN predicts response to IMiD based therapy and survival outcomes. Inhibition of CRBN and its associated complex results in alterations in the IRF4 pathway and blocks E3ligase function.

S18-2

Treatment should not Immediately be Started at Time of Biochemical Relapse

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Biochemical relapse, by definition, is not associated with symptoms or CRAB criteria and can evolve slowly, or fast. Immediate start of therapy is not required in either case, but requirements for monitoring and workup differ significantly. Patients with rapidly increasing M-component (M-C) should receive a thorough clinical exploration and, in addition to basic monitoring, further testing for exclusion or documentation of progressive organ manifestations. A whole body MRI and/or PET/CT will inform about a possible increase of preexisting or occurrence of new bone lesions and of extramedullary manifestations. A bone marrow biopsy should be considered when a disruption of the correlation between M-component level and clonal size, or a light chain escape is suspected. In case no new abnormalities are found, treatment can be withheld temporarily in pts with favorable prognostic factors, but close monitoring is required. In pts with a history of aggressive disease or light-chain induced renal failure, del 17p, t(4; 14), high LDH, and/or plasmablastic morphology, initiation of treatment seems justified even in the absence of overt signs of clinical progression. In pts with slowly evolving M-C, treatment should be withheld until the emergence of early signs of myeloma-associated organ damage. Start of therapy is indicated in case of clear signs of clinical progression (before matching full CRAB criteria) and/or imminent complications. Taken together, instead of a one size fits all strategy, an individualized approach based on the above cited considerations should be applied.

S18-3

Defining the Correct Sequence of Novel Agents in the Treatment of Relapsed Multiple Myeloma.

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During the past 10 years the life expectancy of myeloma patients has doubled due to the approval of several new drugs for the treatment of multiple myeloma, including thalidomide, lenalidomide, and bortezomib. All these drugs had shown efficacy in the treatment of relapsed and relapsed/refractory multiple myeloma. Now, these drugs are often incorporated in frontline regimen. Therefore, defining the correct sequence of novel agents in the treatment of relapsed multiple myeloma has become a challenge.

Most patients with multiple myeloma do eventually relapse. The proportion of patients with good risk or high risk genetics is almost in the same proportion as newly diagnosed myeloma. The genomes of standard risk patients show few changes over time, whereas those of cytogenetically high risk patients show significantly more changes over time. These findings add to the complexity of the management of relapsed multiple myeloma.

The choice of novel agents in the relapsed myeloma is based more on empiric clinical criteria. These include disease-related, patient-related or treatment-related factors. The choices are often predicated on the history of prior drug exposure.

Bortezomib-based, salvage therapy is optimal for patients who have relapsed disease after IMiDs or have high risk genetics and/or renal impairment. Lenalidomide-based salvage therapy is preferable for patients who had prior exposure to bortezomib, patients with significant neuropathy and patients with good risk cytogenetics. Thalidomide-based salvage therapy is preferable for patients presenting with cytopenia, severe renal impairment and have had prior exposure to bortezomib and/or lenalidomide.

S18-4

The Role of Allotransplants in the Era of Novel Therapies

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Allogeneic stem cell transplantation (allo) in patients with multiple myeloma is a controversial treatment method. A re-

cent study of relapsed patients after autologous transplantation (auto) showed that those treated with reduced intensity conditioning allo (RIC/allo) had better progression free survival (PFS) as compared to those that received novel drugs, but overall survival (OS) was similar. Upfront tandem auto/RICallo has been more promising and has shown improved long term PFS and OS as compared to auto alone in two out of six prospective trials. One of these, the EBMT-NMAM2000 study, comprising 357 patients has now been updated at 96 months median follow-up. Patients with an HLA-identical sibling were allocated to auto/RICallo (n=108) and patients without to auto (n=249). Single (n=145) or tandem (n=104) auto were optional. Conditioning for RICallo was total body irradiation 2 Gy plus fludarabine 30 mg/m2/day x 3. PFS was 22% at 96 months with auto/RICallo, as compared to 12% with auto (p=0.027). OS at this time was 49% with auto/RICallo as compared to 36% with auto (p=0.030). Non-relapse mortality at 36 months was 13% after auto/RICallo compared to 3% with auto (p=0.0004). Survival from progression was significantly better with auto/RICallo, i.e. 48% versus 26% at 60 months from progression (p= 0.019) and patients that obtained CR with auto/RICallo had better outcome than those who obtained CR with auto. Auto/RICallo should be combined with novel drugs in future studies and may have a place both upfront in high risk patients and after relapse.

Plenary Session

O-1

Stable Epigenetic Reprogramming of Bone Marrow Mesenchymal Stem Cells is Seen in Patients with Multiple Myeloma

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Multiple myeloma (MM) plasma cells co-cultured with stroma taken from MM bone marrow demonstrates that it is the stroma, rather than the plasma cell, that acts as a major determinant of disease progression in MM. The role of bone marrow mesenchymal stem cells (BMMSC) in the progression of MM and monoclonal gammopathy of undetermined significance (MGUS) was investigated. BMMSC were isolated from control, MGUS and MM bone marrow. The full genetic profile of these cells was examined using microarrays, with detailed pathway analysis to determine the genes involved in disease progression. 30 patients BMMSC were analysed using U133 plus 2.0 GeneChip microarrays; this highlighted 187 genes that had over a 1.5 fold difference in expression between control and disease BMMSC. Pathway analysis of these genes generated several differentially expressed pathways, with Wnt signalling being the most evident. Two Wnt pathway genes whose expression is significantly decreased in disease BMMSC are secreted frizzled-related proteins (sFRPs) 2 and 4. This decrease in expression was confirmed by RT-PCR, with a concurrent increase in methylation status suggesting these genes have become epigenetically silenced. Splice variant analysis of these particular genes showed a differential expression of exons, which may be functionally significant for Wnt signalling. For the first time we show profound silencing of negative regulators of Wnt signalling within MM and MGUS BMMSC, which may help to design early interventions aimed at patients in the premalignant state.

O-2

Identification of Tumor Suppressive MicroRNAs in Multiple Myeloma by Pharmacologic Unmasking

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Deregulation of microRNAs (miRNAs) has been associated with pathogenesis and prognosis of multiple myeloma (MM). Although several causes may lead to miRNA deregulation, epigenetic alterations such as aberrant DNA methylation and/or histone modifications, have emerged as the main culprit. We conducted genome-wide screening for miRNAs induced in MM cells by demethylating agent 5-azacytidine (5' aza), global histone methylation inhibitor DZNep and histone deacetylase inhibitor SAHA respectively. Among 1205 human miRNAs profiled, 32 were consistently upregulated by 5' aza. These miRNAs were closely associated with CpG islands and include miR-155, miR-198, miR-135a*, miR-200c, miR-125a-3p, miR-188-5p which were underexpressed in MM patients, miR-150*, miR-3141, miR-4257 and miR-1471 which were upregulated by all three compounds, as well as miR-483-5p, miR-663, and miR-630 with known tumor suppressor functions in other cancers. Among the predicted mRNA targets of these 13 miRNAs, 305 were upregulated in MM patients (UAMS dataset, GSE2658) and contained a 46-gene signature that was associated with patient survival. Ectopic restoration of miR-155, miR-198, miR-135a*, miR-200c, miR-663 and miR-483-5p significantly repressed MM cell proliferation, colony formation and migration. In summary, we have revealed important, epigenetically silenced tumor suppressor miRNAs by pharmacologic reversal of epigenetic silencing. These miRNAs are of functional relevance and affect genes that are associated with survival in myeloma.

O-3

Early Detection of Osteolytic Lesions in Multiple Myeloma Using Natural Calcium (Ca) Isotopes

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There is need for real time monitoring of bone metabolism in multiple myeloma (MM). Better markers of incipient or asymptomatic bone destruction could be used to evaluate the need for and duration of bone specific therapies. We propose that measuring serum levels of naturally occurring Ca isotopes should be further explored as such a marker. Natural changes in the Ca isotope composition of urine and blood provide quantitative information on short-term changes in net bone mineral balance (BMB), information unavailable from conventional biochemical measures of bone metabolism. Specifically, net bone gain and net bone loss cause blood and urine to be respectively enriched or depleted in heavy Ca isotopes. Based on studies in which bed rest was used to induce bone loss, net bone mineral loss rate of about <4%/year are detectable with current analytical techniques. Osteolytic lesions that occur in >80% of MM patients should cause negative shifts in BMB detectable by Ca isotopic analysis. In a pilot study, Ca of blood from patients with MGUS was significantly isotopically heavier than Ca in blood of patients with MM (p=0.01, Mann-Whitney test). This difference likely reflects negative bone mineral balance caused by osteolytic lesions in MM patients. As the onset of osteolytic lesions is a common clinical manifestation of progression from MGUS or smoldering MM, their early detection would be of value in monitoring the progression of the disease and in evaluating which patients are at highest risk for rapid progression.

O-4

High Risk Cytogenetics and Achievement of Molecular Remission after Tandem Transplantation for Multiple Myeloma

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Within a prospective protocol the incidence and impact of achievement of molecular remission (mCR)and high risk cytogenetics was investigated in 73 patients with multiple myeloma (MM) after auto-allo tandem transplantation. After induction chemotherapy patients received melphalan 200 mg/m2and autologous stem cell transplantation (SCT) and after 3 months melphalan 140 mg/m2 and fludarabine 180 mg/m2 followed by allogeneic SCT. 16 patients had high risk cytogenetic features defined by positive FISH for del(17p13) and/or t(4;14).Overall, 66% achieved complete or near complete remission and 41% molecular remission, which was sustained negative (at least four consecutive samples negative) in 15 patients (21%), and did not differ between high risk cytogenetics and others (p=0.7).After a median follow-up of 6 years the 5 year progressive-free survival was 29 % without difference between del 17p13/t(4;14) harbouring patients and others (24% vs. 30%, p=0.7). The 5 y PFS differs substantially according to the achieved remission and was for PR, CR, mCR, and sustained mCR 17 %, 41 %, 57 %, and 85

%, respectively. These results suggested that auto-allo tandem transplantation may overcome negative prognostic effect of del(17p13) and/or t(4;14) and achievement of molecular remission resulted in long-term freedom from disease. (registration: NCT 00781170).

O-5

Pomalidomide Cyclophosphamide and Prednisone is Active in Lenalidomide Relapsed/Refractory Multiple Myeloma

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Background: Patients failing novel agents represent an unmet medical need. The median event-free survival is 5 months and overall survival is 9 months1. Pomalidomide has shown to rescue patients relapsed or refractory after lenalidomide and bortezomib. Aims: This phase 1/2 study determined the maximum tolerated dose (MTD) of pomalidomide-cyclophosphamide-prednisone in myeloma patients relapsed or relapsed/refractory to lenalidomide. Methods: Pomalidomide was administered at doses ranging from 1 to 2.5 mg/d, cyclophosphamide at 50 mg every other day, and prednisone at 50 mg every other day, for six-28 day cycles, followed by maintenance with pomalidomide-prednisone. Thromboprophylaxis with aspirin 100 mg/d or low-molecular weight heparin was recommended at physician's discretion. Results: Sixty-nine patients were enrolled. The MTD was 2.5 mg/d. Fifty-five patients enrolled at the MTD were evaluated after completing at least 1 cycle. Best responses included 5% of complete response, 24% of at least very good partial response, 51% of at least partial response and 71% of at least minimal response. The median time to response was 1.83 months. After a median follow-up of 14.8 months, median progression-free survival was 10.4 months and 1-year overall survival was 69%. Grade 3-4 toxicity included anemia (9%), thrombocytopenia (11%), neutropenia (42%), neurologic (7%), dermatologic (7%), infections (5%) and thromboembolism(2%). Conclusions: Pomalidomide-cyclophosphamide-prednisone induced high response rates, prolonged progression-free survival, with manageable toxicity.

	>VGPR	>PR	Median PFS	1-year OS
All patients (N=55)	24%	51%	10.4	69%
Relapsed after lenalidomide (N=18)	39%	61%	15.7	88%
Refractory to lenalidomide (N=37)	16%	46%	8.6	60%
Refractory to bortezomib (N=20)	30%	55%	8.6	73%
Double refractory to both lenalidomide and bortezomib (N=16)	19%	50%	8.6	66%
Outcome after IMIDs and bortezomib therapy (N=213)*	7%	24%	5	50%

CR, complete response; VGPR, very good partial response; PFS, progression-free survival; OS, overall survival; IMIDs, immunomodulatory drugs
*Kumar SK et al, Leukemia (2012) 26, 149-157

O-6

Phase II Study: Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (Dex) in High Risk SMM (Early Myeloma)

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BACKGROUND. Multiple myeloma is consistently preceded by a precursor state. High risk smoldering multiple myeloma (SMM) or "early myeloma" has a 72-76% risk of progression at 5 years. Emerging QUIREDEX data show 26% nCR/CR response rate after a median of 15 (2-41) LEN/DEX maintenance cycles and (vs follow-up) overall survival benefit (HR=3.5, p=0.01). METHODS. This phase II single arm study for high risk (Mayo clinic or PETHEMA models) SMM patients treats with dosing schedule (8x28 day cycles) CFZ IV 20/36 mg/m2 on days 1, 2, 8, 9, 15, 16; LEN 25 mg days 1-21; and DEX IV/oral 20/10 mg on days 1, 2, 8,

9, 15, 16, 22, 23; >SD receive LEN maintenance 10 mg days 1-21. Primary endpoint: response rate; secondary endpoints: PFS, DOR, safety, and correlative assays focusing on minimal residual disease (MRD) eradication. RESULTS. Thus far, 8 patients (median age 55 yrs; range 48-61) meeting eligibility criteria have been enrolled; 83% obtained nCR/sCR after a median of 4.5 (range 1-7) cycles; Table. Mean serum M-protein was 1.9 g/dL (1.1-2.9). Toxicities >grade 3 include non-hematologic: 1 CHF, 1 rash; hematologic: 2 lymphopenia, 1 neutropenia. No patients have progressed to multiple myeloma. CONCLUSIONS. Based on small numbers, 83% of high risk SMM patients obtained nCR/sCR after a median of 4.5 cycles CFZ/LEN/DEX therapy. Updated results (more patients, longer follow-up) with extensive correlative assays will be presented at the meeting. "Early myeloma" may represent a key interventional time point before development of "metastatic myeloma" with debilitating end-organ damage.

Figure. Clinical Response Following Carfilzomib, Lenalidomide, and Dexamethasone (CRd) Combination Therapy in High Risk Smoldering Multiple Myeloma ("Early Myeloma")

Response	CRd Cycles delivered				
	After 1 cycle, n/N*	After 2 cycles, n/N	After 4 cycles, n/N	After 6 cycles, n/N	Best Responses+ n/N* (%)
PR	5/6	2/5	0	0	1/6 (17%)
≥VGPR	1/6	3/5	4/4	2/2	5/6 (83%)
VGPR	1/6	2/5	0	0	0/6 (0)
nCR	0	1/5	3/4	0	3/6 (50%)
sCR	0	0	1/4	2/2**	2/6 (33%)

*Six out of eight patients enrolled are evaluable for toxicities and response

**One out of two sCR patients are MRD negative by flow cytometry of the bone marrow

+Median of 4.5 (range 1-7) cycles

O-7

Cyclophosphamide-Lenalidomide-Dexamethasone vs Autologous Transplant in Newly Diagnosed Myeloma: a Phase 3 Trial.

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Background : Novel agents question the role of autologous stem cell transplant in the treatment of younger Multiple Myeloma (MM) patients.This trial evaluated the efficacy and safety of Cyclophosphamide-lenalidomide-dexamethasone (CRD) versus Melphalan 200mg/mq (MEL200). Methods and Materials: 389 patients (< 65 ys) with newly diagnosed MM were enrolled. All patients received Rd induction (four 28-day cycles lenalidomide 25 mg d 1-21 and low-dose dexamethasone 40 mg d 1,8,15,22). The consolidation treatment consisted of CRD [six 28-day cycles of Cyclophosphamide (300 mg/mq d 1,8,15), dexamethasone (40 mg d 1,8,15,22) and lenalidomide (25 mg d 1-21))] or MEL200 [tandem melphalan 200 mg/m2 with stem-cell support]. Primary study endpoint was PFS. Results : After induction the PR rate was 60%, VGPR rate was 18% including 4% CR. After consolidation VGPR rate was 48% (including 16% CR) in the CRD arm (N 126) versus 43% (including 15% CR) in the MEL200 arm (N 118). Median follow-up was 27,4 months. The 2-year PFS was 61% for CRD arm and 72% for MEL200 arm (p=.02) and OS was 92% and 88% respectively (p=.32). In the CRD and MEL200 arms the incidence of grade 3-4 infections (21% vs 0%, p<.001). The incidence of thromboembolic events (VTE) was 3.87% after induction. In the CRD and MEL200 arms the incidence of grade 3-4 VTE was 2% and 0% respectively. Conclusions: In this trial MEL200 significantly improved PFS as compared to CRD. As expected MEL200 induced higher hematologic and non-hematologic toxicities. Longer follow-up is needed to assess OS.

O-8

Randomized Phase 3 Trial in Elderly NDMM Comparing MPT Followed by T Maintenance Versus MPR Followed by R Maintenance.

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In Europe standard therapy of newly diagnosed patients ineligible for autologous stem cell transplantation is a melphalan-based regimen (M), combined with prednisone (P) and a novel agent. Currently, in first line this novel agent is either thalidomide (MPT) or bortezomib (MPV). Results from the MM015 study showed that MPR followed by R maintenance therapy is also superior to MP. However, these regimens have not been compared head to head.

We compared MPT-T versus MPR-R in elderly symptomatic NDMM. We determined that a sample size of 668 patients would provide a power of 90% to detect an improvement of

PFS with a HR of 0.714 for patients receiving MPR-R. The study was closed for inclusion at October 19, 2012.

Demographic data are presented in table 1. Importantly, this study reflects the general elderly population as 41% is ≥ 75 years. Concerning toxicity; 54% of patients experienced a SAE. The main reason for a SAE was hospitalisation; 77%. There was no statistically significant difference in the number and reasons of SAEs in patients <75 and ≥75. Fifty-one% of all off protocol patients discontinued therapy due to toxicity (48% <75 and 55% ≥75 years of age). The number of second primary malignancies were 33 after a median follow up of 14 months (max. 44).

In conclusion, this joint HOVON/NMSG study will reveal whether Lenalidomide in combination with MP will improve outcome of elderly NDMM patients. Data on response and PFS are to be expected at *Q3 2013 and 2014* respectively at the earliest.

Table 1; Demographic data of 648 eligible* patients

	Melphalan-Prednison-Thalidomide + Thalidomide maintenance	Melphalan-Prednison-Lenalidomide + Lenalidomide maintenance
Total	321	327
Male/Female %	51/49	58/42
Median age [range]	73 [60-91]	73 [60-87]
< 75 years %	61	57
≥ 75 years %	39	43
ISS %		
I	22	23
II	43	43
III	22	22
Not verified yet	13	13
WHO %		
0	31	33
1	40	37
2	11	11
3	2	2
unknown	3	4
Not verified yet	13	12

* 20 patients not eligible

O-9

Durable Survival Benefit for Thalidomide Consolidation Post-ASCT: Extended Analysis of the ALLG MM6 Trial

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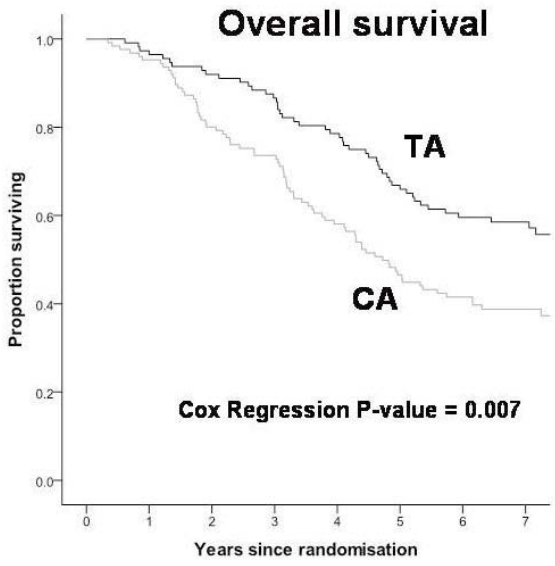
Aims To determine whether the significant PFS and OS advantages seen for thalidomide consolidation post ASCT at 3 yrs post randomization in the ALLG MM6 trial are durable at longer follow-up. To compare overall response rate (ORR) to salvage therapy and secondary primary malignancy (SPM) incidence. Methods 243 newly diagnosed MM patients post single MEL200ASCT were randomly assigned to receive indefinite prednisolone (pred) maintenance (50mg alternate days) alone (CA n=125) or in combination with 12 months of thalidomide consolidation(100mg/d increased to 200mg after 2/52) (TA n=111). PFS and OS were measured from date of randomization. Results After a median follow-up of 5.4 yrs, the post randomization estimated 5 yr PFS rates were 27% and 15% (P=0.005; hazard ratio [HR], 0.16; 95% CI 0.044 to 0.582) and OS rates were 66% and 47% (P=0.007; HR 0.12; 95% CI 0.028 to 0.558) in TA and CA respectively. TA remained beneficial irrespective of pre-ASCT B2M level <4mg/L (p=0.002) and 4+ (p=0.049). Patients required a minimum of 8 months of TA to gain PFS advantage (p=0.017), however only patients who completed 12 months of TA gained OS benefit (p=0.001). There was no difference in ORR to salvage therapy including thalidomide-based salvage, and no difference in SPM incidence. Conclusion The PFS and OS advantages ascribed to thalidomide consolidation post ASCT remain highly significant at 5 years, however the full 12 months of thalidomide was required to derive OS benefit. Further recapitulating previous findings, thalidomide did not impact on ORR to salvage therapy at relapse.



O-10

Carfilzomib, Lenalidomide, Low-dose Dexamethasone (CRd) in Elderly Patients with Newly Diagnosed Multiple Myeloma (NDMM)

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Background We previously reported results from a Ph1/2 trial of CRd demonstrating a favorable efficacy /safety profile in NDMM (median age 59y, range 35-81; Jakubowiak et al Blood, 2012). To assess CRd in elderly patients (pts), we report herein outcomes in the >=65y subset of this study. Methods Pts received 28-day (d) cycles (C) of carfilzomib (CFZ) 20-36mg/m2 IV (d1/2/8/9/15/16), lenalidomide (LEN) 25mg PO (d1-21), dex 40/20mg PO wkly (C1-4/5-8). CRd was given with modified CFZ schedule (d1/2/15/16) for C8-24; LEN alone >C24. Stem cell transplant was an option >C4. Response was assessed by IMWG+nCR. Results Of 53 pts enrolled, 23 were >=65y (median 72y, range 65-81). Baseline characteristics were similar to overall pt data except higher ISS II/III (70%). All 23 pts were evaluable with 100% achieving >=PR, 87% >=VGPR, 78% >=nCR, 65% sCR after median 12C (range 1-25). Response improved during tx with 100% >=VGPR, 94% >=nCR, 88% sCR for >=8C (n=17). Of 13 pts in CR, 12 had no minimal residual disease by multicolor flow cytometry. AE rates were comparable to overall pt data with trends of higher thrombocytopenia, neutropenia, and hyperglycemia (G3/4 30%, 35%, 43%, respectively) and dose changes (56%). All pts >=65y were progression-free and alive at median follow-up of 13 mo (range 6-25). Conclusions In this subset analysis, CRd was highly active and well tolerated in pts >=65y, with a sCR rate of 65% and all pts progression-free and alive at median follow-up of 13 mo. Results compare favorably with other tx in elderly and support a Ph3 NDMM study of CRd in all age groups.

O-11

Bortezomib (btz)- Versus Non-btz-based Induction Prior to ASCT in Multiple Myeloma (MM): Meta-analysis of Phase 3 Trials

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An integrated analysis was conducted using data from all phase 3 studies of IV btz-based vs non-btz-based induction in ASCT-eligible patients (pts) with previously untreated MM. Pt-level data from 3 studies (btz-dex vs VAD; btz-doxorubicin-dex vs VAD; btz-thalidomide-dex [VTD] vs thalidomide-dex [TD] induction) were pooled in a thorough integrated analysis of efficacy and safety. Study-level data from a 4th study (VTD vs TD; pt-level data not available due to local legal restrictions) supplemented the pt-level analysis. Key efficacy endpoints were post-ASCT complete+near-complete response (CR+nCR) rate and progression-free survival (PFS). Pt-level data for 1572 pts (787 btz-based, 785 non-btz-based induction) were included. Post-ASCT CR+nCR rate was significantly higher following btz-based vs non-btz-based induction (38% vs 24%, OR 2.05, p<0.0001); benefit remained similar (pooled OR 1.96) upon inclusion of data from the 4th study. Median PFS was 35.9 vs 28.6 months (HR 0.75, p<0.0001) with btz-based vs non-btz-based induction; 3-year overall survival (OS) rates were 79.7% and 74.7% respectively (HR for OS 0.81, p=0.0402). Median induction duration was 11 weeks in both treatment groups. Peripheral neuropathy (PN) rates during induction were 34% vs 17% (grade >=3: 6% vs 1%). Overall, 3% and 4% of pts died during btz-based and non-btz-based induction. Btz-based induction resulted in significant improvements in response and PFS/OS vs non-btz-based induction and was generally well tolerated, with a higher rate of PN but no increase in the risk of death during induction.

O-12

Visualizing Multiple Myeloma Progression Through the Intact Bone Using Multi-color Light Sheet Fluorescence Microscopy

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Despite therapeutic advances, multiple myeloma (MM) remains largely incurable and efficient preclinical testing of new drugs is needed. To advance this goal we established two highly reproducible bioluminescent MM mouse models combined with a novel multi-color light-sheet fluorescence microscopy (LSFM) approach (Brede et al. J Clin Invest. 122, 4439-4446, 2012) to visualize MM progression in 3D through the intact bone. We generated firefly luciferase+ and eGFP+ murine MOPC-315 and newly patient-derived UMM3 cell lines and monitored multifocal growth of both MM cell lines in hematopoietic compartments by non-invasive bioluminescence imaging (BLI) in BALB/c or NSG mice, respectively. Ex vivo imaging and histological analyses validated in vivo BLI data and revealed multiple osteolytic lesions. Multi-color LSFM was employed after decalcification, specific deep-tissue antibody staining and clearing of the bones. We recorded 1500 optical sections for three individual channels (488/532/647nm), which allowed scanning the whole bone marrow compartment of the sternum in single-cell resolution. With this innovative microscopy technique, we were able to visualize clusters of CD138+ cells within a collagen IV+ network. To prove the applicability for preclinical testing, we compared new treatment approaches to standard melphalan therapy. BLI measurements revealed reduced tumor burden compared to vehicle-treated mice. Our innovative preclinical MM mouse models may lead to better insights into the pathogenesis of MM and serve for further preclinical testing of new therapeutic approaches.

O-13

A New Scoring System to Identify Pts at High-risk of Early Death in the Context of Novel Agent-based Intensive Therapy

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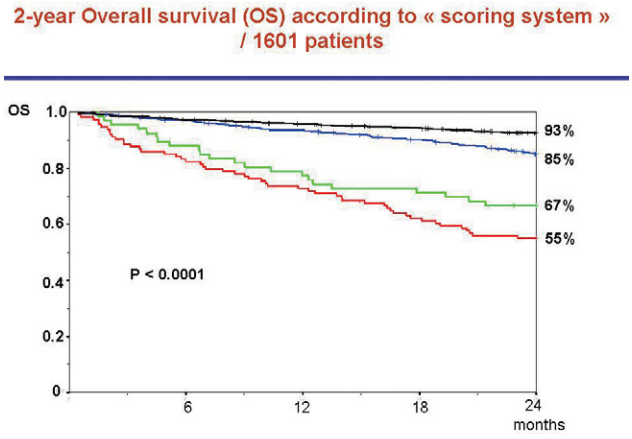
Several biological parameters are used to classify patients with multiple myeloma at high risk of progressive disease (PD). However, none of these enable the identification of the subgroup of patients at high risk of early death from PD. We investigated prognostic parameters of patients enrolled in the IFM2005-01 trial. In a multivariate logistic regression analysis, the risk of death from PD (not toxicity) within the first two years from the start of therapy was found to be related to three independent adverse initial characteristics: high LDH (p=0.0014), International Staging System (ISS) 3 (p=0.0097) and cytogenetic abnormalities defined by the presence of either t(4;14) or 17p deletion (p=0.0002). These three variables enabled the creation of a simple scoring system, which predicts for overall survival (Table 1). This score was subsequently validated in a large population of patients (n=1601) enrolled in four recent phase 3 studies conducted by different European myeloma cooperative groups (IFM, GIMEMA, HOVON/GMMG, PETHEMA), which all compared a bortezomib-based induction regimen to induction without bortezomib prior to ASCT. Two-year OS was found to differ significantly according to the categories defined by our scoring system: 93% (score 0), 85% (score 1), 67% (score 2), 53% (score 3) (p<0.0001). We have devised a simple scoring system that allows the identification of a group of patients with very high-risk disease and shortened survival despite the use of novel agent-based intensive therapy, who might be candidates for innovative therapeutic approaches.



O-14

New Assay Predicts Myeloma Survival and Progression

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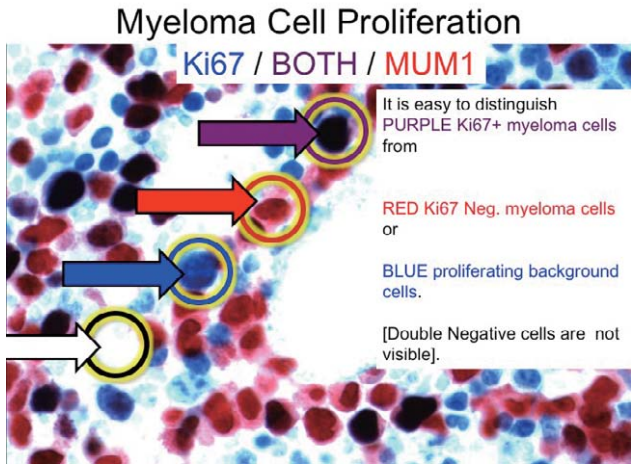
There are now several treatment options for myeloma but little data to help decide which drugs to use. A proliferation assay devised in the 1980s showed proof of principle, that assessment of proliferation is an accurate predictor of clinical behavior. Since then, for technical reasons, clinical implementation of a proliferation assay has not been successful. We invented an immunohistochemical platform (U.S. patents applied) to assess myeloma proliferation. Unlike prior methods, it is performed at the single-cell level, on routinely-preserved marrow, using standard laboratory equipment. The test can be read manually or via image analysis, using our software (U.S. copyright applied) which runs on any PC or Mac. Our prospective analysis of patients followed 14 years after an IRB-approved BMT trial showed an inverse correlation between survival and myeloma cell proliferation (P = 0.006). Also, our retrospective cohort study showed that each 1% increase in proliferation was associated with a 3% increase in risk of progression (P = 0.02). PFS was 232 weeks vs. 110 weeks for <10% vs. >10%, respectively (P = 0.03). Our new assay provides reliable prognostic information that can be used to approach care on a patient-specific basis. Because our assay can be performed currently in any diagnostic laboratory, we believe patients would benefit from its standard use in clinical trials. It would improve upon current practice by providing biologic tumor behavior data. Such data might predict well, which drugs would work best in an individual patient.



O-15

Impact of POM + LoDEX on Disease Parameters and Cytogenetic Status in Relapsed and Refractory Multiple Myeloma (RRMM)

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Background: The MM-002 phase 2 study showed that pomalidomide (POM) had clinical activity in RRMM patients (pts) who had received many prior therapies. Methods: Pts with >=2 prior therapies including lenalidomide and bortezomib, and refractory to their last treatment, were randomized to POM+LoDEX (POM 4mg/day, days 1-21 of a 28-day cycle; LoDEX 40mg/week) or POM alone. Changes in critical end-organ functional parameters for pts in the POM+LoDEX arm were measured. Outcomes were analyzed in pts with high-risk [del(17p13) and/or t(4p16/14q32)] and standard-risk cytogenetic profiles. Results: In the POM+LoDEX arm (N=113), ORR (>= partial response) was 34%, median PFS was 4.6 mos. During treatment, platelet counts, calcium, and serum creatinine levels improved in 60%, 93%, and 39% of pts with abnormal values at baseline, respectively. Albumin levels increased by >=0.5g/dL in 15% of pts and hemoglobin

levels increased by >=2g/dL in 18% of pts by cycle 8. Thirty pts (27%) had high-risk cytogenetics; median PFS was 3.1 mos, median OS was 13.2 mos, duration of response was 4.9 mos, and ORR was 23%. Outcomes for pts with standard-risk cytogenetics are described in the table. Overall, the most common grade 3/4 AEs were neutropenia (41%), anemia (22%), thrombocytopenia (19%) and pneumonia (22%). Conclusions: POM+LoDex is associated with a consistent improvement in critical end-organ functional parameters and shows promising activity in RRMM pts with adverse cytogenetics. These data strongly favor future combination strategies, including proteasome inhibitors, especially in high-risk pts.

Table. Response rates based on cytogenetic profile.

	High-risk cytogenetics (n = 30)	Standard-risk cytogenetics (n = 57)
Median PFS, mos (95% CI)	3.1 (1.9–3.9)	5.5 (3.7–8.7)
Median OS, mos (95% CI)	13.2 (4.7–19.8)	21.7 (12.4–NR)
ORR (≥ PR), n (%)	7 (23)	23 (40)
Time to response,[a] mos (range)	1.2 (0.9–2.8)	1.9 (0.9–14.4)
Median duration of response,[a] mos (95% CI)	4.9 (1.9–13.1)	10.1 (7.7–NR)

26 of 113 pts were not evaluable for cytogenetics.
[a]For pts who achieved at least PR.
CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients.

O-16

Impact of Minimal Residual Disease and Induction Therapy on Outcome Post ASCT: Insights from the MRC Myeloma IX trial

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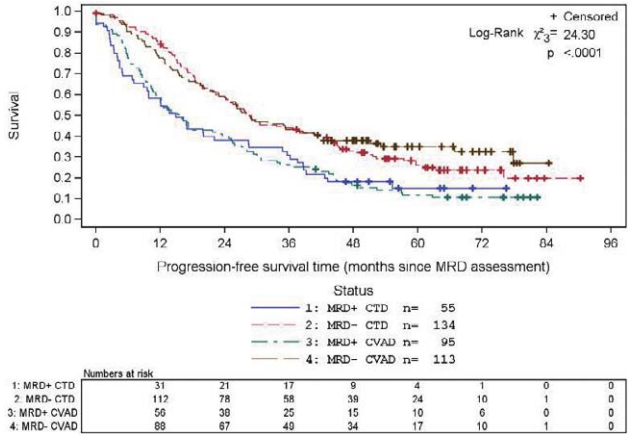
The overall outcome for patients with multiple myeloma has greatly improved over the last decade. It is unclear whether this relates to the unique biological effects of novel combinations or simply reflects the increasing incidence of high quality responses. In order to investigate this we have used multiparameter flow cytometry to assess MRD in patients treated in the intensive arm of the MRC Myeloma IX trial. Of the 397 patients examined 208 received induction with CVAD whilst 189 received CTD. All patients were assessed at day 100 post ASCT. 247/397 (62.2%) became MRD-negative following ASCT and this was associated with a superior outcome (PFS 28.6 versus 15.5 months p<0.0001 and OS 80.6 versus 59.0 months, p=0.018). When MRD status post ASCT was assessed according to induction CTD appeared superior to CVAD (71% MRD-negative versus 54%, p<0.0001). When outcome was assessed according to both MRD status and induction regimen it was noted that MRD had a similar effect on outcome irrespective of induction regimen received. The outcome of CVAD-treated patients who became MRD-negative was identical to that of MRD-negative CTD-treated patients. Similarly the outcome of MRD-positive patients was identical in both CVAD and CTD treated cohorts (see Figure below). We would conclude that quality of response is the principal determinant of outcome in myeloma rather than the treatment regimen received. MRD assessment by flow cytometry is a powerful prognostic tool and we would suggest that it be used more widely as an outcome measure in clinical trials.



O-17

Long-term Safety of Continuous Lenalidomide Therapy in Newly Diagnosed Multiple Myeloma (NDMM) Patients: MM-015 Update

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In transplant-ineligible NDMM patients (pts), lenalidomide-melphalan-prednisone induction followed by lenalidomide maintenance (MPR-R) significantly prolonged

progression-free survival (median 31 months) compared with MPR (14 months; P<0.001) or MP (13 months; P<0.001) in a phase 3 randomized trial (MM-015). Here we present an updated analysis of safety data from MM-015 with a median follow-up of 53 months for surviving pts. Newly occurred or worsening grade 3/4 adverse events (AEs) reported in >=5% of pts during maintenance are listed (Table). Three pts developed deep-vein thrombosis (DVT) (2 MPR-R, 1 MPR). Eighteen pts (21%) discontinued lenalidomide maintenance due to AEs compared with placebo maintenance (4% for both MPR and MP arms). AEs leading to dose reduction or discontinuation of lenalidomide or placebo are presented in the Table. Invasive second primary malignancies (SPM) were reported in 14 (MPR-R), 11 (MPR), and 5 (MP) pts, corresponding to low incidence rates per 100 patient-years (IR) of 3.01 (MPR-R), 2.37 (MPR), and 1.01 (MP). SPM IR in MM-015 are similar to those observed with bortezomib-containing regimens: VMPT-VT (0.9) vs VMP (1.5) (Palumbo, ASH 2012, abstract 200), and consistent with SEER data for age-matched population (<75 yrs, IR 1.9 and >=75 yrs, IR 2.3). In conclusion, the safety profile of continuous therapy with MPR-R was predictable and manageable with little evidence of cumulative toxicity and low SPM risk in transplant-ineligible NDMM. Lenalidomide maintenance was efficacious and well tolerated, allowing for continuous long-term treatment.

Table. Safety outcomes in pts receiving maintenance.

	MPR-R (n = 88)	MPR-p (n = 94)	MP-p (n = 102)
AE,[a] n (%)			
Neutropenia	6 (7)	0	1 (1)
Anemia	7 (8)	3 (3)	5 (5)
Thrombocytopenia	8 (9)	3 (3)	2 (2)
Pts with ≥ 1 AE leading to dose reduction of lenalidomide or placebo	29 (33)	5 (5)	2 (2)
Neutropenia	10 (11)	0	1 (1)
Anemia	3 (3)	3 (3)	0
Thrombocytopenia	5 (6)	0	0
Pts with > 1AEs leading to discontinuation of lenalidomide or placebo	18 (21)	4 (4)	4 (4)
Acute myeloid leukemia	4 (5)	0	0
Diarrhea	3 (3)	0	0
Neutropenia	2 (2)	0	0
Acute renal failure	0	0	2 (2)

[a]Grade 3/4 adverse events occurring in ≥ 5% of pts.

O-18

Idiopathic Bence Jones Proteinuria (Smoldering Monoclonal Light-chain Proteinuria): Clinical Course and Prognosis

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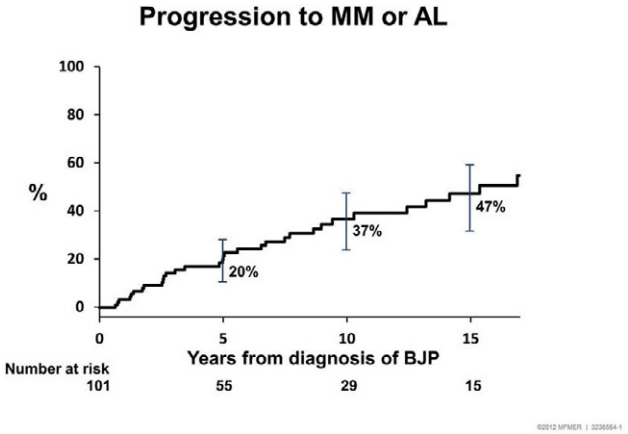
Idiopathic Bence Jones Proteinuria (Smoldering Monoclonal Light-Chain Proteinuria), is defined as the presence of a monoclonal light chain in the urine > 200 mg/24h, absence of an intact immunoglobulin M protein (IGH expression) in the serum and no evidence of MM, AL amyloidosis or other related plasma cell disorders. From January 1, 1960 through June 30, 2004, 101 Mayo Clinic patients fulfilled the criteria for diagnosis. The M protein ranged from 200 mg/24h to 4.7 g/24h (median value, 500 mg/24h); 29% had > 1 g/24h. Kappa light chain accounted for 49.5%. A monoclonal light chain was present in the serum on immunofixation in 62%. The median bone marrow plasma cell level was 9% (range 0-35%). Concentration of uninvolved (normal, polyclonal or background) immunoglobulins were reduced in 62%. During 900 person years of follow-up, 88% died, 27 patients developed symptomatic MM (relative risk, 140.3; 95% CI, 93.9-201.5) and an additional 7 patients developed AL amyloidosis (relative risk, 104.4; 95% CI, 47.8-198.4). The cumulative probability of progression to active MM or AL was 20% at 5 years, 37% at 10 years and 47% at 15 years. The factors associated with progression to MM or AL included size of urine M protein, percentage of bone marrow plasma cells, abnormal serum free light chain ratio <0.26 or >1.65 and reduction of all 3 uninvolved immunoglobulins. We conclude that patients with Idiopathic Bence Jones Proteinuria (Smoldering Monoclonal Light-Chain Proteinuria) are at risk for the development of MM or AL and must be followed indefinitely.



O-19

Long-term Outcomes of Autologous Stem Cell Transplantation for POEMS Syndrome; A Single Center Experience of 23 Cases

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POEMS syndrome is a rare plasma cell disorder characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes associated with multiorgan involvement. The pathogenesis of POEMS syndrome is not well understood, but overproduction of VEGF probably secreted by plasma cells is considered to be responsible, and ASCT has been reported to be a successful treatment strategy. Here, we assessed the long-term clinical out- comes of 23 POEMS patients treated with ASCT at our institution from 2004 to 2012. The median age at ASCT was 52 (range, 34-64), and the median interval from diagnosis to ASCT was 9 months. Fifteen patients (65.2%) received thalidomide before ASCT. Nine patients presented poor PS of 3 to 4 due to peripheral neuropathy. All patients achieved prompt engraftment. Engraftment syndrome was observed in 5 patients (21.5%), but they all responded well to corticosteroid therapy. Improvement of clinical symptoms and reduction of VEGF were observed in 22 patients (95.6%). No transplant related death was observed. Five patients experienced disease relapse. At median observational period of 51 months, 2y OS and PFS was 95.6% and 77.3%, and 5y OS and PFS was 64.6% and 59.8%, respectively. ASCT is an effective therapy for POEMS syndrome, and by stabilization of serum VEGF level with induction therapy, transplant related mortality was low and peri-engraftment complications were manageable. However, certain number of patients experience disease relapse. Therefore, all patients should be followed carefully, and effective salvage strategies are required.

Poster Session

Section A: Basic Biology

P-1

A Metabonomic-based Strategy for the Discrimination of Different Stages in the Progression of Multiple Myeloma

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Mulitple Myeloma (MM) is often preceded by a Monoclonal Gammopathy of Undetermined Significance (MGUS) which does not represent an emergency but should be closely monitored due to a significant risk (1%/year) of progression to MM. MGUS is 100 more time frequent than MM. Reliable predictors of progression have not been identified yet and information on prognosis is limited. The differentiation of MGUS from MM or any other gammopathy is usually difficult and is mainly based on the presence or absence of end-organ damage. It is impossible to differentiate MGUS patients from those who will subsequently develop smoldering MM or overt MM at the time of the initial presentation. Metabonomics is an emerging technology that can evaluate the impact of a pathological condition on the overall metabolic profile of an organism from the spectroscopic analysis (mainly NMR and Mass spectrometry) of its biofluids (urine, blood, saliva ...). The main objective of this pilot study was to identify a urinary "metabolic signature" that could help in discriminate patients suffering of over multiple myeloma (MM) versus other gammopathies, i.e MGUS, smoldering myeloma, Waldenstrom disease and primary amyloidis. Our preliminary results show a clear difference in metabolic profiles of 10 patients with gammopathies (MGUS, MM and Waldenstrom disease) as compared to a cohort of healthy subjects. Moreover, some data indicate that the metabolic signature obtained for Waldenstrom patient is different from MM patients. This has still to be confirmed in larger cohorts of patients.

P-2

Identification of Calcineurin as a Novel Therapeutic Target in Multiple Myeloma

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Many novel drugs, including HDAC inhibitors, are currently undergoing preclinical and clinical evaluation for multiple myeloma therapy. Treatment of myeloma cell lines with LBH589, an HDAC inhibitor, inhibits their proliferation. Here, we report that protein expression of PPP3CA, a catalytic subunit of calcineurin (an important signal mediator in NFAT transcription), is suppressed by LBH589 without a decrease in mRNA. This indicates that LBH589 induces degradation of PPP3CA protein. HDAC inhibitors are shown to target HSP90, a molecular chaperone HSP90 essential for the protein-folding and stability of several proteins. PPP3CA levels were reduced by 17-AAG, an inhibitor of HSP90, and HDAC inhibitors are suggested to induce the degradation of PPP3CA via inhibition of the chaperone function of HSP90. Furthermore, co-treatment with LBH589 and FK506 enhanced the anti-proliferative effect of LBH589. FK506 is a selective inhibitor of calcineurin B, a regulatory calcineurin subunit. Co-treatment of NOD/SCID mice bearing human myeloma cells with LBH589 and FK506 was also effective. These results indicate that the calcineurin signaling pathway plays an important role in the proliferation of myeloma cells. In clinical samples, expression of PPP3CA tends to be high in more advanced disease. Surprisingly, bortezomib also suppressed PPP3CA via inhibition of HDAC6. This is the first report to identify calcineurin as a novel oncogene and an important target of HDAC inhibitors in the treatment of multiple myeloma. These findings will be helpful in establishing a new therapeutic strategy.

P-3

MOS Gene as a Prognostic Marker for Relapsed Multiple Myeloma Patients after Autologous Stem Cell Transplantation.

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Objectives. We performed gene expression profiling with microarray data to better dissect the molecular phenotypes and prognoses of relapsed multiple myeloma (MM). The aim of the present study was to examine the prognostic impact of MOS expression in both MM cell lines and relapsed MM patients' bone marrow samples. Methods. Using gene expression and clinical data, we applied gene expression signatures reflecting deregulation of oncogenic pathways to highlight molecular changes in MM cell lines and bone marrow aspirate from 24 patients with relapsed MM after autologous stem cell transplantation (ASCT). The patient subgroups were defined according to relapse-free interval, within 6 months versus more than 6 months. Results. Realtime analysis indicated that the expression of MOS gene was higher in samples from patients with relapsed MM than MM cell lines (p=0.0021). IL-6, sIL-6R, and HGF expression in patients who relapsed within 6 months after ASCT was higher than that of the patients whose relapse-free interval were longer than 6 months. Treatment of shRNA MOS gene in U266 and MOLP8 dramatically led to decreasing IL-6/sIL-6R mediated ERK phosphorylation and HGF-mediated MET phosphorylation. Similar results were noted for cluster genes for MOS-MAPK. Result for MOS gene expression meets the level of significance to predict relapse after ASCT. Conclusion. Our analysis suggested that MOS gene is a novel prognostic marker for relapse of MM. The importance of the MOS-MAPK pathway as a prognostic marker in relapsed MM should be reassessed in the era of novel therapeutic agent.

P-4

Frequent Involvement of *PVT1* in Multiple Myeloma with 8q24 Abnormality and Novel Chimeric Genes *PVT1-NBEA* and *PVT1-WWOX*

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Genetic abnormalities play a crucial role in the pathogenesis of various malignancies, including multiple myeloma (MM). The 8q24 rearrangements, including *MYC* and *PVT1*, are occasionally found in MM and are associated with MM progression. 8q24 rearrangements were detected by fluorescence *in situ* hybridization (FISH) in 12 of 54 MM patients (22.2%) and in 8 of 11 MM cell lines (72.7%). The breakpoints of 8q24 in 10 patients and in all cell lines were assigned to a 360 kb segment, which was divided into four regions: 120 kb centromeric to *MYC* (5' side of *MYC*), the region centromeri-

cally adjacent to *PVT1* (170 kb region, including *MYC*, of 5' side of *PVT1*), the *PVT1* region, and the telomeric region to *PVT1*. *PVT1* rearrangements were most common and found in 7 of 12 patients (58.3%) and 5 of 8 cell lines (62.5%). A combination of spectral karyotyping (SKY), FISH, and oligonucleotide array delineated the candidate genes within partner loci of 8q24 rearrangements, *MMSET*, *EPHA5*, *NBEA*, and *WWOX* at 4p16, 4q13, 13q13, and 16q23, respectively. Two novel chimeric genes were identified: *PVT1-NBEA* in the AMU-MM1 cell line harboring t(8;13)(q24;q13) and *PVT1-WWOX* in RPMI8226 cell line harboring der(16)t(16;22) ins(16;8)(q23;q24). The *PVT1-NBEA* chimera in which *PVT1* exon 1 was fused to *NBEA* exon 2 and the *PVT1-WWOX* in which *PVT1* exon 1 was fused to *WWOX* exon 9 were associated with the expression of abnormal *NBEA* and *WWOX* lacking their N-terminus respectively. These findings indicate that *PVT1* rearrangements may play significant roles in myelomagenesis via fusion to cancer-related genes.

P-5

RSK2Ser227 is an Universal Therapeutic Target for Multiple Myeloma with Diverse Molecular Signatures.

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The search for new therapeutic target molecule upon which various multiple myeloma (MM)-promoting signalings converge is essential for the development of more effective therapy for MM. We studied the association with 90 kDa ribosomal S6 serine/threonine kinases, RSK2, activation and chromosomal status, especially focusing on RSK2Ser227, and the value of RSK2 as the therapeutic target. Twelve human myeloma cell lines and primary MM cells were utilized in this study. BI-D1870, a RSK2 inhibitor, was purchased from Symansis Limited (Auckland, New Zealand). RSK2Ser227, an N-terminal kinase domain for downstream substrate phosphorylation, was shown to be phosphorylated in all 12 MM cell lines examined and 6 of 9 primary MM cells regardless of types of chromosomal aberration or the phosphorylation status of ERK-1/2, a major upstream signaling molecule of RSK2. Both RSK2Ser227 inactivation by BI-D1870 and RNAi for RSK2 inhibited the proliferation of MM cells via induction of cell death through caspase-independent apoptosis. Both BI-D1870 treatment and RNAi for RSK2 caused down-regulation of cyclin D2, c-MYC and p21. BI-D1870 showed additive/synergistic anti-MM effects with various agents, including novel agents such as MS275 (a HDAC inhibitor), RAD001 (mTOR inhibitor), or ABT-263 (BH3 mimicking inhibitor of BCL-2/BCL-XL). We found no cross resistance between RSK2 inhibition by BI-D1870 and bortezomib (BTZ) in BTZ-resistant cell lines. In conclusion, RSK2, especially RSK2Ser227, may be an universal therapeutic target for MMs with diverse molecular signatures.

P-6

Comparison of Vascularity and Adhesion Molecule between Extramedullary Plasmacytoma and BM Specimen in Multiple Myeloma

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Purpose: In recent study, of patients with multiple myeloma who were treated with thalidomide, none of the patients with extramedullary plasmacytoma (EP) showed any reduction in the size of their plasmacytomas. Although some of these patients had a significant decrease of serum M-protein, they had progressive EP. The lack of response of highly vascularized tissues, such as EP or extramedullary multiple myeloma (EMM), supports the theory that the response of MM to thalidomide might be as a result of mechanisms other than the inhibition of angiogenesis. It may be related with that in the bone marrow (BM) stroma and plasmacytoma, where modulation of adhesion molecules and modulation via cytokines may play a role in the action of thalidomide. This report analyzes the expression of CD56, Ki-67 and CD34 from extramedullary sites and compare this expression with that from BM tissues. Subjects and methods: 26 paraffin-embedded BM specimens and EMM tissues from patients with multiple myeloma who were diagnosed from January, 1990 to December, 2004 were studied. Immunohistochemical staining for CD56, Ki-67 and CD34 was utilized. Results: The adhesion molecule CD56 expression was 28.46% (range 0-80%) in EMM while 0.15% (1% expression in two cases and no expression in other cases) in BM (p=0.006). However, Ki-67 (36.69% vs 18.77%) and CD34 expression (43.85% vs 26.83%) were not significantly different in EMM and BM tissues. Conclusions: We assume that the highly decreased expression of adhesion molecule in EMM compared to BM contributes poor response of EMM to thalidomide therapy.

P-7

Evaluation of Novel CD8 T Regulatory Cells in Patients with Multiple Myeloma at Baseline and after Len-dex Treatment

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Regulatory T cells (Tregs) play a significant role in maintaining immune homeostasis in healthy individuals. In cancer patients Tregs were considered as immune suppressors due to their expansion. In multiple myeloma (MM), we and others have shown the suppressive role of CD4 Tregs. In the present study, we investigated novel regulatory cells expressing CD8 marker (CD8 Tregs) in MM patients at baseline and after lenalidomide plus dexamethasone (LD) treatment. Peripheral blood (PB) samples were collected at baseline and after 4 cycles of LD treatment from a cohort of 16 MM patients. As a control group, 10 healthy donors (HDs) PB samples were also collected. CD8 Tregs were identified as CD8+CD25hi+FoxP3+. These CD8 Tregs share similar phenotypic features of CD4 Tregs in terms of expression of CD127 and CTLA-4. Baseline CD8 Treg numbers were significantly increased in MM patients compared to HDs (median: 0.51% vs. 0.12%; P<0.01), but no other significant differences were observed with respect to total lymphocytes, CD4 and CD8 T cell numbers. Analysis of CD8 Tregs at baseline and after LD treatment clearly showed a significant increase in CD8 Treg numbers after LD treatment (median: 1.35% vs. 0.51%; P<0.01). Functional studies revealed that CD8 Tregs from MM patients at baseline and after LD treatment were suppressive (inhibited CD4 T cell proliferation and IFN- γ secretion) as similar to CD8 Tregs from HDs. These findings suggest that increase in CD8 Treg numbers might promote immune impairment, thereby, predisposing MM patients to infections and disease progression.

P-8

Cell Cycle Genes Coexpression in Multiple Myeloma and Plasma Cell Leukemia

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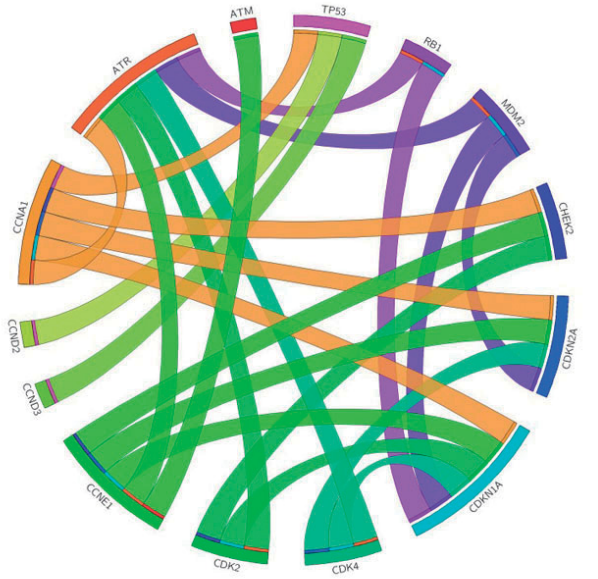
The regulation of cell cycle is dynamic and is determined not by the absolute level of any regulator, but by the aggregate balance between positive/negative cell-cycle regulators and the interplay among them. The objective of study was to describe coexpression correlations of cell cycle regulatory genes in MM and PCL. Chosen genes, responsible for G1-to-S cell-cycle progression, were divided into 2 groups based on their regulatory role: activators and blockers. Comparison of gene expression (qRT-PCR) in MM and PCL revealed up-regulation of *CDKN2A* (2.7-fold change, p=0.045) and *CCND1* (7.9-fold change, p=0.005) in PCL samples. In PCL cohort, *CCND1* and *CDK6* expression lost correlation with blocker genes and *CDKN1B* expression lost correlation with activator genes. For *CDKN2A* and *CDKN1A* blocker genes loss of correlation with some activators were associated with significant increasing of correlation with other ones. Such reaction can be explained by compensation mechanisms. Univariate Cox proportional hazards survival model with one explanatory variable showed prognostic impact for *CDKN2A* (HR 1.022 [HR95%CI: 1.004; 1.040]; p=0.016) and *CCND3* (HR 1.489 [HR95%CI: 1.112; 1.993]; p=0.008) in MM cohort. Thus, our data highlight changes in correlations between cell cycle blockers and activators during MM to PCL progression. Despite compensation mechanisms activation (*CDKN2A*, *CDKN1A*) whole regulatory complex seems to be imbalanced (*CCND1*, *CDK6*, *CDKN1B*), which can be explained by severe cell cycle dysregulation during progression to PCL. This work was supported by grants NT11154, NT13190.



Cell Cycle Genes Coexpression Correlation Changes in Multiple Myeloma *vs* Plasma Cell Leukemia
Lines represents existence of statistically significant difference

P-9

Forced Expression of miR-16 in Multiple Myeloma Induces Growth Arrest but May Confer Drug-resistance

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Background: Several miRNAs were abnormally regulated in MM cell lines (MMCL) and primary MM cells, which play critical roles in the pathogenesis of MM. We have already demonstrated a significant down-regulation of miR-16 in plasma cells from MM patients compared with healthy controls. Exposure to melphalan and bortezomib resulted in a marked up-regulation of miR-16 in MMCL (NCI-H929,RPMI-8226,MM1.S) by dose and time dependent manner. Now, we evaluated the biological functions of miR-16 in MM and its potential role in chemotherapy resistance. Methods and Results: over-expressed miR-16 was established in H929 cells and a significant cell growth arrest was measured by CCK-8 assay. Cell cycle analysis and the disregulated expression of cyclin A/E and p21 indicated S-phase arrest. Unexpectedly, miR-16 over-expressed cells were more resistant to melphalan and bortezomib. Furthermore, we found that hsp90 decreased and hsp70 increased in those cells, which may confer drug resistance as previously published (Vladimir, Oncogene 2005). Target prediction (miRanda, PicTar, TargetScan) identified CDC37L1 as a potential target of miR-16. CDC37L1 acts as a co-chaperone of hsp90, participating in the maturation and function of many client proteins. In a panel of MMCL, CDC37L1 mRNA were indeed negatively correlated with miR-16. In addition, miR-16 over-expression reduced CDC37L1 mRNA level in H929. Conclusions: Forced expression of miR-16 inhibits MM proliferation and may confer drug resistance through heat shock protein and its co-chaperone. However, the mechanism needs further investigation.

P-10

The Relationship of Myeloma Cells, Stromal Cells and Monocyte in Bone Marrow Microenvironment

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The Bone marrow (BM) microenvironment plays crucial role in pathogenesis of multiple myeloma (MM). Paracrine secretion of cytokines in BM stromal cells promotes multiple myeloma cell proliferation and protects against drug-induced cytotoxicity. In current study, monocytes, component of BM cells, can directly promote mesenchymal stem cells osteogenic differentiation through cell contact interactions. Down-regulation of inhibitors such as DKK1 drives the differentiation of mesechymal stem cells into osteoblasts. In this study, we examined the role of monocytes as a potential niche component that supports myeloma cells. We investigated the proliferation of MM cell lines cultured alone or co-cultured with BM stromal cells, monocytes, or a combination of BM stromal cells and monocytes. Consistently, we observed increased proliferation of MM cell lines in the presence of either BM stromal cells or monocytes compared to cell line-only control. Furthermore, the co-culture of BM stromal cells plus monocytes induced the greatest degree of proliferation of myeloma cells. In addition to increased proliferation, BMSCs and monocytes decreased the rate of apoptosis of myeloma cells. Our results therefore suggest that highlights the role of monocyte as an important component of the BM microenvironment.

P-11

Association of SNPs in P-glycoprotein 1 with Longer Time to Event in Bortezomib-treated Multiple Myeloma Patients

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Background: Single nucleotide polymorphisms (SNPs) in P-glycoprotein 1 (MDR1) and multiple drug resistance protein 1 (MRP1) genes may mediate drug resistance. Therefore, association of three SNPs and their haplotypes in MDR1 and one in MRP1 gene (rs4148356) with outcomes in patients (pts) with multiple myeloma (MM) was evaluated. Methods: In total, 235 MM pts (112F/123M) was included in our study. All pts underwent bortezomib-based treatment in these treatment lines: 1st (20.4%; 48/235), 2nd (40.9%; 96/235), 3rd (28.9%; 68/235), 4th (7.7%; 18/235), over 5th line (2.1%; 5/235). Regimen CVD-cyclophosphamide, Velcade (bortezomib), dexamethasone was used in 63.8% (150/235) of pts. Genotypes were determined using TaqMan real-time PCR allelic discrimination. Results: All SNPs were in Hardy-Weinberg equilibrium. All pts with no copies of haplotype TGT (rs1045642, rs2032582 and rs1128503) in MDR1 gene had longer time of survival up to 2 years from the beginning of therapy (median 23.1 vs. 11.4 months; p=0.017), longer time of progression-free survival (PFS; median 9.1 vs. 7.5 months; p=0.007) and longer time to progression (TTP; median 13.0 vs. 9.1 months; p=0.017) than pts with one or two copies of this haplotype, no association was found in MRP1 gene. Conclusion: We found significant pharmacogenetic association of specific haplotype in MDR1 gene with two-year outcome of pts with MM treated with bortezomib. Further studies are needed to determine if such data can be used for individualization of the treatment. Supported by grants: IGA NT13190 and NT11154.

P-12

Correlation of Gene Expression Profiles of Bone Marrow Stromal Cells and Clinical Presentation of Multiple Myeloma

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Bone marrow (BM) microenvironmental cells play important roles in the pathogenesis of multiple myeloma (MM). The aim of this study is to investigate expression profiles of BM stromal cells to explore their relationship with clinical presentations of MM. BM stromal cells were cultured from BM aspirates of 12 patients newly diagnosed with MM and 13 controls. Fluorescence in situ hybridization (FISH) studies for *IGH*, *RB1*, 1q, p16, *IGH/FGFR3*, *IGH/MAF*, *TP53* were performed. Gene expression profiles were analyzed using Illumina HumanHT-12 BeadChips. FISH study did not show any abnormalities in BM stromal cells from MM patients. In clustering analysis of gene expression profiles, MM and control groups did not form clearly separate clusters. However, the gene expression profiles of BM stromal cells of MM patients revealed preferential grouping reflecting clinical presentations. Many of differentially expressed genes of BM stromal cells from patients with multiple bone lesions were involved in cell to cell interactions and formation of extracellular matrix, and those of BM stromal cells from patients with renal failure were associated with cell proliferation. BM stromal cells from an MM patient with amyloidosis demonstrated significant higher expression levels of the lambda light chain gene. The gene expression profiles of BM stromal cells in MM patients were different between patients with different clinical presentations, and we could suggest that these genes may play important roles in MM pathogenesis and manifestation of clinical symptoms.

P-13

Chaetocin Enhances Tumor Specific Dendritic Cell Response on Myeloma Cells

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We investigated whether chaetocin could be used to induce apoptotic bodies for loading into DCs to enhance myeloma specific antitumor responses. Chaetocin showed to induce apoptotic cells mostly from tumor cells and led to increase the expression of heat shock protein 90 (HSP90) at a level comparable to bortezomib. The transfer of activating signal from chaetocin induced tumor cells to induce DCs maturation is mediated by the exposure of HSP90 on the surface of apoptotic cells. The HSP90 inhibitor geldanamycin can block

this immunogenicity. Chaetocin up-regulate the expression of cancer testis antigens MAGEA3 and MAGEC1/CT7, which are commonly expressed in MM and the potent targets for active immunotherapies. The cytokines production during uptake tumor antigens and maturation was comparable in DCs loaded with either irradiated MM cells or chaetocin-induced MM cells. However, DCs loaded with chaetocin-induced MM cells can reduce the production of an inhibitory cytokine (IL 10) after stimulation with CD40 ligand. CTLs stimulated by chaetocin-induced MM cells-loaded DCs showed the increasing of CD8+ T cells and displayed a greater number of IFN γ secreting cells than did those stimulated by other DCs loaded with MM cell made by other conditions. These results indicate that antimyeloma drug-induced apoptotic cells can be used as the source of myeloma antigens to loading onto DCs that could elicit potent antimyeloma activity of CTLs due to the expression of heat shock proteins and cancer testis antigens as a mechanism of immunogenic death of human MM cells.

P-14

Lenalidomide Synergistically Enhances the Effect of Dendritic Cell Vaccination in Mouse Multiple Myeloma Model

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The purpose of this study was to investigate the immunomodulatory effects of lenalidomide in combination with DCs vaccine to treat MM in vivo mouse model. After tumor growth, LEN (50 mg/kg/day) was injected intraperitoneally at three consecutive days to cover the DC vaccination. The tumor growth inhibition effect and the antitumor activity of splenocytes from vaccinated mice were evaluated to reveal the synergistic effect of DCs and LEN. The combination of LEN and DC vaccine efficiently inhibited tumor growth in mouse MM model when compared to single therapeutic agent. These vaccinated mice exhibit the reduction of myeloid-derived suppressor cells (MDSC) and regulatory T cell (Treg) in spleen. Inhibition of MDSC and Treg resulted in the increasing proportion of CD4+ and CD8+ T cell in the spleen. High ratio of Th1- to Th2-type cytokines was induced by LEN plus DC vaccine. LEN also enhance the innate immune response by modulating NK cell number and function. In addition, LEN also can enhance the population of effector memory T cells in the spleen of vaccinated mice. Furthermore, the treatment of LEN can down-regulate the levels of VEGF and TNF- α on tumor tissues of vaccinated mice. These results suggest that a treatment combining the immunomodulatory drug lenalidomide with DC vaccine can improve antitumor immunity in mouse MM model by inhibiting immunosuppressor cells and recovering effector cells, as well as superior polarization of the Th1/Th2 balance in favor of Th1 type immune response.

P-15

Ex Vivo Evaluation of the Effect of Regulatory T Cells (TREG) on Bortezomib in Multipl Myeloma

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Multiple myeloma (MM) is a hematological cancer which is characterized by malign proliferation of plasma cells and their precursors. Although MM cells express antigens which can be recognized by host T cells they can be rarely eradicated by the immune system because of the immunsupression by tumor microenvironment. It is determined in the literature that the immunsuppressive regulatory T cells (Treg) with CD4+CD25+Foxp3+ fenotype are increased in peripheral blood of MM patients which have key roles on oto-immune control, T-cell homeostasis, immunmodulation of all the immune response. According to this knowledge, we aimed to evaluate the ex vivo effect of CD4+CD25+Foxp3+ Treg cells on the proteosome inhibitor bortezomib which is being used for the first-line therapy and also for relaps patients as a targeted therapy. We collected peripheral blood and bone marrow samples from newly diagnosied 16 MM patients and isolated CD4+CD25+Foxp3+ Treg cells from peripheral blood mononuclear cells (PBMC) and confirmed by flowcytometric analysis. We evaluted the viability of CD138+ myeloma cells in subgroups of bortezomib, CD4+CD25+Foxp3+Treg and their combinations compared to their controls in primary bone marrow cultures of each patient. In this study, Treg cells showed variable effects on bortezomib by increasing, decreasing or not changing its effects. According to the results of this study, Treg cells can not be suggested as a therapeutical effect enhancer of bortezomib on MM. The clinical basis of these different effects among patients should be explored in the future studies.

Case	Gender	Age	ISS	Bone lesion	Effect of Tregs on Bortezomib efficiency in CD138+ myeloma cell viability
1	M	76	2	-	increased
2	F	49	2	-	not changed
3	M	70	2	-	not changed
4	M	57	1	-	increased
5	F	57	1	+	increased
6	M	52	3	-	increased
7	M	52	3	-	increased
8	M	51	1	+	increased
9	M	55	2	-	decreased
10	F	57	3	+	decreased
11	M	56	3	+	decreased
12	F	63	2	+	increased
13	M	74	2	+	increased
14	M	70	3	-	not changed
15	M	70	3	-	decreased
16	M	62	1	+	not changed

P-16

Serum Microrna as a Marker of Multiple Myeloma

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Background. MicroRNA (miRNA) are small non-coding RNA playing a significant role in pathogenesis of multiple myeloma (MM). We have identified a specific serum miRNA profile in MM patients (pts) and correlated it with clinical parameters. Methods. 133 serum samples: 103 (51M/52F) from newly diagnosed MM pts and 30 (14M/16F) from healthy donors (HD) were tested. A screening of 667 serum miRNA was performed on 4 MM and 4 HD with TaqMan Low Density Arrays (TLDA). Expression of differentially expressed miRNA was validated by RT-PCR. Area under curve (AUC), specificity, sensitivity and correlation with clinical parameters was analyzed.Results. Based on TLDA, 14 miRNA were differentially expressed between MM and HD ($p<0.05$). Out of them, five miRNA were validated by RT-PCR: miR-744 ($p=0.0004$), miR-130a ($p=0.0002$), let 7d ($p<0.0001$) and let-7e ($p<0.0001$) were significantly downregulated and miR-34a ($p<0.0001$) was significantly upregulated. ROC analysis showed highest sensitivity (80.6%), specificity (86.7%) and AUC (0.898) for a combination of miR-34a and let-7d. Positive correlation was observed between low levels of miR-744, let-7d and let-7e and levels of hemoglobin, thrombocytes and albumin (all $p<0.0001$), negative correlation between low miRNA levels and levels of creatinine and $\beta 2$ microglobulin was found (all $p<0.0001$). Expression of miR-744, let-7d and let-7e showed an inverse correlation with ISS stage (all $p<0.0001$).Conclusion. Our study shows that miRNA may be a promising biomarker for MM pts. Grants support: NT12130, MSM0021622434, CZ.1.07/2.3.00/20.0019 and NT11154.

P-17

Inhibition of miRNA-451 Contributes to Enhance Anti-myeloma Agents Effectiveness by Activating mTOR Pathway in SP Cells

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Side population (SP) cells are an enriched source of cancer stem cells (CSC) properties, which has be acted as a unique hallmark for no specific marker of multiple myeloma (MM) CSC study. The biological significance of microRNA associated with MM SP cells is unknown. Based on previous results in successful isolation and identification SP cells of myeloma, miR-451 was revealed with significantly higher expression in SP by miRNA expression profiling and confirmed by Q-RT-PCR. Bioinformatic analysis predicted the high-probability interesting target gene of calcium-binding protein 39 (CAB39) regulated to mTOR signaling pathways of deregulated miR-451. In function analysis, inhibition expression of miR-451 did not affect the proliferation, apoptosis, and cell cycle in NCI-H929 cells. However, after MM cells treatment with As2O3, bortezomib, and lenalidomide, knockdown of miR-451 showed a dramatically increases in apoptosis (24%, 15%, and 8% elevation of apoptosis compared to control, respectively), S-phase cell cycle (10%, 8%, 5% elevation compared to control cells, respectively), and CAB39 expression, moreover inh-miR-451 synergily elevated CAB39 expression with anti-myeloma novel agents. Finally, a specific inhibitor of mTOR, rapamycin, was found to reduce remarkably the SP fraction within NCI-H929 cells, which contained 1.3%-3.57% SP cells and 0.05% SP after treatment. These findings suggest inh-miR-451 is essential to enhance anti-myeloma novel agents' effectiveness and harbor potential target to attenuate mTOR pathway for developing myeloma SP therapy.

P-18

Analysis of the GEP Dataset Identifies lncRNAs Differential Expression Pattern and Prognosis Model of Multiple Myeloma

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Long noncoding RNAs (lncRNAs) are an important class of pervasive genes involved in a variety of biological functions, yet their potential involvement in multiple myeloma (MM) is under defined. We employed a practical and economics computational method for lncRNA analysis according to Liao's report (Nucleic Acids Res. 2011). We firstly re-annotated the Affymetrix HG_U133plus2 Array probes corresponding to both coding and non-coding (CNC) genes, and constructed a CNC network based on existing microarray data, which can be publically employed in NCBI GEO GEP-dataset of myeloma, including GSE2658、GSE3369、GSE4204、GSE4452、GSE4581、GSE5900、GSE7116、GSE9031. NcFANs predicts functions for the lncRNAs using module-based, hub-based and co-location-based. Nine lncRNAs were identified as differentially expressed (>2 fold, P <0.05). Combined with Arkansas dataset's GSE24080 (n=509), we are intriguing found that five of nine lncRNAs differentially expressed, GAS5, CRNDE, LOC400657, PMS2P3, and TCL0000445, which were associated with inferior prognosis and corresponded with 70 genes with 30% mapped to chromosome 1 (P < 0.001). GO enrichment analysis these differentially expressed lncRNAs enriched for cell cycle pathway (P<10-35)and apoptosis(P<10-27). Our data suggests that lncRNA expression profiling can be screened based on a CNC network construction method, and lncRNAs might be used to identify prognosis and guide therapeutic interventions. Further analysis, however, to confirm their expression in myeloma samples as well as to reveal their functions, needs to be performed.

P-19

Interaction between B7-H1 Molecules on Myeloma Cells and PD-1 Molecules on T Cells Induces Myeloma Cell Drug Resistance

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B7-H1 (CD274) is a co-inhibitory molecule detected on various cancer cells and may evade tumor-specific cytotoxic T lymphocytes (CTLs). Our previous study demonstrated that B7-H1-expressing multiple myeloma (MM) cells had a proliferative advantage and were resistant to antimyeloma chemotherapy (Tamura et al. Leukemia 2012). However, the mechanism of this phenomenon was not clarified. In this study, to investigate the mechanisms by which B7-H1 on MM cells is associated with tumor cell proliferation, we established B7-H1-expressing MM cell lines (MOSTI) that express high levels of CD38 and CD138 from the bone marrow mononuclear cells of MM patients. Knockdown of B7-H1 expression significantly suppressed the proliferation of MOSTI-1 cells, demonstrating that B7-H1 expression is directly associated with tumor cell growth. To examine the reverse signal derived from B7-H1 molecules binding to their receptors (PD-1 and CD80) on myeloma cells, we used bead-coupled PD-1-Ig or CD80-Ig fusion proteins. B7-H1 molecules on MOSTI-1 cell surfaces were bound to PD-1-Fc more strongly than to CD80-Fc. This binding produced a reverse signal from PD-1, but not from CD80, to MM cells, which induced the resistance of myeloma cells to melphalan. However, this reverse signal did not induce cell growth. Our study revealed a new mechanism via which the interaction between B7-H1 on MM cells and PD-1 molecules on T cells not only inhibits CTLs but also induces drug resistance of MM cells. Further studies are in progress to clarify the disease progression mechanism via B7-H1 molecules.

P-20

Glycolysis Inhibition Enhances the Susceptibility of Myeloma Cells to DR4-mediated Immunotherapy

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TRAIL-mediated immunotherapy is an attractive anti-tumor maneuver because of its tumor-specific activity. However, we found that exposure to lactic acid reduced the expression of the TRAIL receptor DR4 in myeloma (MM) cells. Because MM cells robustly secrete lactate through enhanced aerobic

glycolysis, we hypothesized a link between glycolysis and DR4 editing in MM cells. The present study was therefore undertaken to clarify the role of glycolysis in DR4 editing in MM cells. Cocultures with osteoclasts (OCs) enhanced the levels of hexokinase (HK) II, a critical glycolytic enzyme, in MM cells and their lactate secretion along with the suppression of their DR4 expression, which was abrogated by the inhibition of the PI3K-Akt pathway by LY294002. Treatment with metoformin, anti-diabetic stimulator of glycolysis, up-regulated lactate production by MM cells, and substantially down-regulated the DR4 expression in MM cells; conversely, 3-bromopyruvate (3BrPA), an inhibitor of HKII, enhanced their DR4 expression, suggesting inverse relation between glycolytic activity and DR4 expression in MM cells. Importantly, the cytotoxic effects of an anti-DR4 agonistic antibody on MM cells were markedly enhanced in combination with 3BrPA. We previously reported that "side population" cells had highly enhanced glycolytic activity compared to "main population" MM cells (Nakano et al. 2011). Taken together, present observations warrant further study for the combinatory treatment of TRAIL-mediated immunotherapy with glycolysis inhibition to target drug resistant-"side population" cells.

P-21

Hyperhaploid Multiple Myeloma (MM): A Rare Karyotypic Subgroup Retaining Disomy 18 and 1q12∼23 Amplification

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We have identified 22 patients with hyperhaploid karyotypes that are defined by clones with chromosome numbers in the 24-34 range. They share the same set of odd-numbered chromosomes, including 3, 5, 7, 9,11,15,19, and 21, found in hyperdiploid MM, except that these specific chromosomes are found in disomy instead of trisomy. The single exception is that in the hyperhaploid karyotypes the chromosome 18 was retained in 18 of 22 patients, and all or part of 1q was retained or newly amplified in five patients. We investigated nine cases utilizing metaphase fluorescence in-situ hybridization (FISH) and spectral karyotyping. FISH identified two of the nine cases with IGH translocations, one with a t(4;14), while in the other, the receptor of the IGH signal was not identified. Deletions of 17p were found in all nine samples. The only recurring structural aberrations were amplifications of 1q12∼23 or jumping translocations of 1q identified in five cases. Three patients showed a 1q21 copy number (CN) of 2, one with a CN of 3, and one with a CN of 2-6. The most striking amplification of 1q involved the formation of 1q triradials on both the 1q and 3pter, thus demonstrating that amplification of 1q can subsequently occur on different chromosomes after initiation on 1q. The retention of disomy for chromosome 18 and amplification of 1q provides evidence that these chromosomes are important in the survival and progression of these clones. The median survival time for these patients from diagnosis was 32 months, suggesting a poor prognosis for hyperhaploid MM.

P-22

HLA (Human Leukocyte Antigen) Polymorphism and the Risk of Developing Multiple Myeloma (MM)

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Ethnic and familial distribution of myeloma suggests a genetic basis for development of myeloma. We attempted to define the predisposing and protecting HLA specificities in Caucasian (CAU) and African American (AFA) individuals with MM using the National Marrow Donor Program (USA) registry and Center for International Blood and Marrow Transplant Research (CIBMTR) databases. MM cases were identified from the CIBMTR/ NMDP database (2887 US CAU and 509 AFA). Controls (500,000 US CAU and 439,423 AFA) were recruited donors to the NMDP. Cases and controls were compared using multivariate logistic regression model. Among CAU, single HLA specificity HLA-B*07 and C*07:02 were associated with higher odds of (OR: 1.24, p=0.0003 and OR: 1.22, p= 0.005, respectively) but B*44:02 with lower odds of MM (OR:0.85, p=0.049). The role of the B*07, C*07 and B*44 alleles were confirmed in ABCDRB1 doublets and haplotypes including these alleles. HLA-B*07 did not reach statistical significance among AFA cases (OR:

1.33, p=0.07). However among healthy AFA subjects the protective B*44 allele was relatively infrequent (14% population frequency in CAU vs. 6.8% in AFA). Among AFA, HLA B*27 homozygosity and allele DRB1*11 were associated with higher odds of MM (OR: 2.76, p= 0.013 and OR:1.43, p=0.01 respectively). This population based study based on the largest sample size identifies the common HLA allele variants and haplotypes associated with MM risk. The relative infrequency of MM protective HLA variants in AFA controls may explain the higher risk of plasma cell dyscrasia in AFA.

Significant variants including B*44 , B*07 and C*07 among Caucasians

A	B	C	DR	Odds Ratio	Lower CI	Upper CI	P
A*02	B*44			0.75	0.62	0.90	0.002
A*02:01	B*44:02			0.77	0.63	0.94	0.01
	B*44		DRB1*04	0.78	0.62	0.99	0.04
	B*44		DRB1*13	0.64	0.41	0.99	0.05
A*02	B*44		DRB1*04	0.67	0.50	0.91	0.009
A*02:01	B*44:02		DRB1*04:01	0.65	0.47	0.91	0.01
A*02	B*44	C*05	DRB1*04	0.64	0.42	0.99	0.05
A*02:01	B*44:02	C*05:01	DRB1*04:01	0.60	0.36	0.99	0.05
A*02:01	B*07:02			1.26	1.01	1.58	0.04
	B*07		DRB1*15	1.23	1.07	1.43	0.005
	B*07:02		DRB1*15:01	1.23	1.06	1.43	0.007
	B*07:02		DRB1*15:01	1.24	1.01	1.52	0.05
		C*07:02		1.22	1.06	1.39	0.005
A*03	B*07	C*07	DRB1*15	1.23	1.00	1.52	0.05
A*03:01	B*07:02	C*07:02	DRB1*15:01	1.24	1.01	1.52	0.05

P-23

Genomic Mapping of Glucocorticoid Receptor Binding in Multiple Myeloma

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Glucocorticoids (GC) are a cornerstone of myeloma treatment, however, little is known about mechanisms which induce cell death or post-receptor mechanisms to obviate resistance. Our overall goal is to define the direct targets of GC actions which induce cell death and identify druggable targets of GC signaling pathways that can be used to overcome resistance to GC in the absence of a functional glucocorticoid receptor (GR). The induction of apoptosis by GCs primarily involves trans-repression of growth inducing genes. Mechanisms for GR-mediated trans-repression include GR tethering to and inhibiting growth inducing transcription factors (TFs) through protein-protein interactions; by interactions with growth inducting TFs at composite GREs or by direct DNA binding to newly described negative GREs (nGRE). The TFs which interact with GR have not been identified in myeloma and are likely cell specific. In addition, global GR-chromatin interactions have not been investigated in myeloma. Chromatin immunoprecipitation combined with massively parallel sequencing (ChIP-seq) of GR in conjunction with bioinformatics platforms to integrate ChIP-seq data with GR-induced changes in gene expression have been used to globally elucidate the primary targets of GC trans-repressive actions. These data are presented here and will provide the basis of downstream target identification for drug development.

P-24

Potential Role of PPAR-γ and HO1 in Multiple Myeloma (MM) Cell Death

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Peroxisome-proliferator-activated-receptor- γ(PPAR- γ) is a transcription factor that regulates immune and inflammatory responses. Normal and malignant B cells, including MM, express PPAR- γ. Moreover, while certain PPAR- γ ligands induce apoptosis of MM cells and PPAR- γ over-expression decreases MM cell growth, silencing PPAR- γ expression by RNAi increases survival of B cells. Heme Oxygenase 1 (HO1) is an enzyme that plays a pivotal role in inflammation, oxidation and apoptosis. It is able to regulate PPAR- γ by enhance its expression and different PPAR- γ agonists upregulates HO1. It has been recently described that bortezomib is able to increase HO1 expression but a correlation between bortezomib, HO1 and PPAR- γ has not been actually investigated. We have treated human MM cells with rosiglitazone, a synthetic agonist of PPAR- γ, or with bortezomib and evaluated cell viability by flow cytometer analysis, PPAR- γ and HO1 expression by real-time PCR and HO1 enzymatic activity by a colorimetric assay. Rosiglitazone was able to induce apoptosis in MM cells and a relevant increase of PPAR- γ (30 folds) and HO1 (12 folds) expression. Bortezomib decreased cell viability and, more notably, was able to increase HO1 (40 fold) and PPAR- γ expression (16 folds). Our results indicate that rosiglitazone, a PPAR- γactivator, is able to induce apoptosis in MM cells and HO1 expression. In addition, bortezomib is able to increase the expression of HO1 and PPAR- γ suggesting a potential role of PPAR- γ and HO1 in MM-drug induced cell death.

P-25

Myeloid Derived Suppressor Cells are Increased in Multiple Myeloma but not in MGUS

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Introduction In Multiple Myeloma (MM) the immune function is impaired but the role of microenvironment on this dysfunction is unknown. Methods In 60 consecutive newly diagnosed MM and 70 MGUS we studied myeloid subpopulations and lymphoid paresis, evaluating the percentage and absolute count of circulating myeloid suppressor cells (MDSC) in peripheral blood assessed by flow cytometry, their phagocytic activity using a commercially available kit (Phagotest R), dosage of inhibitory molecule arginase-1 (Arg-1), and in-vitro immunosuppressive assays. Results MDSC were significantly higher in MM vs healthy ($p=0.002$) and MGUS ($p=0.001$). The capability of phagocytosis MDSC from MM patients at diagnosis was significantly reduced compared to healthy subjects ($p<0.001$) and MGUS ($p<0.0001$), and partially restored after induction chemotherapy. After PHA-P stimulation, normal T-lymphocytes missed the expression of activation markers CD71, CD69, CD25, CD3 ζ in presence of MM-MDSC, and in a more moderate way in presence of MGUS-MDSC. MDSC-associated immune inhibitory molecules ARG-1, BV-8 and reactive oxygen species (ROS) were significantly increased in MM MDSCs, evidenced by flow cytometry and RT-PCR analysis and positively correlated with advanced disease. Finally, in MM, but not in MGUS, increased levels of circulating MDSC correlated with regulatory T-cells (Treg) and were negatively associated with the expression of CD200+ T-lymphocytes, and L-selectin (CD62L) expression on CD8+T-lymphocytes, suggesting the myeloid contribution to the T-cell arm impairment and MM progression from MGUS.

P-26

Hypoxia Reduces CD138 Expression and Induces Immature Phenotype in Myeloma Cells

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[Introduction] Although CD138 expression is a hallmark of plasma cells and myeloma cells, decreased expression of CD138 is occasionally found. We previously reported that 1) CD138 expression decreased by disease progression 2) Myeloma cell lines with reduced CD138 expression had immature phenotype. However, the mechanisms of CD138 down-regulation are still unclear. We examined changes of CD138 and transcription factor expression in myeloma cells under hypoxia, which is an important factor of the BM microenvironment. [Methods] Myeloma cell lines were cultured under normoxic (20% O2) and hypoxic (1% O2) conditions. Changes of CD138 expression and transcription factors were analyzed. [Results] CD138 expression was found to be decreased under hypoxic condition compared to normoxic condition. Plasma cell specific transcription factors were down-regulated under hypoxic condition compared to those under normoxic condition. Oct-4, NANOG, and SOX2, which are stem cell specific transcription factors, were up-regulated under hypoxic condition. Interestingly, the decreased CD138 expression rendered under hypoxic condition recovered when they were treated by All-trans retinoic acid (ATRA) along with decrease of stem cell specific transcription factor expressions.[Conclusions] We conclude that hypoxia induces down regulation of CD138, accompanying immature phenotype. The differentiation stimulating agent ATRA can render these changes. Our findings suggest not only the mechanism of CD138 down-regulation but also a new treatment strategy for CD138 negative or low myeloma cells.

P-27

Histone Demethylase Inhibitor Overcomes Reversible Tolerance to Bortezomib

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The proteasome inhibitor bortezomib has shown impressive clinical activity alone and in combination with conventional and other novel agents for the treatment of multiple myeloma (MM). However, resistance to bortezomib as a single agent develops in the majority of patients, and activity in other malignancies has been less impressive. To overcome bortezomib resistance, we compared differential gene expression profiles of bortezomib-resistant IM-9 and sensitive IM-9 cells in response to bortezomib. The differential gene expression profiles of bortezomib-resistant IM-9 and bortezomib-sensitive IM-9 cells in response to bortezomib was performed using Affymetrix GeneChip. To confirm the results, real-time PCR and Western blot analysis were performed. bortezomib-resistant IM-9 cells were treated with or without bortezomib and/or histone demethylase inhibitor, trans-2-phenylcyclopropylamine hydrochloride (2-PCPA). At concentrations

that effectively inhibited proteasome activity (maximum dose with 100nM), bortezomib induced cell death in bortezomib-sensitive IM-9 cells, but not in bortezomib-resistant IM-9. In comparison of differential gene expression profiles between bortezomib-resistant IM-9 and bortezomib-sensitive IM-9 cells, we showed overexpression of KDM3A and KDM5A, which are associated with chromatin-mediated reversible drug-tolerant state, Moreover, 2-PCPA overcame bortezomib resistance in a dose-dependent manner. Histone lysine-specific demethylase inhibitors as combination with bortezomib may be useful for overcoming bortezomib-resistance in myeloma cells.

P-28

Myeloma Cells in a Hypoxic Milieu Modulate Bone Marrow Angiogenic Activity via Exosomes

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Background: In multiple myeloma (MM), abnormal plasma cells interact with bone marrow (BM) stromal cells and vascular cells among others. A part of the BM milieu is considered highly hypoxic, and myeloma cells *in situ* may be influenced by circumstances other than normoxia *in vitro*. Hence, we attempted to confirm the role of hypoxic, MM-derived exosomes in the BM microenvironment, since our previous study showed that cell-cell communication between tumor and endothelial cells occurs via exosomes (Umezu et al., Oncogene 2012). Design and Methods: We established a new hypoxia-resistant cell line, RPMI-8226HR, derived from RPMI-8226 cells cultured for >4 months under hypoxia (1% O_2), as a model of MM cells localizing in an extensively hypoxic milieu. Exosomes derived from RPMI-8226 or RPMI-8226HR cells cultured in normoxia (20% O_2) or hypoxia (1% O_2) for 24 h were used for validating angiogenesis, and tube formation assay was performed using human umbilical vein endothelial cells (HUVECs) as targets. Exosomal miRNA profiling of myeloma cell lines was performed using a Taqman low-density array. Results and Discussion: Exosomes secreted by the RPMI-8226HR cells under hypoxia significantly increased tube formation of HUVECs than those from RPMI-8226 cells under normoxia and hypoxia. The level of an miRNA subset, including miR-210, was significantly elevated inside the cells as well as exosomes derived from RPMI-8226HR cells. Our results suggest that exosomal miRNAs secreted by MM cells in a hypoxic milieu may, in part, affect the angiogenic activity in the BM microenvironment.

P-29

MMSET Knockdown Induced Apoptosis in T(4;14) Multiple Myeloma Cells through Regulating IRF4 Expression

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Multiple myeloma (MM) is characterized by recurrent chromosomal translocations. The multiple myeloma SET domain (MMSET), identified by its fusion to the IgH locus in t(4;14) MM, is universally overexpressed and has been suggested to play an important role in tumorigenicity in t(4;14) MM. In order to identify downstream functional targets of MMSET, we knocked down MMSET expression with shRNAs in KMS11, a t(4;14) MM cell line, and identified differentially expressed genes by gene expression microarray analysis. The results indicated 321 genes were down regulated and 375 genes were up regulated upon MMSET knockdown. Functional clustering analysis using DAVID Bioinformatics Resource 6.7 indicated MMSET knockdown affected key pathways essential for cell cycle/division, response to nutrient and nucleotide binding. Importantly, the knockdown reduced the transcription levels of the transcription factor IRF4 (interferon regulatory factor 4), which is required for myeloma cell survival with recent evidence. Quantitative-PCR analysis confirmed the transcription levels of IRF4 were reduced upon MMSET knockdown in t(4;14) MM cells (KMS11, KMS18, KMS28BM). Flow cytometric analysis indicated MMSET knockdown could induce apoptosis in KMS11 cells, and ectopic expression of IRF4 could rescue KMS11 from the apoptosis induced by MMSET knockdown. Furthermore, IRF4 knockdown could also induce apoptosis in KMS11 cells by flow cytometric analysis. Overall, our preliminary data suggested that MMSET knockdown induced apoptosis in t(4;14) MM cells through regulating IRF4 expression.

P-30

Polymorphisms of IL-10, IL-17A, IL-17F and IL-18 Affect the Clinical Features of Multiple Myeloma in Japanese Patients.

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Background: We examined the SNPs of cytokines including IL-10 (−1082A/G, −819T/C, and − 592A/C), IL-17A −197G/A, IL-17F 7488 T/C, and IL-18 (−137G/C and −607A/C) in multiple myeloma(MM) patients, and analyzed the relationship between these SNPs and the susceptibility and clinical features. Methods: Ninety three patients [age, 35-83 years; male/female 44/49; IgG (n=55), IgA (n=15), IgD (n=2), non-secretory (n=3), Bence Jones (n=18)] with MM and 192 healthy controls were examined. Genotyping were determined by the polymerase chain reaction based methods. Results: No significant differences were observed in the allele or genotype frequencies of IL-10 and IL-17 polymorphisms between MM patients and the control group. However, patients with MM had a significantly higher frequency of the IL-18-137 CC genotype compared to the control group (7.5% vs 2.0% P<0.05). In the clinical features, IL-10 592 CC genotype was significantly associated with advanced ISS and higher β2 microglobulin level (p<0.05). IL-17A-197 non GG (AA+GA) genotype was significantly associated with advanced ISS (P<0.05). Patients with IL-10-592 CC or IL-18-607 AA genotype showed tendency to more unfavorable survival (p=0.07). A multivariate analysis demonstrated that Bence Jones protein, ISS 3, the use of new drugs, IL-10-592CC genotype, and IL-17 AA were independent adverse prognostic factors. Conclusion: These results indicate that cytokine polymorphisms are associated with prevalence and clinical feature of MM in Japanese patients.

P-31

Functional Aspects of Decreased Bone Marrow Plasma Concentrations of Decorin in Patients with MGUS and Multiple Myeloma

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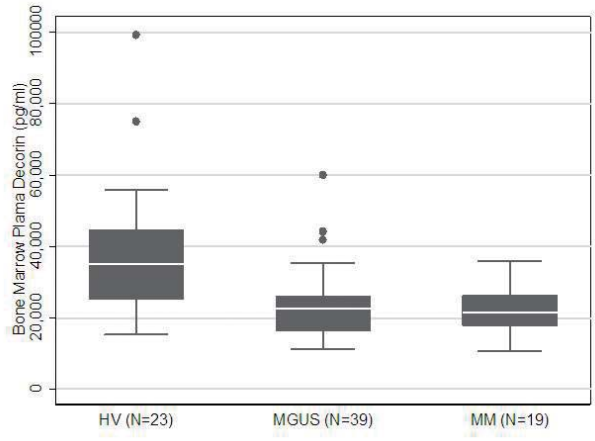
Decorin is a stromal-produced small leucine-rich proteoglycan known to have antitumor effects. It has recently been shown that decorin interacts with the HGF receptor c-Met (Goldoni et al, JCB 2009), a potential key pathway in multiple myeloma (MM). We aimed to measure the levels of decorin in peripheral blood and bone marrow plasma in MGUS and MM patients by a commercial ELISA kit (DuoSet, R&D Systems), and investigated the functional aspects of HGF and decorin interactions in vitro in MM. We found that the concentration of decorin was significantly higher (p<0.05) in bone marrow (BM) plasma from healthy volunteers (median 35.2 ng/mL, range 15.3-99.1) compared to MGUS (median 22.5 ng/mL, range 11.1-59.5) and MM patients (median 21.5 ng/mL, range 10.6-35.9). Decorin levels were lower in peripheral blood than in BM plasma in all groups with a BM/PB ratio of 3.9, 3.4 and 2.5 for HV, MGUS and MM, respectively. A positive correlation (Spearman' s rho=0.51, p<0.05) was found between simultaneously measured levels of HGF and decorin in BM plasma in healthy volunteers, but not in MM or MGUS samples. Functionally, we found inhibition of HGF-induced Transwell migration and viability (measured by the ATP-based CellTiter-Glo assay) of myeloma cell lines (INA-6 and ANBL-6), but no down-regulation of the c-Met receptor determined by flow cytometry after decorin exposure. In conclusion, we show here for the first time that decorin is down-regulated in MM and MGUS bone marrow plasma and that it in vitro abrogates some of the functional effects of HGF on myeloma cell lines.



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Measurement of Myeloma Cell Survival in Co-culture with Bone Marrow Stromal Cells

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The aim of this work was to establish a robust and simple method for the measurement of drug sensitivity in myeloma cells under conditions mimicking aspects of the bone marrow microenvironment. In particular we wanted to measure drug sensitivity in myeloma cells cultivated in the presence of stromal cells. We analyzed survival of myeloma cells co-cultured with BMSC using an automated fluorescence microscope, ScanR. ScanR is a microscope based screening station. By staining the cell nuclei with DRAQ5, we were able to discriminate between BMSC and myeloma cells, based on their staining intensity and nuclear shape. Using the apoptotic marker YO-PRO-1, the effects of drug treatment on the viability of the myeloma cells in the presence of stromal cells could be measured. The main advantages of this method are the lack of cell manipulation before co-culture (e.g. staining or viral transduction), and the low number of myeloma cells (5000 primary cells) that are needed per measurement, which makes the method ideal for experiments with purified primary myeloma cells. In fact, the analysis was easier and more robust when using slowly growing cells, i.e. by using primary myeloma cells compared to more rapidly proliferating myeloma cell lines. This method should be well-suited for high throughput analysis, as the cells are stained in situ with no washing, centrifugation, or fixation steps before analysis. Examples of the results obtained will be presented.

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ST3GAL6 is Upregulated in Multiple Myeloma and is Associated with Inferior Survival.

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Aberrant expression of cell surface carbohydrates is a feature of cancer progression and metastases, therefore glycosylation gene expression may be dysregulated in MM. Deregulated glyco-genes in MM were identified and results were validated using quantitative PCR (QPCR). Lectin microarrays were used to profile the surface glycosylation of MM cell lines. Protein expression was assessed by immunohistochemistry (IHC) on primary MM bone marrow.Functional studies were performed following gene knockdown (KD) in MM1S and RPMI cell lines. Glyco-genes are differentially regulated in MM, including, notably, the sialyltransferase gene ST3GAL6. ST3GAL6 plays a central role in the synthesis of functional selectin ligands with reduced leucocyte rolling and homing in knockout mice.Upregulation of ST3GAL6 was confirmed by QPCR in MM cell lines and primary cells.Higher expression of ST3GAL6 in MM patient bone marrow vs. healthy cells is seen on IHC.Lectin arrays show binding of MM cell surface proteins to sialic acid specific lectins.Analysis of the MRC Myeloma IX microarray dataset (n=260) confirmed a statistically significant reduction in overall survival with increased expression of ST3GAL6 (median OS 35.7 vs. 48 months, log rank test p=0.04).Preliminary functional studies reveal that ST3GAL6 KD reduces adhesion to fibronectin in comparison to scrambled controls. ST3GAL6 is upregulated in MM with higher expression associated with inferior survival.Further studies are ongoing to evaluate the full role of this critical regulator of selectin ligand function in MM cell adhesion and trafficking.

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The Role of Aryl Hydrocarbon Receptor Activation in Multiple Myeloma

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Background: The cause of multiple myeloma (MM) is unknown, although some data suggest a role for aromatic hydrocarbon exposure. The aryl hydrocarbon receptor (AHR) is expressed by some lymphocytes and by many human cancers. We explored AHR expression and signaling in MM, hypothesizing its possibility as a novel therapeutic target. Methods: AHR and CYP1A1 were assessed by real-time PCR. Cell viability (measured via Trypan blue exclusion assay) and CYP1A1 mRNA expression were assessed after 72 hours of in vitro culture with AHR agonist (FICZ), antagonist (CH-223191), or vehicle. Results: U266 and OPM2 MM cell lines, healthy donor plasma cells, and primary MM cells constitutively express AHR. Primary MM cells and MM cell lines also constitutively express CYP1A1. Compared to control in OPM2 cells, AHR agonist expanded MM cells 16.8 ± 9.9% (P = 0.03, n = 3) and increased CYP1A1 mRNA expression (indicating AHR activation) by 14.5 ± 0.34-fold (P = 0.005, n = 2). Conversely, AHR antagonist suppressed MM cell viability by 35 ± 8.7% (P = 0.02, n = 3) and inhibited CYP1A1 expression by 120 ± 1.9-fold (P = 0.05, n = 2). AHR signaling also modulated MM cell surface phenotype. Conclusions: AHR is expressed by healthy and MM plasma cells, and function contributes to MM cell viability. We have shown previously that AHR plays a role in normal natural killer cell development, and the present data suggest a complementary, inverse role for AHR signaling in MM. These data support further inquiry into AHR as a possible immunomodulatory and therapeutic target for MM.

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Longitudinal Gene Expression Signatures in Multiple Myeloma

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What causes an individual patient to progress from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM) is still incompletely understood. Previous gene expression array studies have either examined unrelated MGUS and MM donors, or compared donor-matched smouldering (S) MM with MM. We have assembled a biospecimen bank comprised of a large number of matched MGUS and MM clinical samples taken from patients at the time of diagnosis and performed a pilot study using 12 of these samples. RNA was extracted from purified plasma cell populations (CD138+CD38++CD19-) and gene expression profiling performed using Illumina microarrays. Bioinformatics revealed a number of individual genes whose altered expression had not previously been associated with disease progression. Reductions in TLE1, BIRC3, SMAP2 and MERTK gene expression upon MGUS to MM transition were validated using quantitative PCR. Pathway analysis revealed a gene signature indicative of an increase in specific cytokine signalling upon MGUS to MM transition. These analyses will be extended to a larger cohort of patients, and validated using established in vitro and in vivo models of myeloma. This longitudinal study of MM patients will provide a much clearer picture of gene expression changes which accompany disease progression. Moreover, these studies will enable us to establish a list of candidate genes/proteins which play a role in MGUS to MM transition and allow us to define their significance as prognostic indicators of disease progression and/or as novel therapeutic targets.

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Silencing of Sumo-1 Gene Modulates Beta-catenin Protein Stability and Enhances Myeloma Cells' Sensitivity to Doxorubicin

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Multiple myeloma (MM) is a malignant plasma cell disorder, with the sumoylation pattern being greatly enhanced. However, the precise targets of sumoylation during myeloma pathogenesis remain uncertain. In our study, the constitutive Sumo-1 modification of beta-catenin, the key protein in the canonical Wnt pathway, was detected in myeloma cell line NCI-H929 by means of immunoprecipitation and immunofluorescence . We then transfected NCI-H929 with Sumo-1 siRNA to suppress the conjugation of Sumo-1 and beta-catenin. Downregulation of Sumo-1 was confirmed by real-time PCR and western blot. Besides, immunoprecipitation result showed a decreased level of sumoylated beta-catenin. Interestingly, the protein level of beta-catenin decreased following sumo-1 silencing, indicating a role for sumoylation in the regulation of beta-catenin protein stability. Moreover, the downstream genes of Wnt pathway, such as c-Myc and cyclinD1, were down regulated by about 50% and 70% respectively. Functional assays indicated a marginal difference in cell proliferation and apoptosis when inhibited cells

were compared with negative controls. However, we found that the transfection of siRNA increase cell death significantly from 30% to 80% when treated with doxorubicin at a concentration of 100nM, indicating that silencing of Sumo-1 enhanced myeloma cells' sensitivity to doxorubicin. These results suggested that sumoylation of beta-catenin might play an important role in the pathogenesis, as well as drug resistance of MM.

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Characterization of Plasma Cell Disorders with Subclones Having Distinct DNA Content as Identified by Flow Cytometry

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Plasma cell (PC) proliferative disorder cases with either diploid and aneuploid PCs (12 cases) or multiple aneuploid PCs (13 cases) were identified by 8-color flow cytometry (FC) that measures PC phenotype and DNA content. The diploid and aneuploid cases all had hyperdiploid subclones. In the 13 multiple aneuploid cases, 1 was hypodiploid and hyperdiploid, 2 were hyperdiploid and tetraploid, and 10 had two hyperdiploid subsets. The FC findings are summarized in Table 1, the primary difference between groups was the more frequent diminution of normal PCs in the multiple aneuploid group. 2 multiple aneuploid cases had repeat studies, in both the paired results were similar. Clinical history was available for 6 cases in each group, in 4 of the 6 diploid and aneuploid cases the clinical diagnosis was MGUS, 1 was newly diagnosed multiple myeloma (MM), and one relapsed MM. In all 6 multiple aneuploid cases the clinical diagnosis was relapsed or refractory MM. Table 2 summarizes the cytogenetic data. As expected abnormalities were more readily detected by FISH, however these methods combined detected the presence of multiple DNA content populations in only a single case. In 4 multiple aneuploid cases FISH identified adverse genetic events. Novel 8-color FC detects DNA content clonal heterogeneity in PC disorders that are not readily identified by cytogenetic methods. Furthermore, the presence of multiple aneuploid subclones is strongly associated with relapsed/refractory MM and adverse laboratory attributes whereas the presence of diploid and aneuploid subclones is not.

	Diploid and Aneuploid (n=12)	Multiple Aneuploid (n=13)
Median, % Abnormal PCs, Of total events collected	4.5%	4.5%
Range, % Abnormal PCs, Of total events collected	0.7% to 47%	0.1% to 38%
Cases with <5% Normal PCs, Of total PCs collected	5 of 12	10 of 13
Cases with PC S-phase>1.5%, Of total abnormal PCs	2 of 12	3 of 13

Table 1

	Diploid and Aneuploid	Multiple Aneuploid
Metaphase Studies Performed	7 of 12	11 of 13
Metaphase Studies Abnormal	1 of 7	3 of 11
Multiple Clones by Metaphase	0 of 1	0 of 3
PC FISH Studies Performed	5 of 12	9 of 13
PC FISH Studies Abnormal	5 of 5	9 of 9
Multiple Clones by PC FISH	1 of 5	0 of 9

Table 2

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Unconventional Prefoldin RPB5 Interactor Over-expresses in Multiple Myeloma and Regulates its Developement

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Unconventional prefoldin RPB5 Interactor (URI) is associated with the RNA polymerase II subunit 5, which has been recognized as oncoprotein in solid tumors. But its role on multiple myeloma (MM) remains unclear. First, we detected the expression of URI in MM patients and healthy volunteers, finding that URI is overexpressed in MM at both protein and mRNA levels. Side population (SP) cells of MM cell lines showed much higher level of URI than non-SP cells. Use of lentivirus-delivered shRNA, we established stable URI knockdown MM cell lines. Cell proliferation assays showed that cells were inhibited to grow significantly in U266 after URI knockdown. Cell cycle assays suggested that these cells were arrested in S phase. Colony-forming assays were carried out in NCI-H929 and LP-1. After URI knockdown, the numbers of clones reduced by 61% and 45.6%, respectively. Tumor growth assays in NOD/SCID mice further confirmed the promotion role of URI during MM development in vivo. Then, the mRNA levels of stemness and inflammatory genes were examined and Bmi1, together with other stemness genes, IL-6 and its downstream genes IL-8, CCL5 and TNF α decreased in URI knockdown cells. Transient overexpression of

URI, in turn, elevated the mRNA expression of IL-6. Finally, we stimulated cells with IL-6 and found that the level of pSTAT3 in URI knockdown cells was much lower than control cells. In conclusion, URI may play an important role in MM development through activating IL-6/STAT3 pathway.

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Development of a Therapeutic sgRNA for Multiple Myeloma Based on TRUE Gene Silencing

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tRNase ZL-utilizing efficacious gene silencing (TRUE gene silencing) is one of the RNA-mediated gene regulation technologies that have therapeutic potential (1-3). This technology is based on the observation that tRNase ZL can cleave any target RNA at any desired site under the direction of an appropriate artificial small guide RNA (sgRNA). In order to find candidate myeloma therapeutic sgRNAs, we constructed a library composed of 160 heptamer-type sgRNAs, and examined them for inducing apoptosis in human myeloma cell lines. We found seven highly effective sgRNAs, which were taken up easily by myeloma cells without any transfection reagents, activated caspases, and induced DNA fragmentation. None of them displayed observable cytotoxicity in human peripheral blood mononuclear cells. We further analyzed the action mechanism of one of the effective sgRNAs, H15540, and found that this sgRNA induces reactive oxygen species in myeloma cells. Furthermore, DNA microarray and 3′ -RACE analyses suggested that one of the target RNAs of H15540 may be a mitochondrial mRNA. These observations imply that TRUE gene silencing may pave the way to new therapies for multiple myeloma. 1. Nakashima, et al. (2007) Gene-silencing by the tRNA maturase tRNase ZL under the direction of small guide RNA. Gene Therapy 14, 78-85. 2. Takahashi, et al. (2012) Elimination of specific miRNAs by naked 14-nt sgRNAs. PLoS ONE 7, e38496. 3. Takahashi, et al. (2013) A naked RNA heptamer targeting the human Bcl-2 mRNA induces apoptosis of HL60 leukemia cells. Cancer Letters 328, 362-368.

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Flow Cytometry to Identify Symptomatic MM Pts with MGUS-like Signature at Diagnosis Associated with Long-term Survival

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The degree of clonality assessed by flow cytometry (MFC) has become relevant to identify pts with MGUS or smoldering MM at different risk of progression. Here, we hypothesize that the balance between malignant and normal PCs may also help to identify symptomatic MM pts with an MGUS-like signature, in whom attaining CR may not be critical to achieve long-term survival. We have generated a phenotypic library (composed by the frequency of BMPCs, clonal and normal PCs) that included 698 transplant-eligible newly-diagnosed symptomatic MM and 497 MGUS pts. Principal component analysis of the phenotypic library revealed a subset of MM pts that clustered with MGUS cases (n=59). When compared to the overall population, MGUS-like-MM pts showed a markedly superior TTP (10y: 59% vs 14%; P<10-6) and OS (10y: 65% vs 29%; P<10-4). When the survival analysis was restricted to MM pts that were unable to achieve CR after HDT/ASCT, TTP (38m vs NR; P<10-4) and OS (54m vs NR; P=.003) decreased in the overall population but not in MGUS-like MM pts, respectively. Thus, MGUS-like-MM pts failing to achieve CR showed similar TTP (P=.81) and OS (P=.24) as compared to those attaining CR. In summary, MFC identifies a subset of symptomatic MM pts with an occult MGUS-like signature. The prospective identification of this signature may contribute to discriminate a sub-optimal response that requires additional treatment from a residual "MGUS-like component" that may remain stable without

further treatment. This new biomarker is also effective to predict risk of transformation in MGUS and smoldering MM.

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HGF Expression in Multiple Myeloma

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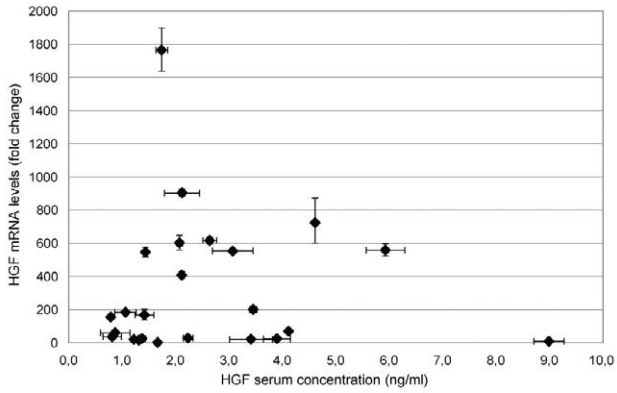
Hepatocyte growth factor (HGF) is a pleiotropic growth factor important in cell survival, tissue remodeling and wound healing. In multiple myeloma, patients often show elevated HGF serum levels which correlate with poor prognosis. Furthermore, we have earlier found that myeloma cells may produce HGF. We therefore questioned whether myeloma cells are responsible for the excess HGF serum levels found in myeloma patients. Here, we quantified HGF levels in 30 patients followed by measurement of HGF mRNA levels in CD138+ plasma cell samples from the same patients. The results showed that about half of the patients investigated have elevated and one third highly elevated HGF serum values. However, we could not find a correlation between HGF serum and HGF mRNA levels (Figure). Thus, there were patients that had high serum HGF but little or no myeloma cell HGF mRNA, and vice versa. Furthermore, myeloma cell diploidy had no effect no HGF expression. We sequenced the HGF promoter region in myeloma cells from ten patients but we could not find any aberration. The data obtained revealed however a distinct set of SNPs and a highly polymorphic deoxyadenosine tract element located about -700 bp relative to the HGF transcriptional start. We also co-cultured myeloma cell lines with bone marrow stromal cells and measured HGF concentrations in the cell culture supernatants. Depending on myeloma cell line used in the co-culture, we could measure elevated concentrations of secreted HGF, suggesting that interaction between myeloma and stromal cells induced HGF secretion.



Comparison of HGF concentrations in patient sera with HGF mRNA levels in primary CD138+ cells. Plot shows the alignment of HGF serum and HGF mRNA levels in 24 myeloma patients. HGF concentrations in blood serum of these patients were determined by ELISA. CD138+ cells purified from bone marrow of corresponding patients were used to quantify HGF mRNA levels by real-time PCR. Data shown are mean HGF serum concentrations (ng/ml) ± standard error of the mean and mean HGF mRNA fold change ± standard deviation.

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Myelodysplastic-phenotypic Alterations Detected in MM Pts Predict Myelodysplasia-associated Cytogenetic Abnormalities

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The progress made in MM treatment has been accompanied by an increasing concern for therapy-related secondary primary malignancies (SPMs). Consequently, it would be relevant to identify pts at higher risk of developing SPMs, preferably using routinely available techniques. Here, we investigated if the presence of myelodysplastic-associated phenotypic alterations (MDS-FC) predicted for cytogenetic abnormalities. The presence of MDS-FC was previously investigated in 70 pts and was detectable by flow cytometry (FC) in 23 (33%). In these later cases FACS purified CD34+ hematopoietic stem cells (HSC), neutrophils, monocytes and erythroblasts were analyzed by FISH (in male pts, n=12), for the detection of -5/del(5q), -7/del(7q), del(20q), trisomy 8, and -Y. Conversely, in female pts (n=11) these cell populations were screened for clonality using the human androgen receptor X-chromosome inactivation test (HUMARA). Four male pts (33%) showed cytogenetic abnormalities; 3 cases with del(5q31) and 1 with -Y, both abnormalities being detected in all 4 cell populations. Six of the 11 (55%) female pts showed a clonal HUMARA test. The presence vs absence of MDS-FC alterations pre-

dicted for a clonal HUMARA test in the correspondent cell compartment, namely HSC (100% vs 11%;P=.005) and neutrophils (67% vs 0%;P=.05), with a similar trend being also found in erythroblasts (80% vs 29%;P=.08). Our results show that immunophenotypic dysplastic features are present in approximately one-third of MM pts at diagnosis and that in half of them these are associated with clonality at the genetic level.

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Can Immunophenotypic CR be also Achieved in Relapsed Multiple Myeloma (MM) Patients?

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Although the introduction of IMiDs and proteasome inhibitors has significantly improved response rates and outcome in relapse MM, the management of these pts remains challenging and prognostic biomarkers to identify pts at different risk are scarce. Here, we hypothesized that in parallel to the front-line setting, novel therapeutic options and auto or alloSCT may induce MRD clearance and that this may translate into extended survival in the relapse setting. 27 pts achieving CR after rescue therapy and referred for MRD investigation by MFC are the focus of the study. The majority (82%) of pts was initially submitted to ASCT and only 11% were exposed to >=1 novel agent up-front. Rescue therapy immediately preceding CR was usually based with novel agent combinations (89%), followed by alloSCT in 33% of cases and autoSCT in 26%. The remaining 41% were not transplanted. From the 27 pts in CR, 14 (52%) also achieved immunophenotypic CR whereas the remaining 13 (48%) were MRD+. MRD clearance was most likely in pts submitted to SCT vs those who were not (79% vs 21%;P=.03). Only 2/14 (14%) MRD- cases experienced subsequent relapse as compared to 93% in MRD+ cases (P<.001); median TTP NR vs 14 months (P=.01), respectively. Median OS was NR vs. 57 months (P=.22), respectively. It should be noted that only 2/14 MRD- pts have died (both from GVHD without MM progression) in contrast to 7/13 MRD+ cases (P=.03). We show that achieving immunophenotypic CR is possible in a subset of relapse MM pts particularly after SCT, and identifies a subset of cases with long term relapse free survival

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Identification of Poly (ADP-ribose) Polymerase as a Novel Target for Antitumor Effects of Bufalin in Multiple Myeloma

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In multiple myeloma (MM), therapies remain unsatisfactory, and Poly(ADP-ribose) polymerase1 (PARP1) inhibitors are newly investigated to fight MM cells when combined with proteasome inhibitor in vitro. Here, we explored a traditional Chinese agent bufalin and found its potent anti-tumor effect on MM cells, mainly via PARP1 inhibition. We firstly tested the effect of bufalin on the proliferation of MM cells including NCI-H929, U266, RPMI8226 and MM.1S cells. The results showed that the proliferation of cells was markedly inhibited by 10-20 nM bufalin. Secondly, we isolated the CD138+ cells from 5 cases of MM patients and also found significant reduction of cell survival when cultured with bufalin. Based on the suppose that bufalin has some close relationship with PARP1, we carried out DARTS analysis in MM cell lysates and proved that bufalin could directly bind to presumed target protein, and resulted in PARP1 activity inhibition. Thereafter, we carried out docking simulation for binding mode, and predicted the catalytic domain of PARP1 was the possible bufalin targeting domain by amino acid sequence processing. In addition, the inhibition of PARP1 activity by bufalin was sufficient for the suppression of PAR activation (which reveals the PARP1 activity in response to DNA damage), G2-M transition, and accumulation of p-AKT in H929 cells. Of importance and interest, bufalin was found to have synergistic effect when combined with AKT inhibitor in H929 cells. In conclusion, we identified bufalin was a potent therapeutic agent in MM cells, which mainly via PARP1 inhibition.

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Knockdown of RalA Induces Apoptosis in Ras Mutant Multiple Myeloma Cells

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INTRODUCTION: Up to 40 percent of primary multiple myeloma (MM) cases harbor activating point mutations in K- or N-Ras, which confer oncogenic Ras-dependence in these cells. Ral counts among the potential Ras effector candidates and may relay illegitimate cell survival signals originating from mutant Ras. We tested the effects of shRNA-mediated Ral knockdown on the survival MM cells. METHODS: ShRNA expression vectors against RalA and RalB isoforms were transiently transfected to MM cell lines by electroporation. Cells were co-transfected with EGFP expression vector and strongly transfected cells were selected by cell sorting. Ral isoform specificity was verified by depletion of (over)expressed HA-tagged RalA and RalB protein, respectively. Cell survival was measured by flow cytometry after 4 days using annexin V/APC-staining. RESULTS: Both Ral isoforms were expressed in all MM cell lines tested (n=10). Expression levels were heterogeneous and without obvious correlation to the presence of mutant Ras. Knockdown of RalB generally conferred moderate apoptotic effects in transfectable cell lines (n=6), whereas knockdown of RalA reduced cell survival preferentially in Ras mutant cells. Combined depletion of both Ral isoforms did not relevantly enhance cell death compared to single isoform knockdown. CONCLUSION: RalA may confer tumor cell survival in MM with oncogenic Ras. Like Ras, Ral is currently not pharmacologically druggable. To exploit this pathway for potential therapeutic intervention, characterization of Ral signaling effectors is warranted.

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Gain of Chromosome 1q21: Pathogenesis, Prognostication, and Treatment of a Time-lapsed Multiple Myeloma

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BACKGROUND. Chromosome 1q21-gain is a cenerentolesquely investigated frequent genetic alteration in multiple myeloma, poorly understood in terms of pathogenic, prognostic and clinical relevance. METHODS. We analyzed 1246 CD138-purified plasma cell samples by iFISH and gene expression profiling (n=902) alongside clinical parameters, including patients at either early stage (n=139), or undergoing high-dose therapy and autologous stem cell transplantation (n=1068). RESULTS. i) Patients with 1q21-gain show faster progression from asymptomatic to therapy-requiring myeloma. ii) Symptomatic 1q21+-patients reach a faster and deeper remission after induction treatment and autologous stem cell transplantation, but subsequently relapse faster with adverse event-free and overall-survival. iii) 1q21-gain is copy-number-dependently associated with proliferation and iv) shows a characteristic gene expression pattern. CONCLUSIONS. 1q21-gain hijacks myeloma into a time-lapsed unique biological, clinical, and treatment related entity, that should be assessed in all myeloma patients. Patients with 1q21-gain might benefit from maintenance treatment independent if in (near) complete remission and additional cell cycle targeting treatment.

P-48

A Tumor Cell Maturation Heirachy in MM Extending from CD20+ CD38- Tumor B Cells and Its Role in Therapeutic Resistance

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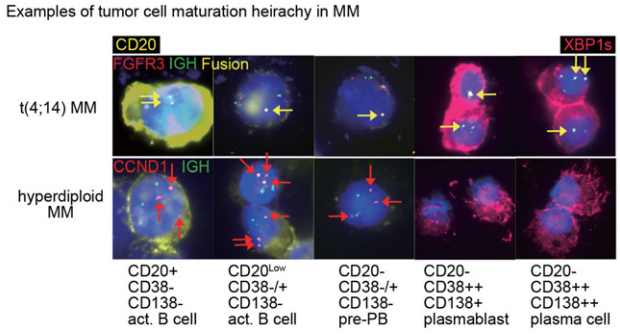
Primary multiple myeloma (MM) tumors are shown to contain an ongoing differentiation program mediated by precursor subpopulations that correspond to maturation stages between B cells and plasma cells (see figure). We show that secondary acquired genetic events such as del(1p) and del(17p) occur in early tumor progenitors including CD20+ CD38- CD138- B cells that these early precursors likely contribute continously to the bulk tumor plasma cell population, acting as tumor stem-like cells. The MM tumor cell maturation heirachy identified is shown to contribute to therapeutic resistance in the clinic. Proteasome inhibitors are a mainstay of treatment for MM but fail to cure. We show that XBP-1snegative tumor pre-plasmablasts and B cells survive bortezomib therapy, and other chemotherapies, preventing cure. MM tumor maturation-arrest at pre-plasmablast stage enables progressive disease on proteasome inhibitor treatment. Mechanistically, suppression of XBP1s in MM cells is found to induce bortezomib resistance via de-comittment of tumor cells to plasma cell maturation and immunoglobulin production, diminishing endoplasmic reticulum stress and ERAD dependence. This suggests that IRE1 α inhibitors currently in development may be ineffective or deleterious for the treatment of MM and that MRD studies in MM should include evaluation of tumor progenitors. These results highlight the

diversity of tumor cell maturation in MM and its role in therapeutic failure. We conclude that a spectrum of MM progenitor stages must be addressed by future treatment strategies to achieve cure.



P-49

Pyk2 Mediates Niche Specific Multiple Myeloma Cell Survival.

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Multiple myeloma (MM) is an incurable malignancy, in part, due to the influences of the bone marrow microenvironment. Therefore, identification of niche-specific survival signaling determinants is critical for the rationale design of therapy. Collaborative signaling between fibronectin (FN)-adhesion and IL-6 affords a more malignant phenotype via preferential amplification of IL-6-induced JAK/STAT3 activation in MM cells (Shain et al 2009). Phosphoproteomic analysis of MM cells under co-stimulatory conditions identified 338 differentially phosphotyrosine (pY) peptides. Among these were proteins involved focal adhesion assembly including Pyk2, paxillin, p130CAS, CASL, and Tyk2. Targeting of Pyk2 with siRNA or the Pyk2 inhibitor PF562571 attenuated Jak1/STAT3 phosphorylation, thereby identifying a co-stimulation specific to the Pyk2/JAK1/STAT3 signaling axis. Targeting this axis with antisense oligonucleotides to both Pyk2 and STAT3 promoted apoptosis under co-stimulatory conditions (FN+ IL-6), but not when cells were stimulated with either effector alone. Activation of the Pyk2/Jak1/STAT3 signaling cascade was also observed upon co-culture of MM cell lines and patient tumor cells in direct contact with patient bone marrow stromal cells (BMSC), but not under transwell conditions. Targeting Pyk2 and STAT3 induced apoptosis in BMSC-adherent MM cells from patients. Similar attenuation of Pyk2 and STAT3 reversed BMSC-induced melphalan resistance. In summary, the Pyk2/JAK1/STAT3 axis represents a niche-specific MM cell survival pathway and putative anti-myeloma target.

P-50

Establishment of Novel Mice Model for Extramedullary Plasmacytoma

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Background: Extramedullary myeloma (EMD) is defined as a plasma cell tumor that occurs outside the bone marrow or adjacent soft tissues. EMD seems to have a different pathogenesis from medullary myeloma and is often characterized by a more aggressive clinical course. To date molecular mechanisms of the development of EMD have not fully understood, because of lack of the good in vivo model. Methods: A human MM cell line, IM-9 was serially selected in vivo using SCID-bg mice. IM-9 cells were inoculated intravenously and harvested from the tumor developed in BM and liver, aiming to establish BM-prone and liver-prone clones. Tumor progression was periodically checked by BLI and confocal imaging. After four rounds screening, the selected clones of both BM- and liver-prone were characterized by gene and protein expression and cellular function assays. Results: We obtained three liver-prone sub-clones after four round in vivo selections. These cells had equal or lower in vitro proliferation rate compared to the original or BM-prone cells, but exhibited more aggressive phenotype in vivo. Two of the three clones had significant high migration activity. Gene and protein expression analysis revealed that each liver-prone clone had a remarkable higher expression of sets of inconsistent chemokine receptors. Discussions; We established the EMD-prone human MM cell lines that reproducibly developed liver plasmacytoma. These cells exhibited higher migratory ability and overexpression of several chemokine receptors that may contribute to the aggressive phenotype observed in vivo.

P-51

IL-6 Does Not Protect against Myeloma Cell Death Induced by CD28-CD86 Blockade

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CD28 and CD86, surface molecules better known for their key roles in T-cell costimulation, have recently been shown to play important roles in the generation and maintenance of normal long-lived plasma cells. Myeloma cells are malignant versions of normal plasma cells, and high expression of CD28 or CD86 are known to be poor prognostic markers for myeloma patients. Previous data from our lab has shown that CD28-signaling can protect myeloma cells from cell death induced either by drug treatment, or growth-factor deprivation. Using lentiviral-mediated shRNAs targeting either CD28 or CD86, we found that ablation of expression of CD28 or CD86 results in cell death in 3 myeloma cell lines (RPMI8226, MM1.s, and KMS18). To determine if we could recapitulate this using a pharmacologic agent, we treated myeloma cells with CTLA4-Ig, a reagent that blocks the interaction between CD28 and CD86. We found that treatment of RPMI8226, MM1.s, and KMS18 cells with CTLA4-Ig resulted in apoptosis after 2-3 days. Since myeloma cells rely heavily on the bone marrow milieu for growth and survival signals, we next determined whether co-treatment with IL-6 could protect against cell-death induced by blocking CD28-CD86 signaling. Interestingly, our data show that IL-6 co-treatment does not protect against cell death induced either by knockdown of CD28 or CD86, or CTLA4-Ig treatment. These data suggest that CD28 and CD86 are important in maintaining myeloma cell viability, and that blocking this pathway in myeloma cells may be a new therapeutic avenue that warrants further investigation.

P-52

Genomic Characterization of the Putative MM Stem Cells Reveals Alterations Possibly Correlated with the Disease Origin

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Although advances in MM therapy, the disease remains incurable. The existence of Myeloma Propagating Cells (MPCs) is supposed to be one of the major causes of MM drug-resistance and relapse. Little is known about the molecular characteristics of MPCs, even if according to some studies, their phenotype resembles the memory B cells. CD138+ and CD138-19+27+ cell fractions obtained from BM PBL of 50 newly diagnosed MM, 7 MGUS and 15 relapsed patients were molecularly characterized by SNPs array 6.0. BM and PBL CD138+ cell fractions shared exactly the same genomic macroalterations, whereas any of them was shown in BM and PBL CD138-19+27+ cell fractions. The B memory cells were characterized by several microalterations (range 1-834 Kb) located out of any genomic variants region and involving genes related to cholesterol metabolism, embryonic development and transcriptional regulation. By applying a stringent analysis, the CD138-19+27+ cells obtained from all pts showed a unique microdeletion (410 Kb) on chr 14, involving JAG2, BRF1, PACS2, NUDT4 and BTBD6, which has been already described in the chr.14q pediatric syndrome, characterized by developmental disorders and mental retardation. Data suggest that the MM CD138+ clone might resume the end of the myelomagenesis process, proven by the presence of numerous macroalterations, possibly due to an established genomic instability. In contrast, the memory B cells displayed several microalterations, supporting the idea that these post germinal center cells might be involved in the transforming event that originate the neoplastic clone.

P-53

The Phosphatase of Regenerating Liver-3 (PRL-3) is Essential for IL-6-mediated Survival of Myeloma Cells

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PRL-3 is a protein expressed in myeloma (MM) cells, but not in normal plasma cells. PRL-3 was previously shown to be induced in MM cells by IL-6 and other growth factors, to promote MM-cell migration (Fagerli et al, 2008), and has been identified as a marker gene for a subgroup of patients with MM (Broyl et al, 2010). We permanently overexpressed PRL-3 in INA6 cells by retroviral transduction and found that it increased cell proliferation and survival in the absence of IL-6. PRL-3 overexpression led to a significant increase in phosphorylation of STAT3 both in the presence and the absence of IL-6. A pharmacological inhibitor of PRL-3 reduced survival of the MM cell lines INA6, ANBL6, IH1, OH2 and RPMI8226. The inhibitor also induced apoptosis in 5 of 5 samples of purified primary myeloma cells. Treatment with the inhibitor down-regulated the anti-apoptotic protein Mcl-1 and led to activation of the intrinsic apoptotic pathway. Inhibition of PRL-3 reduced IL-6-induced phosphorylation of STAT3. Treatment with 10 μM of PRL-3 inhibitor I also significantly reduced migration against an SDF-1 α gradient and HGF-, IGF-1- and SDF-1 α-mediated adhesion of the cell

line INA-6. PRL-3 overexpression mediated a major increase in adhesion, whereas the migration was reduced. In conclusion, PRL-3 expression renders MM cells less dependent on IL-6 for survival and proliferation, and has an important role in cell migration and adhesion. IL-6 and other MM growth factors induce expression of PRL-3, which in turn amplifies STAT3 phosphorylation and cause expression of Mcl-1.

P-54

Cyclin D1 Expression is Associated with Shorter Survival in Myeloma Patients with Moderate Plasma Cell Infiltration.

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Background: The aim of this study was to evaluate the association of cyclin D1 (Bcl-1) expression with survival of patients with multiple myeloma and whether plasma cells percentage in bone marrow (BM) modifies this. Methods: Ninety-seven consecutive patients with symptomatic myeloma diagnosed and treated at the Department of Medicine/ Orebro University Hospital during 2000-2005 were evaluated. Immunocytochemical staining for cyclin D1 was performed on formalin-fixed and paraffin-embedded BM cloths taken at diagnosis. Survival analysis was performed using Cox regression adjusted for important prognostic factors. Results: Positive cyclin D1 staining of plasma cells was found in 47 (48.5%) patients. The median survival (and 95% CI) in the patients with positive cyclin D1 was 3.60 years (2.55, 5.31), and 4.74 years (3.01, 6.42) among cyclin D1 negative patients. The adjusted hazard ratio (HR) for the effect of cyclin D1 was 0.98 (95% CI: 0.60, 1.59). Patients were divided in three groups by BM plasma cell infiltration: <10% (n=19), 10-20% (n=28) and >20% (n=50). Worst survival associated with positive cyclin D1 (compared with negative cyclin D1) was among patients with 10-20% BM plasma cell infiltration (p=0.007 for interaction terms) with HR of 3.71 (1.37, 10.05). Conclusions: There was no overall statistically significant association of plasma cell cyclin D1 positivity with survival. However, in a subset of patients with moderate BM plasma cell infiltration cyclin D1 expression was associated with a raised mortality risk, possibly reflecting variations in diagnostic group by percentage infiltration.

P-55

Silencing of Insulin Like Growth Factor Binding Protein 7 is Linked to Myeloma Tumor Growth, Survival and Bone Disease

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Insulin like growth factor binding protein 7 (IGFBP7) was found to act as secreted tumor suppressor in various solid tumors. More recently, IGFBP7 was shown to play a role in hematological diseases as well. In this study we aimed to characterize the role of IGFBP7 in the pathophysiology of MM. Microarray analysis of BMP signaling antagonists revealed downregulation of IGFBP7 in MGUS (n=22) and MM patient samples (n=329) as well as MM cell lines (MMCLs)(n=17) compared to normal plasma cells (n=10)(P<0.02). IGFBP7 silencing in MM cells was found to be regulated by methylation, confirmed by pyrosequencing and by upregulation of expression after 5-aza-2-deoxycytidine treatment in 4 of 7 MMCLs (P<0.05). Treatment with recIGFBP7 decreased viable cell numbers in 6 of 7 MMCLs tested (P<0.05) accompanied by an upregulation of p21. Furthermore, we observed decreased expression of IGFBP7 in BMSCs after co-culture with MMCLs (P<0.001). Treatment with recIGFBP7 stimulated osteoblast activity up to 1.8 fold (P<0.001). In line with this, we found an association of IGFBP7 expression with myeloma bone disease (P<0.05) in primary MM cells of 61 patients of another series. Furthermore, high IGFBP7 expression correlated with longer OS (median survival 62 vs. 20 months, P=0.06). In conclusion, our data show that IGFBP7 is downregulated in MM cells by methylation, which likely contributes to loss of cell cycle control and enhanced proliferation of myeloma cells. Silencing of IGFBP7 in myeloma and BM stromal cells likely contributes to myeloma bone disease and adverse outcome.

P-56

Autophagy as a Novel Regulator of ER Homeostasis Required for Myeloma Cell Viability.

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Proteasomes and protein homeostasis are valuable therapeutic targets in Multiple Myeloma (MM). We recently reported that normal plasma cells require autophagy for critical containment of endoplasmic reticulum (ER) size, ER stress signaling and Ig production. To gauge its role in myeloma, we characterized a panel of MM lines, revealing remarkable differences in basal autophagic flux. Bortezomib-sensitive lines showed accumulation of insoluble p62, a cargo receptor for selective engulfment of ubiquitinated protein aggregates, denoting insufficient autophagy. We then compared the proteome of two MM lines hallmarked by differential autophagic efficiency by SILAC mass spectrometry. Attesting to a relevant homeostatic function, insufficient autophagy correlated with higher amounts of ER resident and anti-oxidant response proteins. Moreover, pharmacological inhibition of autophagy synergized with bortezomib and overcame bortezomib resistance, implying a crucial cooperation of proteasomes and autophagy. Furthermore, genetic disruption of autophagy was lethal, and resistant populations emerged that displayed significant upregulation of proteasome activity. Finally, we defined p62 as an integrated stress sensor, able to report efficiently on proteasomal and autophagic activity. In particular, its distribution in intracellular aggregates proved a reliable, easy-to-detect predictor of bortezomib sensitivity. Altogether, our data support a crucial role for autophagy in MM, and prompt further studies to identify novel therapeutic targets and predictive single-cell markers.

P-57

CD28 Signaling in Multiple Myeloma Regulates Survival and Antibody Production by Enhancing Metabolism under Cell Stress.

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Multiple myeloma depends upon stromal interactions within the bone marrow microenvironment for survival and antibody production. In order to maintain elevated antibody titers in a nutrient starved environment like that of the bone marrow, myeloma cells must possess a high level of metabolic activity for protein synthesis and proliferation. However, the signaling pathways that regulate metabolism in multiple myeloma are not well characterized. It has been demonstrated that CD28 is expressed on myeloma cells, and we have shown that CD28 signaling in myeloma is necessary for cell survival and sustained antibody production. In T cells, CD28 is known to regulate glycolysis during activation. What is unclear is how CD28 may regulate metabolism in myeloma. Here we demonstrate that CD28-mediated signaling induces glut1 expression and that poisoning glycolysis inhibits proliferation and antibody production in multiple myeloma cells. Interestingly, inhibition of glycolysis inactivates AMPK, a major metabolic sensor responsible for facilitating fatty acid oxidation (FAO). Furthermore, induction of AMPK by AICAR could not rescue the defects induced by glycolytic inhibition and in fact decreased cell viability in the absence of glycolysis, suggesting that multiple myeloma cells require CD28-mediated glycolytic end products for both antibody biosynthesis and oxidative energy production. By understanding the metabolic regulation of myeloma cell survival, proliferation, and function, we may be able target metabolism in myeloma cells for more efficacious therapeutic intervention.

P-58

Metabolomics Identifies Circulating Biomarkers of Multiple Myeloma Development and Progression

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The development of multiple myeloma relies on vicious interactions with the bone microenvironment, a deeper knowledge of which is needed to identify prognostic markers and potential therapeutic targets. To achieve an unbiased, comprehensive assessment of the extracellular milieu of myeloma, we performed metabolic profiling of patient-derived peripheral and bone marrow plasma by UHPLC/GC-MS. In multivariate analyses, metabolic profiling of both peripheral and bone marrow plasma successfully discriminated active disease from control conditions (health, MGUS or remission), and correlated with bone marrow plasma cell counts. Independent disease vs. control comparisons consistently identified a panel of metabolic alterations hallmarking active disease, including increased levels of the complement C3f peptide, HWESASLL, of specific amino acid metabolites, and decreased lysophosphocholines. In vitro tests on cell lines and patient-derived myeloma cells revealed a previously unsuspected trophic function of lysophosphocholines on malignant plasma cells. Our metabolomic study provides relevant information on the complex interactions established by multiple myeloma with the bone marrow environment, and identifies unanticipated

disease markers to develop more accurate early diagnostic strategies.

P-59

AMD3100 Enhances in Vitro Anti-myeloma Activity- a Rationale to Target Bone Marrow Adhesion in Future Myeloma Therapies

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Introduction: The interaction between malignant plasma cells and their microenvironment is central in the pathogenesis of multiple myeloma (MM). Binding of MM cells to bone marrow (BM) stroma cells alters the expression of SDF1 α, its receptor CXCR4 and other adhesion molecules, in turn promoting tumor growth and drug resistance.

Methods: Expression of CXCR4, CD49d, CD11a and CD44 was evaluated in BM samples of MM patients (pts, n=59), MGUS (n=3) and healthy volunteers (HV, n=7) using flow cytometry (see Tab.1) and automated microscopy. Cytotoxic effects of specific anti-MM agents (bortezomib, vorinostat, pomalidomide) were tested with (w) and without (w/o) M210B4 stroma support and w and w/o the CXCR4 inhibitor AMD3100. Experiments were performed using MMCLs (U266, RPMI-8226, L363, NCI-H929), MM-pt BM samples and the T-cell line MOLT-4 as a control. Cell viability was assessed via trypan blue- and annexin V / PI-staining.

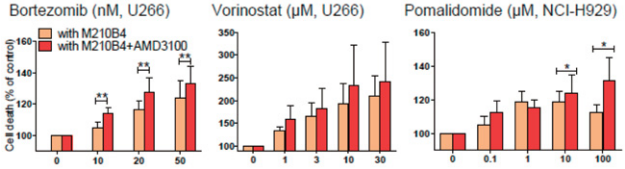
Results: Cytotoxic effects on MMCLs confirmed prior cytotoxic doses of bortezomib, vorinostat and pomalidomide. Cocultivation w stroma substantially reduced apoptosis and induced tumor protective effects. CXCR4 expression was blocked after additional AMD3100 treatment in both MMCLs and primary MM cells. AMD3100 restored sensitivity to drug treatment w/o inducing cytotoxicity by itself (see Fig.1). The expression of CD49d, CD44 and CD11a remained widely unchanged.

Conclusions: Our findings underline the critical role of adhesion and migration molecules in MM and may pave the way for novel therapeutic strategies which also target these accessory mediators.

Table 1. Expression of adhesion and stem cell markers in MM vs. MGUS vs. HV and correlation w the extent of BM infiltration (BM-inf)

CD marker	Spearman Correlation Coefficient (w BM-inf) p-value		Kruskal Wallis p-value HV vs. <5% vs. 6-49% vs. >50% BM-inf	Kruskal Wallis p-value HV vs. MGUS vs. MM
Positive correlation				
CXCR4+/CD138+	0.48	<0.0001	0.0010	0.0763
CXCR4+	0.21	0.1067	0.0652	0.0292
CD49d+/138+	0.54	<0.0001	0.0002	0.0045
CD44+/138+	0.56	<0.0001	0.0003	0.0238
CD45-/CD38+	0.49	<0.0001	0.0001	0.0023
Negative correlation				
CD34+	0.23	0.0217	0.0015	0.0136
CD45+	0.33	0.0008	0.0001	0.0001
CD45+/38+	0.099	0.3312	0.0362	0.1969

Figure 1. Viability (% of control) of MMCLs (U266, NCI-H929) in vitro after treatment with bortezomib, vorinostat and pomalidomide for 72h in presence of M210B4 coculture with and without AMD3100 (PI-method, n=3, * P<0.05, **P<0.01, ***P>0.001)



P-60

Effect of DNA Dosage into Gene Expression in Patients with Multiple Myeloma

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Whole genomic methods represents effective tool for studying genomic changes in cancer cells. Aim of this study was to find and describe genes whose expression is dependent on the DNA copy number (gene dosage) in patients with multiple myeloma. Total of 57 patients with MM were simultaneously examined by arrayCGH for DNA copy number variations (gain/losses) utilizing Agilent Human Genome CGH Microarray 4x44K Arrays and for gene expression utilizing Affymetrix GeneChip Human Gene 1.0 ST. Gene dosage-dependent genes were defined by Spearman correlation[R>0.5, p(FDR)<0.05]of CNV status and expression level and analysed using DAVID Bioinformatics software.

Total of 852 fromall 27391 transcripts were strongly and significantly dependent ongene dosage. Cytogeneticaly, majority (25%) of all 852 genes were located on chromosome 1 (with 19 genes mapped to 1q21 locus). Other involved genes were mostly located on chromosomes 15 (8.7%), 19 (8.7%), and chromosome 13 (8.6%). Pathway analysis showed most genes to be involved in PDGF pathway, ubiquitin proteasome pathway, Ras pathway and TNFR1 signaling pathway.

Although almost all chromosomes have been at least once affected by either gain or loss of genetic material, number of genes with affected exrrpession is relatively low. We anticipate two mechanism for expression level compensations: i)

increase of related supressors activity in case of gains ii) impact of second allele in case of losses.

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Section B: Bone Disease (including Imaging)

P-61

A Comparative Imaging Study of Multiple Myeloma; FDGPET, Methionine PET and Thiothymidine PET

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[Objective] FDG-PET/CT is known to be more accurate to localize active myeloma lesions than other imaging modalities. 11C-methionine (MET)-PET, reflecting the increased protein production in myeloma cells, may be useful for active myeloma lesions. [methyl-11C]4' -thiothymidine(4DST) is a tracer for DNA synthesis, reflecting in vivo cell proliferation (J Nucl Med 2012;53:199). 4DST-PET may detect myeloma cell's proliferation. To search better imaging methods for active myeloma, we compared three PET studies to CT, and to aspiration cytology. [Methods] 1. 55 focal lytic lesions of 24 patients by CT were examined by FDG, MET and 4DST-PET. The tracers accumulation were visually evaluated. 2. 29 patients who had aspiration cytology results (positive or negative) of sacroiliac joint were evaluated by accumulation of FDG, MET and 4DST in the lesions. [Results] 1. The tracers accumulation in lytic lesions by CT were, 33 positive, 10 equivocal, 12 negative by FDG-PET, 39 positive, 3 equivocal, 13 negative by MET-PET, 40 positive, 1 equivocal, 14 negative by 4DST. 2. Compared to cytology, PET showed sensitivity (73% by FDG, 91% by MET, 91% by 4DST) , specificity (78%, 78%, 72% respectively), positive predictive value (67%, 71%, 67%), negative predictive value (52%, 93%, 93%), and overall accuracy (76%, 83%, 79%). [Conclusions] MET & 4DST-PET detected active lesions of MM among the lytic lesions by CT more clearly than FDG-PET. The sensitivity by MET-PET and 4DST-PET were higher than FDG-PET. In addition to FDG, MET or 4DST-PET provide better characterization of MM.

P-62

p38 MAPK in Myeloma Cells Induces Bone Destruction

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p38 mitogen-activated protein kinase (MAPK), which is constitutively activated in human myeloma, has been implicated in bone destruction by this cancer, but the processes it recruits are obscure. In this study, we show that p38 activity in myeloma inhibits osteoblast differentiation and bone formation but also enhances osteoclast maturation and bone resorption. p38 regulated the expression and secretion of the Wnt pathway antagonist DKK-1 and the monocyte chemoattractant MCP-1. Attenuating p38, DKK-1 or MCP-1 were each sufficient to reduce bone lesions in vivo. Although it is well known that DKK-1 inhibits osteoblast differentiation, we found that together with MCP-1, it could also promote osteoclast differentiation and bone resorption. The latter effects were mediated by enhancing expression of RANK in osteoclast progenitor cells and by upregulating secretion of its ligand RANKL from stromal cells and mature osteoblasts. In summary, our study defined the mechanisms by which p38 signaling in myeloma cells regulates osteoblastogenesis, osteoclastogenesis, and bone destruction. Our findings, which may have implications for bone invasion by other cancers where p38 is elevated, strongly suggests that targeting p38 for inhibition might offer an effective therapeutic approach to treat osteolytic bone lesions in patients with myeloma.

P-63

Second Primary Cancers in Patients with Multiple Myeloma and Monoclonal Gammopathy of Unknown Significance

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The exact frequency of PET/CT incidental detection of additional primary cancers during evaluation of MM is not well known. Purpose of this study was to evaluate PET/CT using [18F] fluorodeoxyglucose (FDG) in detecting a second primary cancer at the time of diagnosis and initial staging of MM and MGUS. Methods: A total of 240 patients with MM and 92 patients with MGUS were enrolled in the study. All patients underwent 18F- FDG PET/CT examination at the time of intial paging for MM or MGUS before any therapy. Routine diagnostic tests including biochemistry, conventional radiograpphy and ultrasound examination were done. Results: A total of 9 second primary malignant tumors were identified in group of 240 MM patients (5%). PET/CT found focal lesions indicative of a second primary cancer, which were not detected by routine examination and staging of MM. Second primary cancers included: 3 patients with carcinoma of thyroid gland, 3 patients with carcinoma of colon, 1 patient with carcinoma of breast, 1 patient with carcinoma of lung, 1 patient with lymphoma. In one patient with MM dwou oter cancers were detected, carcinoma of kidney an carcinoma of coln. In group of 92 patents with MGUS were no other primary cancers detected.All patiens were succesfully treated and because their disese was diagnosed early. Conclusion: PET/CT is useful for screening a second primary cancer with a high sensitivity. Second clinically asymptomatic cancers were detected in 5% of MM patiens. All these unexpectedly detected cancers were succesfully treated. Supported by grant IGA MZ CR NT 12215-4/2011

P-64

Vertebral Fracture Risk of Multiple Myeloma Assessed by a CT-based Finite Element- and Trabecular Structure Analysis

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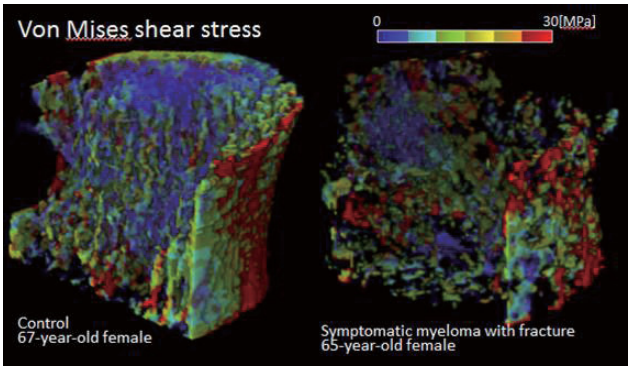
Purpose: By using microstructural analysis and finite element modeling based on MDCT, the purpose of our study was to compare trabecular properties in myeloma with different clinical stage and control subjects and assess fracture risk of vertebral bone. Materials and Methods: We examined trabecular properties in patients with MGUS (n=20), asymptomatic myeloma (n=26), symptomatic myeloma without spinal fracture (n=25), symptomatic myeloma with spinal

fracture (n=22), and 90 controls by using a 64-detector CT. Microstructural and mechanical properties of L3 vertebral bodies were compared between the five groups using post hoc test. Multivariate regression model was constructed to identify the best predictors that differentiated between patients with- and without vertebral fracture. To evaluate the diagnostic performance of significant contributors to fracture, comparisons of the receiver operating characteristic (ROC) curves were performed. Results: Multivariate regression analysis demonstrated that failure load and apparent trabecular width (app Tb.W) in male patients and failure load in female patients contributed to risk for pathologic fracture when comparing with non-fractured myeloma patients. Area under the curves were 0.91 for failure load and 0.90 for app Tb.W for male patients. Conclusions: Our results demonstrate that images from clinical 64-detector CT can be used to create finite element models capable of distinguishing unfractured from fractured vertebrae in patients with multiple myeloma.



P-65

Dynamic Contrast-enhanced MRI Parameters are Correlated to Parameters of Disease Activity MGUS and Multiple Myeloma

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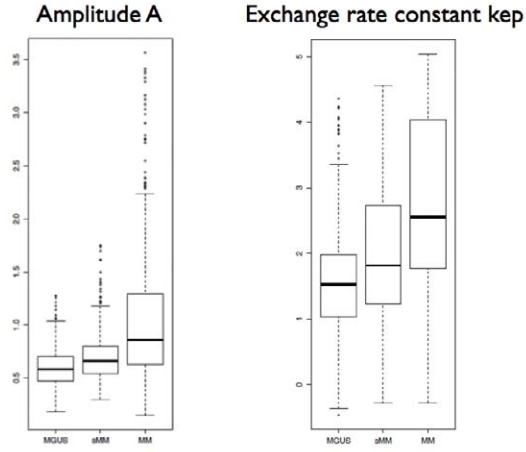
Bone marrow microenvironment is an important pathophysiologic and prognostic factor in monoclonal plasma cell diseases. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive tool to display microcirculation. In a prospective study we examined 33 healthy controls and 289 untreated patients with monoclonal gammopathy of undetermined significance (MGUS n=68); smoldering myeloma (sMM n=89) and symptomatic myeloma (MM n=132) with DCE-MRI of the lumbar spine. The parameters amplitude (A) reflecting the maximum blood flow and exchange rate constant (kep) linked to vascular permeability were compared between the 3 patient groups and correlated to parameters of disease activity. The analysis revealed significant differences of both MRI-parameters between MGUS, sMM and MM patients ((ex)p<0.001 respectively) with an increase of the parameters from MGUS over sMM to MM. SMM and MM (Fig. 1) but not MGUS patients showed significantly different values compared to controls. Amplitude A was positively correlated to beta2 microglobulin ((ex)p<0.001), high riskcytogenetics (p=0.009), immunoparesis ((ex)p<0.001) and negatively correlated to albumin ((ex)p<0.001), hemoglobin ((ex)p<0.001) and age ((ex)p<0.001). These preliminary data show that DCE-MRI is able to display increasing bone marrow microcirculation from MGUS over sMM to MM and that the DCE-MRI parameters are significantly correlated to other characteristics of disease activity and prognostic factors. Analyses of the prognostic significance of the data are currently in progress.



P-66

Prognostic Significance of a Gadolinium Contrast Agent for Survival and Renal Function in Patients with MGUS and Myeloma

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Magnetic resonance imaging (MRI) is increasingly applied in the diagnostic work-up of patients with monoclonal plasma cell diseases. Recent data suggested that Gadolinium-based contrast agents commonly used in MRI promote plasma cell growth in vitro and in vivo. To investigate the clinical significance of these data we retrospectively compared survival and renal function of 323 patients with symptom-

atic myeloma (MM), 154 patients with smoldering myeloma (sMM) and 148 patients with monoclonal gammopathy of undetermined significance (MGUS) who were examined with MRI either with (n = 290) or without (n = 324) the gadolinium containing contrast agent Gadopentetat-Dimeglumin. For progression free survival no significant difference between the 2 groups was found respectively (P = 0.49 for MM; P = 0.45 for sMM and P = 0.65 for MGUS). In systemically treated MM patients with an initial MDRD lower than 60 ml/min/1.73m2 who had not received the Gadolinium-based contrast agent renal function had significantly improved after one year while it had not in the group who was examined with contrast medium (P = 0.03). We conclude that the application of the contrast agent Gadopentetat-Dimeglumin does not have an adverse prognostic significance in terms of PFS and OS for patients with monoclonal plasma cell disease. However, an improvement of renal function after systemic therapy in patients with a low MDRD at baseline was suppressed by the application of the contrast medium.

P-67

Severity of Osteoporosis in Multiple Myeloma and the Prognostic Role of Lumbar Spine QCT

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Aim: To determine the frequency and severity of osteoporosis in patients with multiple myeloma and its relationship with disease activity. Design: Prospective single centre study. Methods: 108 consecutive patients with biopsy-proven multiple myeloma were evaluated over a 10-year period. The data collected comprised of clinical demographics, serum biochemistry, paraprotein estimations, bone resorption markers, spinal radiography and bone densitometry (DXA: dual-energy X-ray absorptiometry and QCT: quantitative computed tomography). Patient data was expressed as mean + 1 SD. Relationship between BMD and variables of myeloma activity was assessed using regression multivariate analysis. Results: There were 56 men and 52 women with a mean age of 69 years. 35% (n=36) presented with stage III disease. The mean lumbar spine QCT T-score = minus 3.3, lumbar spine DXA T-score = minus 2.1 and femoral neck DXA T-score = minus 1.4. Osteoporosis as defined by lumbar spine QCT T-score lt -2.5 occurred in 57% (n=62) of patients. There was no correlation between the lumbar spine QCT and either serum calcium, paraprotein or Hb. The lumbar spine QCT was a major independent variable contributing to myeloma-related deaths (chi square=12.63, P=0.02). Conclusions: Although osteoporosis is frequent in myeloma, the value of lumbar spine QCT in this condition is not fully appreciated. This study suggests that lumbar spine QCT T-scores are markedly reduced in myeloma and may contribute independently to both the morbidity and mortality of the disease.

P-68

Can IDEAL-MR Imaging of Multiple Myeloma be Used as a Biomarker for Predicting Symptomatic Myeloma?

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Purpose: To evaluate the effectiveness of the iterative decomposition of water and fat with echo asymmetric and least-squares estimation (IDEAL) MRI to predict symptomatic myeloma without visible focal lesions. Materials and Methods: The lumbar spine was examined with 3T-MRI in 47 patients with multiple myeloma (MGUS + asymptomatic myeloma, 23; symptomatic myeloma, 24). The fat-signal fraction (FSF) was calculated as the mean value from three vertebral bodies. For data analysis, univariate and multivariate logistic regression analyses, as well as receiver operating characteristic (ROC) curves were used. A difference with P < .05 was considered significant. Results: Univariate analysis results demonstrated that MRI signal pattern on T1-weighted image, FSF, the proportion of plasma cells in the bone marrow, the serum monoclonal protein level, the reduction in uninvolved immunoglobulins, β2-microgrobulin (β2m), and β2m/albumin ratiowere significantly associated with symptomatic myeloma. Results of multivariate analysis demonstrated that β2m, FSF, and the reduction in uninvolved immunoglobulinshad significant effects in differentiation between non-symptomatic and symptomatic patients. Area under the curves were 0.793 for the fat-signal fraction and 0.844 for the β2m. Conclusions: Fat quantification using the IDEAL sequence in MRI was significantly different when comparing patients with symptomatic myeloma and those with asymptomatic myeloma. The fat-signal fraction and β2m facilitated discrimination of symptomatic myeloma from non-symptomatic myeloma.

P-69

The Diagnostic Value of 18F-FDG PET/CT in Older Patients with Transplant-ineligible Multiple Myeloma

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The value of 18F-FDG PET/CT in diagnosis and follow up of multiple myeloma (MM) has been demonstrated predominantly for younger patients eligible for autologous stem cell transplantation. In the present study, we evaluated the diagnostic value of 18F-FDG PET/CT in 36 untreated patients with symptomatic MM, of whom 81% were age over 65. The patients were diagnosed as symptomatic MM between January 2009 and September 2012. Fifteen were male and 21 were female with median age of 71 (47-79). The number of the patients with IgG, IgA, BJP and non-secretory types were 26, 6, 1, and 3, respectively. The serum levels of CRP (mg/L), LDH(IU/L), and B2MG(mg/L) were 2.5(0.2-84), 183(103-562) and 4.2(1.6-17.8), respectively. Abnormal uptake of 18-F FDG was found in 86% of the patients. For these patients, 42% had >3 focal lesions (FLs), 39% had diffuse lesions (DLs), and 11% had extramedullary diseases (EMDs), according to the classification proposed by Zamagni et al (Blood. 2011;118:5989-). A median SUV of these lesions was 6.3 in total (1.7-17.3), with increment in accordance with disease progression (2.2 in patients with 1 to 3 FLs, 4.8 with >3FLs and/or DL, and 8.8 with EMDs). Compared with the previous reports with younger populations, our patients seemed to have more progressed diseases with >3 FLs and higher SUVs, although serum levels of CRP, LDH, and B2MG were lower than those in the previous reports. The treatment outcomes of these patients are now under investigation.

P-70

Diffusion-weighted Magnetic Resonance vs Skeletal X-ray and Magnetic Resonance of the Spine in Multiple Myeloma

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Diffusion-weighted (DW) magnetic resonance (MR) is a functional MR that detects water diffusion through cells. This prospective study compared whole-body (WB) DW-MR with skeletal X-ray (XR) and MR of the spine (MRS) in symptomatic multiple myeloma (MM) patients. The aims were to assess whether DW-MR could detect more focal lesions (FL) than XR and MRS, to correlate FL with response and survival, and to compare DW-MR with conventional WB-MR. XR, MRS, DW and WB-MR were done at enrolment (time 1, T1), after treatment (T2), and 6 months after treatment (T3). MR exams were done in one 45-minute session on a 1.5 T scanner. DW-MR consisted of multiple stacked axial EPI sequences, evaluated by MIP and MPR reconstructions at 4 b-values (maximum b value=1000). 36 symptomatic pts with newly diagnosed (43%) or recurrent MM (57%) were enrolled. At T1, the DW-MR detected more FL than XR ($p<0.01$), MRS (trend, $p=0.08$) and WB-MR ($p=0.02$). At T2, DW-MR detected similar FL than XR and MRS ($p=0.99$, $p=1.00$), and more than WB-MR ($p=0.01$). At T3, the DW-MR detected similar FL than XR ($p=0.27$), and more FL than MRS ($p=0.05$) and WB-MR ($p<0.01$). Overall, DW-MR detected more FL than XR, MRS and WB-MR ($p=0.01$, $p=0.02$, $p<0.01$). FL number by DW-MRI and MRS at T2 correlated with response ($p=0.04$ both), XR and WB-MR did not ($p=0.55$, $p=0.13$). DW-MR detected a median of 4 FL at T1. Pts with <=4 FL had better PFS (72 vs 50% at 2 years, $p=0.02$) than those with >4 FL. In conclusion, DW-MR detects more FL than XR, MRS, and WB-MR in symptomatic MM (table 1), predicts PFS, and correlates with response to treatment.

Table 1. Focal bone lesions detected by DW-MR, XR, MRS and WB-MR

	Whole-body exams						Spine exams		
Timepoint	DW-MR	XR	p	DW-MR	WB-MR	p	Spine DW	Spine MR	p
1	306	117	0.005	306	225	0.02	165	116	0.08
2	97	104	0.99	97	60	0.01	20	20	1.0
3	88	62	0.27	88	45	0.003	24	11	0.05
Overall	491	283	0.01	491	330	<0.0001	209	147	0.02

Abbreviations: DW-MR=whole body diffusion-weighted-magnetic resonance imaging; XR=full skeletal X-ray; WB-MR=whole-body MR.

P-71

Selective Histone Deacetylase 6 Inhibition Shows a Beneficial Effect on Multiple Myeloma (MM) Bone Disease

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Histone deacetylase (HDAC) 6, in addition to its cytoplasmic actions, binds Runx2 in the nucleus and represses its activity, thus affecting osteoblast (OB) differentiation. Here we evaluated the role of HDAC6 on bone turnover in the context of MM bone disease. Micro-CT analysis on the femurs of HDAC6 knockout (KO) mice showed an increase in trabecular and cortical bone. Moreover, markers of bone formation were slightly increased in bone marrow stromal cells (BMSC) isolated from the KO mice compared to wild-type (WT). Importantly, when murine MM cells were cultured with KO vs WT BMSC-derived OB, a decrease in MM cell migration was observed, suggesting that a microenvironment lacking HDAC6 reduces MM cell migration. To further evaluate the role of HDAC6 inhibition, we used a selective HDAC6 inhibitor ACY-1215 (Acetylon Pharmaceuticals). ACY-1215 in combination with bortezomib has shown potent anti-MM activity in preclinical studies. Here we show that ACY-1215, alone and in combination with bortezomib, both enhanced OB differentiation in MM patient-derived OB as well as inhibited osteoclasts differentiation and function. Using the xenograft model of disseminated human MM cells in SCID mice, we observed a decrease in markers of bone resorption and an increase in markers of bone formation in the serum of the combination treated cohort. Cells isolated from the calvaria from the combination treated group showed a significant increase in mRNA expression of markers of bone formation. These results indicate a potential beneficial role of HDAC6 inhibition on MM-related bone disease.

P-72

Diagnostic and Prognostic Implications of Spine Magnetic Resonance Image at Diagnosis in Patients with Multiple Myeloma

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We prospectively evaluated the diagnostic and prognostic implications of whole-spine MRI at the time of diagnosis in patients with multiple myeloma. Patients who were newly diagnosed with multiple myeloma between 2004 and 2011 at Chungnam National University Hospital were enrolled. A total of 113 patients with a median age of 65 (range, 40-89) years were enrolled in the study. Pathological fractures that were not detected in the bone survey were found in 26 (23.0%) patients, including three (2.6%) patients with no related symptoms or signs. Extramedullary extension of the plasmacytoma was detected in 22 (19.5%) patients, including 15 (13.3%) with epidural extension of the tumor. Of these 22 patients, 11 (50.0%) had no relevant symptoms or signs. The presence of pathological fractures did not influence overall survival, whereas non-epidural extramedullary extension of the plasmacytoma was associated with poor overall survival in multivariate analysis (HR 3.205; 95% CI, 1.430-9.845; P = 0.042). Of the 113 patients, 35 had a diffuse infiltrative pattern, 39 had a micronodular pattern, 15 had a macronodular pattern, 17 had the mixed type, and 7 appeared normal. During follow-up for a median of 21 (range 1-91) months, the overall survival of patients with the mixed type (median 24.0 months; 95% CI, 22.9-25.1) was shorter compared to those with other patterns (median 56 months; 95% CI, 48.9-63.1) (P = 0.030). These results indicate that spine MRI should be included in the initial diagnostic investigations for patients with multiple myeloma.

P-73

Successfully Induced Osteogenesis from Adipose Mesenchymal Stem Cells of Myeloma Patients Had Intensive Therapy

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Introduction Despite the therapeutic advances, bone repair in multiple myeloma(MM) remains unachievable, a problem that may result from impaired osteoblastogenesis of bone marrow mesenchymal stem cells(BM-MSC) caused by MM and/or the anti-MM therapy. In this study, we induced osteoblastogenesis in both adipose-derived MSC(Ad-MSC)

and paired BM-MSC to explore the potential of Ad-MSC as an alternative source for bone repair. Materials & Methods Ad-MSC from gluteal subcutaneous fat and paired BM-MSC were obtained simultaneously from 10 patients who had received bortezomib-based induction and autologous stem cell transplantation(AuSCT). Ad-MSC from 4 healthy donors were used as control. MSC were identified by flow-cytometry. The capacity of proliferation was measured by doubling time(DT), and that of osteoblast differentiation, by Alkaline Phosphatase(ALP) activity. Gene expression levels were measured by Q-PCR. Results The proliferation capacity of patients' Ad-MSC were similar to that of control(DT 31.5 ± 4.5 and 30.2 ± 1.9 hr, respectively), whereas it was worse in paired BM-MSC(120.6 hr, p=0.09). Patients' BM-MSC also had worse differentiation capacity than Ad-MSC did by their inferior ALP activities(0.5 vs. 2.1 ng/ml, p=0.007). The expression levels of ALPL and COL1A1, two bone-formation related genes, were also higher in Ad-MSC than in BM-MSC. Conclusion Though the osteoblastogenesis capacity of BM-MSC is impaired, that of Ad-MSC is reserved even after intensive anti-MM therapy. Ad-MSC, a MSC outside the BM, could be an alternative source of cell therapy for MM bone disease.

P-74

TLR Signaling in hMSC/Osteoblasts Up-regulates Cytokines Promoting Osteoclast Activation and MM-cell Growth

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Toll-like receptors (TLRs) act as sensors for infectious agents. They also recognize host-derived stress signals such as heat shock proteins and extracellular degradation products. In multiple myeloma, infectious agents and endogenous ligands released due to cellular stress in the bone marrow microenvironment can potentially activate TLRs. Objective To investigate the effect of TLR1/2, TLR3 and TLR4 signaling on the cytokine profile and the expression of RANKL/OPG in human mesenchymal stem cells (hMSC). Methods Bone marrow derived human mesenchymal stem cells from 4 different donors were treated with TLR agonists in osteogenic media for one to four days. Cytokine levels in conditioned media were quantified by multiplex assay or ELISA. mRNA expression of cytokines, RANKL and OPG were evaluated by real time PCR. Results We found that human bone marrow derived MSCs treated with the TLR3 agonist polyinosinic-polycytidylic acid (poly(I:C)), a dsRNA analog, or the TLR4 agonist LPS increased the mRNA expression of RANKL. In three out of four donors TLR3-signaling reduced the OPG mRNA expression, thereby changing the RANKL/OPG ratio into a more bone destructive state. Both TLR3 and TLR4 activation increased the expression of MIP1 α , MIP1 β , IL-17 and other pro-osteoclastogenic cytokines, as well as IL-6 known to support survival of MM cells. Conclusion Activation of TLRs increases the expression of RANKL and pro-osteoclastogenic cytokines. Thus, increased levels of TLR agonists in bone marrow of MM patients may indirectly promote osteoclast activation and growth or survival of MM cells.

P-75

Abnormal Medullary Lesions in Appendicular Skeletons on Whole-body CT, High Tumor Burden and Poor Prognosis in Myeloma

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BACKGROUND: This study was performed to determine the incidence and prognostic implications of abnormal medullary lesions (AMLs) in appendicular skeletons (AS) detected by whole-body, low-dose, multidetector computed tomography (WBLD-MDCT) in patients with multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS). PATIENTS AND METHODS: Between January 2008 and July 2012, WBLD-MDCT was performed in 89 patients with MGUS, asymptomatic and symptomatic MM. AMLs were evaluated and the CT values (CTV) of the humerus and femur were measured. The results were compared between MGUS/asymptomatic MM and symptomatic MM. The prognostic implications of CTV in patients with symptomatic MM were also examined. RESULTS: AMLs were detected much more frequently in patients with symptomatic MM than MGUS/asymptomatic MM (83.6% vs. 25%, $P < 0.001$). Mean CTV of symptomatic MM patients was significantly higher than that of MGUS/asymptomatic MM patients (-5.64 vs. -69.99, $P < 0.001$). Symptomatic MM patients with mean CTV > 0 had significantly shorter median overall survival (OS) (40.6 months vs. not reached, $P = 0.040$) than those with mean CTV < 0. In univariate analyses, Cr > 2.0 and CTV > 0 were relevant to survival outcome. On multivariate analysis, CTV > 0 remained marginally significant ($P = 0.054$) on OS. AMLs disappeared completely in 36% (4 of 11) of patients who obtained CR, and clinical relapse was observed only in patients with residual AMLs. CONCLUSIONS: AMLs in the AS in patients with MM reflect high tumor burden and are probably related to high risk of disease progression.

P-76

Bone Turnover in Myeloma: Impact of Novel Agents on Osteoblast and Osteoclast Function within the GMMG-MM5 Trial

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AIM. Evaluation of the impact of bortezomib-based induction treatment, high-dose therapy, and lenalidomide consolidation on alterations of bone turnover, i.e. surrogates of osteoblast- (osteocalcin, OC) and osteoclast- (collagen type I fragments, CTX-I) function,and their induction by myeloma cells (DKK1-level). METHODS. Within the GMMG-MM5 trial (EudraCT 2010-019173-16), serum levels of CTX-I, OC, and DKK1 were assessed by ELISA at inclusion (n=365), after induction therapy with either PAd (n=88) or VCD (n=84), stem cell mobilization using CAD (n=69), high-dose melphalan (n=92), and 2 months lenalidomide consolidation (n=92). DKK1 levels were correlated with the expression in CD138-purified myeloma cells (Affymetrix microarrays, n=365). RESULTS. Prior to treatment, CTX-I levels are increased, those of OC decreased compared to healthy donors (uncoupled bone turnover). DKK1 protein levels are increased and correlate with DKK1-expression in myeloma cells. After induction therapy, osteoclast activity (CTX-I) is decreased below normal values. PAd unlike VCD further decreases osteoblast activity (OC-levels); DKK1-levels are normalized. Subsequent treatment further decreases DKK1-levels below normal values andblocks osteoclast function. After 2 months lenalidomide consolidation, no normalization of osteoblast activity is found. CONCLUSION. The main impact on bone turnover by bortezomib-based induction treatment is a reduction of osteoclast activity alongside a decrease in DKK1-levels. During the reported period, no normalization of decreased osteoblast function was observed.

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The Novel VDR Co-activator, TAF12 Enhances Tumor Cell Growth and Osteoclast Formation in Myeloma

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Vitamin D regulates normal cell differentiation, proliferation, skeletal homeostasis and tumor growth, but its role in multiple myeloma (MM) is not clear. We found that in contrast to other tumors, physiologic levels of vitamin D significantly contributes to myeloma bone disease (MBD) due to increased sensitivity of both MM and bone cells to 1,25-dihydroxyvitamin D_3 (Vit.D). The enhanced Vit.D sensivity results from expression of a novel vitamin D receptor co-activator TAF12, which is highly expressed in $CD138^+$ primary MM cells and marrow stromal cells (BMSC) from patients compared to their nomal counterparts. Treatment with low doses Vit.D increased expression many of the genes involved in tumor growth and bone disease including $\alpha 4$-integrin, VEGF, and RANK ligand (RANKL) in MM cells and VCAM-1, the receptor for $\alpha 4\,\beta 1$, and RANKL in BMSC. Vit.D induced VCAM-1 and $\alpha 4$-integrin expression was NF κB-dependent. The induction of VCAM-1/ $\alpha 4\,\beta 1$ resulted from increased stromal cell/MM cell adhesive interactions that enhanced MM cell growth. Increased RANKL production by MM cells markedly enhanced MM support of osteoclast (OCL) formation. Knockdown of TAF12 in MM cells or BMSC blocked Vit.D-dependent increases in expression of these genes and the enhanced MM cell growth and OCL formation seen in response to VitD. These results suggest that TAF12 is a novel therapeutic target to block the increased cytokine production and adhesive interactions induced by Vit.D in MM cells and BMSC that enhance tumor growth and OCL formation.

P-78

CC-292: a Novel Bruton's Tyrosine Kinase Inhibitor +/- Carfilzomib Impacts Bone Resorption in Multiple Myeloma

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The activation of BTK regulates B-cell development and activation. BTK and the other Tec kinase family member, Tec, regulate osteoclast (OC) differentiation via RANK signaling.

Here, we show that a specific inhibitor of BTK, CC-292 inhibits OC function in MM patients. We examined the effect of CC-292 on MM patient derived OC and observed that OC function was inhibited in the presence of CC-292; however, markers of OC differentiation were increased, suggesting that CC-292 inhibits OC function without affecting OC differentiation.

Given the role of Proline-rich tyrosine Kinase 2 (Pyk2) signaling in sealing zone formation and OC function, we investigated the effect of CC-292 on Pyk2. Interestingly, CC-292 inhibited Pyk2 signal activation and OC sealing zone formation.

We next evaluated the effect of the novel proteasome inhibitor, carfilzomib (CFZ), on OC sealing zone formation and OC differentiation. CFZ did not impact OC sealing zone formation, but significantly inhibited OC differentiation. CC-292+CFZ inhibited both sealing zone formation and OC differentiation, resulting in a more profound suppression of OC function than CFZ alone. Ongoing studies are testing the combination of CC-292 and CFZ in a diffuse NOD Scid MM model and data on effects on tumor and the bone microenvironment will be presented.

Our preliminary data demonstrate that the novel BTK inhibitor CC-292 inhibits OC function via OC sealing zone formation inhibition. Moreover, CC-292+CFZ augments effects against OC and has promising therapeutic potential for the treatment of MM and its related bone disease.

P-79

hMSCs in Mineralized Alginate Beads: A Potential New Tool to Study Interactions between Osteocytes and Myeloma Cells

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Increased osteocytic cell death has been suggested to play a role in myeloma bone disease. However, due to difficulties in culturing and differentiating osteocytes *in vitro*, the interactions between myeloma cells and osteocytes have been scarcely studied. Aim: to develop a biopolymer/hydroxyapatite scaffold that can support growth and differentiation of bone and myeloma cells. Methods: human mesenchymal stem cells (hMSCs) were encapsulated into alginate beads mineralized using calf intestinal ALP to generate a scaffold mimicking the composition of bone. In a separate experiment ANBL-6 cells were encapsulated together with hMSCs. All cells were induced to differentiate in osteogenic direction by adding BMP-2. Results: hMSC in mineralized beads survived and sustained metabolic activity for a period of 21 days *in vitro* as evaluated by live dead staining and alamar blue assay. hMSC in beads expressed higher mRNA levels of type I Collagen, Runx2 and Osterix compared with cells on plastic. Moreover, cells in beads expressed DMP1, a marker for late osteoblasts/osteocytes, whereas cells on plastic did not, suggesting that beads support osteocyte differentiation (Figure 1). ANBL-6 cells survived for 21 days in co-culture with hMSCs inside the scaffolds. Conclusion: hMSC can successfully be differentiated into fully mature osteoblasts/osteocytes in mineralized alginate beads, and myeloma cells can successfully be cultured together with these. Hence, mineralized alginate beads have the potential to enable the study of osteocytes and myeloma cells in a 3D environment mimicking bone.

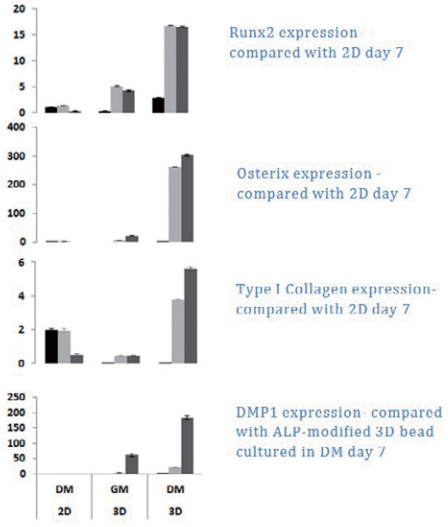

Figure 1 Relative expression of osteoblast/ osteocyte markers after culturing hMSCs in ALP-modified alginate beads or in regular 2D culture. Samples were cultured in either growth medium (GM) or differentiation medium (DM) for 21 days post encapsulation.

P-80

Quantitative In-vivo Monitoring of Bone Formation in Multiple Myeloma Patients after Bortezomib Treatment: a Pilot Study

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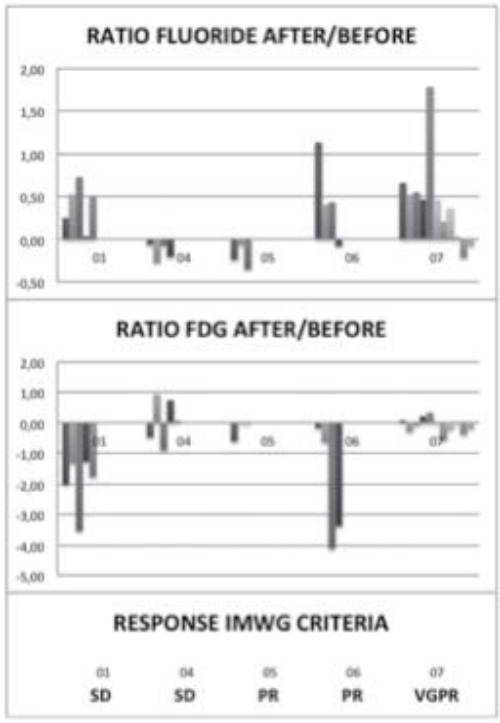
Background: Bone formation is suppressed in multiple myeloma (MM). In vitro data and bone markers suggest that bortezomib stimulates bone formation. However, information on in vivo bone formation is scarce. The gold standard for quantification of bone formation is the mineral apposition rate (MAR) in non-decalcified bone biopsies. A non-invasive alternative could be 18F-Fluoride(18F)-PET. Objective: To validate the ability of 18F -PET scan for quantitative measurement of bone formation in MM patients by comparing the standardized uptake value (SUV) with the MAR and to evaluate the effect of bortezomib on bone remodelling. Methods and Results: 18F -PET-CT, FDG-PET-CT and bone biopsies were performed in 5 patients before and after bortezomib treatment. A strong correlation between the Fluoride uptake of the spina iliaca posterior and the MAR was found (Spearman's coefficient 0.762, p=0.028). There was an inverse correlation between change in Fluoride uptake and response either defined by FDG-PET (patients 01, 04 and 06) or IMWG criteria (patient 07)[figure]. In patient 05 we could not find an increased Fluoride uptake after treatment because of a very high pre-treatment SUV of 40 (reference levels of normal bone: 1.49 ± 1.39) due to rib fractures. Conclusion: The significant correlation between 18F -PET and MAR, indicates that 18F -PET can replace the invasive gold standard for quantification of bone remodelling. 18F -PET showed an increase in bone formation after bortezomib treatment. Whether this is independent of response remains to be determined.

Figure



Inverse correlation of change in Fluoride uptake and response either defined by FDG-PET-CT or IMWG criteria

P-81

A Systematic Review of the Diagnostic Accuracy of Modern Imaging Techniques in Establishing Myeloma Related Bone Disease

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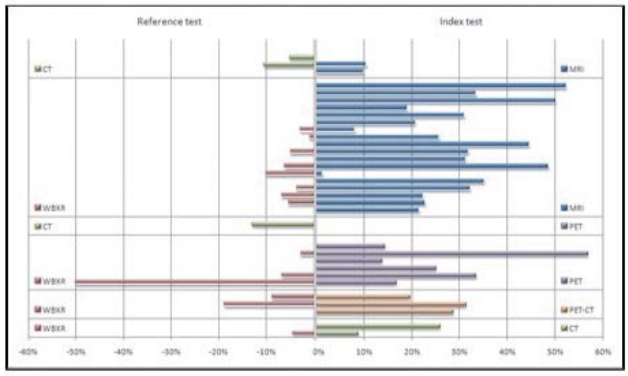
Purpose: We performed a systematic review of studies comparing MRI, FDG-PET, FDG-PET-CT and CT as an index test with Whole Body X-Ray (WBXR) or CT as a reference test in order to provide evidence-based diagnostic guidelines in MM bone disease. Materials and methods: A comprehensive search in 3 bibliographic databases was performed. Methodological quality was assessed using QUADAS criteria (score 1-14). Sensitivity and specificity of the index tests were calculated using STATA software. A descriptive analysis of the detection rate was performed. Results: Data from 32 directly comparative studies were extracted, of whom 3 concerned CT, 22 MRI and 11 FDG-PET(-CT) as an index test. The reference test was either WBXR (n=29) or CT (n=3). The mean QUADAS score was 7.1 (3-11), with quality hampered mainly by a poor description of selection and execution criteria. All index tests had a higher detection rate when compared to WBXR, with up to 82% more lesions detected by the newer imaging techniques; as reflected by figure 1. However, modern imaging techniques detected fewer lesions in the skull and ribs. In a direct comparison CT and MRI perform equally with respect to detection rate, sensitivity and specificity. Conclusion: This systematic review supports that MRI can replace WBXR in the diagnostic work-up of myeloma patients. In our opinion, due to the equal performance, WBCT is a valuable alternative as well. Since lesions of skull and ribs are underdiagnosed by the modern imaging techniques we advise additional X-rays of these regions.

Figure
Differences in detection rate between reference and index tests



The left side of the figure depicts the percentage of lesions that was only detected by the reference test (CT or WBXR), the right side depicts the lesions that were only detected by the index test (MRI, PET, PET-CT or CT). The lesions detected by both techniques are not depicted in this figure.

P-82

Proposal for Risk Scoring System for BRONJ Incidences in Myeloma Patients.

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【INTRODUCTION】 To manage the bone disease in myeloma, many data show the efficacy of bisphosphonates including zoledronate. On the other hand, BRONJ (bisphosphonate-related osteonecrosis of the jaws), one of the important complications, is difficult for prediction. 【METHODS】 We collect the data of 303 cases of cancer patients, who were treated with zoledronate for prevention of SRE (skeletal-related events) in our hospital between Nov. 2008 and Nov. 2012. We analyzed, (i) incidence rate of BRONJ (comparing with BRONJ cases of oral bisphosphonate for prevention for osteoporosis), (ii) risk factors of BRONJ, and (iii) study for usefulness for predictive scoring system for BRONJ. 【RESULTS】 (i) BRONJ incidence rate in preventive treatment for cancer SRE was 2.6% (8/303) and 4.0% (2/51) in myeloma patients, and 0.20% (4/1975) for preventive treatment for osteoporosis, comparably. Any statistical difference was not found among the cancer types. (ii) We identified the two risk factors, dental pre-treatment (p=0.045) and steroid usage (p=0.02) in multivariate analysis following study for many factors, such as, age, gender, total doses, administered duration, duration between ZOL and dental pre-treatment, scale of tooth-extraction, anemia, renal function, pre-existed inflammation, obesity, DM, habit of smoking, alcohol, EPO, THAL treatment, cyclophosphamide treatment, radiologic treatment. (iii) We studied cumulative incidence rate of BRONJ stratified with putative risk scoring system

with above factors, and hazard ratio of score 0+1 vs score 2 was 16.7 (p=0.0001).

P-83

An Acidic Milieu Suppresses Histone Acetylation in Myeloma Cells to Down-regulate the TRAIL Receptor DR4 Expression.

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TRAIL-mediated immunotherapy is an attractive anti-tumor maneuver because of its tumor-specific activity. In osteolytic lesions in myeloma (MM), MM cells and osteoclasts (OCs) create an acidic milieu, which confers drug resistance in MM cells. Here, we explored DR4 editing and the anti-MM activity of an anti-DR4 agonistic antibody in acidic conditions. DR4 expression was markedly reduced at mRNA as well as protein levels in MM cells cultured in media acidified by lactic acid or cocultured with acid-producing OCs. The acetylation of histones, H3 and H4, was suppressed along with the induction of Akt phosphorylation in MM cells at pH7.1 or lower. Treatment with the HDAC inhibitor valproate restored the DR4 expression in MM cells suppressed in the acidic conditions, suggesting HDAC-mediated suppression of DR4 in an acidic environment. Furthermore, the inhibition of the PI3K-Akt pathway by LY294002 or Akt inhibitors abrogated the suppression of histone acetylation and restored the DR4 expression in MM cells in acidic conditions. Although the anti-MM effects of the anti-DR4 agonistic antibody R1-B12 were blunted in acidic conditions, the Akt or HDAC inhibition sensitized MM cells to R1-B12. From these results, an acidic milieu in MM bone lesions is suggested to confer the resistance in MM cells against TRAIL-mediated immunotherapy through the PI3K-Akt-mediated epigenetic regulation of DR4 expression. Furthermore, an acidic microenvironment may epigenetically alter gene expression profiles to endow MM cells with an additional growth and survival potential.

P-84

Whole-body Diffusion-weighted MRI and 18F-FDG PET-CT in the Assessment of Bone Disease in Multiple Myeloma

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Although bone disease is usually present at diagnosis in patients with symptomatic multiple myeloma (MM), the most accurate method to evaluate bone involvement is not still established, being standard bone X-rays largely inadequate. 18F-FDG PET-CT has been claimed to be relevant in MM diagnosis and prognosis. Recently, Whole Body Diffusion Weighted MRI (DWI-MRI) has been proposed as a new functional imaging technique for bone disease detection. We investigated the role of DWI-MRI and apparent diffusion coefficient (ADC) compared with PET-CT in skeletal survey. Twenty patients (median age 59y) with symptomatic MM were studied: 12 at diagnosis (2 also at the end of HD therapy) and 8 at relapse. PET-CT was carried out using standard procedure. The number of focal lesions (FL) and associated standardized uptake values (SUV) were recorded. DWI-MRI was performed with echo planar imaging sequence with short T1 inversion recovery fat suppression. ADC measurement was based on the region of interest method. In 11 patients a positive PET/CT was found, whereas 19 patients had a positive DWI-MRI. A total of 24 (range 1-9, mean 2.18) FL (SUV>3.0) were detected in 11 patients using PET-CT as compared to 249 (3-60, mean 18.3) FL with pathological ADC (<1) in 19 patients. In the 2 patients evaluated before and after therapy, FL changed from 19 and 21 to 1 each, respectively, with DWI-MRI, and from 9 and 4 to 1 each, with PET/CT. Our data indicate that DWI represents a potentially useful technique for bone evaluation in MM with the advantage of preserving patients from radiation exposure.

P-85

Targeting Novel Molecular Bridges in the Myeloma Microenvironment

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Normal plasma cells or their transformed counterparts multiple myeloma (MM) cells depend on their interactions with bone marrow stroma for survival. But the molecular interactions that mediate this are less clear. Clinical studies have independently shown that expression of CD28 or its ligand CD86 on MM portends poor survival in patients. Microarray analysis show that CD28 expression in MM also correlates strongly with the poor prognosis subtype MAF associated with the t(14:16) translocation. We have shown that myeloid DC form a vital part of the MM microenvironment and modulate it via a CD28-CD80/CD86(B7) interaction. While CD28 activation with antibodies or by DC coculture protected MM against cell death, inhibiting DC differentiation and B7 expression with lenalidomide or blocking CD28-B7 reversed this. We delineated key molecules downstream of CD28 that transduce pro-survival signals on myeloma side as well as explored strategies to target DC that help MM survive in the microenvironment. CD28 signaling in MM involves activation of PI3K and NF κB. We show that just like in T cells, CD28 activation is accompanied by association of protein tyrosine kinases, phosphorylation of proximal tyrosine and distal proline motifs in CD28' s cytoplasmic tail followed by association of p85 (PI3K subunit) and Vav1 activation. These events were lost when these motifs were mutated. Our data suggests that targeting DC or using agents that can block the CD28-CD80/CD86 interaction between DC and MM might be viable strategies towards augmenting chemotherapy.

P-86

Enumeration of Bone Microparticles in Plasma of Multiple Myeloma Patients

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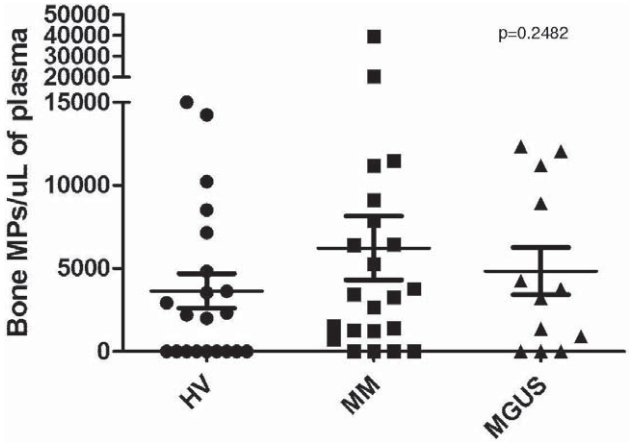
Objective: To develop a non-invasive test that can be used to monitor the dysregulated bone metabolism induced by multiple myeloma (MM). Methods: A novel blood test was developed to enumerate bone microparticles This test utilizes a bisphosphonate conjugated with a fluorophore (Bisphosphonate-Cy5) to bind to hydroxyapatite, a calcium phosphate mineral that is the principal component of bone. Specialized nanoscale flow cytometry is used to enumerate bisphosphonate-Cy5+ microparticle events (diameter 110-880nm) Bone microparticles were enumerated in 3 cohorts: 1) healthy volunteers, 2) patients with monoclonal gammopathy of undetermined significance (MGUS) and 3) patients with newly diagnosed MM. Results: Plasma samples were obtained from 21 healthy volunteers, 12 MGUS patients, and 22 MM patients. Cy5 positive bone microparticle events were $3648 \pm 1034/\mu L$, $4836 \pm 1423/\mu L$, and $6230 \pm 1913/\mu L$ respectively (Figure 1). A significant portion of healthy volunteer plasmas exhibited zero bone microparticle counts/ μL of plasma (9/21) whereas a minor subpopulation of MM patients exhibited zero bone microparticle counts/ μL of plasma (4/22). Conclusion: In a pilot study, we demonstrated the feasibility of this assay and observed high counts of bone microparticles in MM patient plasmas while lower levels were found in normal volunteer plasmas and in patients with MGUS. Results from a larger cohort of patients as well as serial samples from myeloma patients on therapy are ongoing and an update will be presented at the meeting.



P-87

Efficacy and Safety of Percutaneous Vertebroplasty in Patients with Spinal Myeloma Lesions.

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Aim: To evaluate the efficacy and safety of percutaneous vertebroplasty (PV) in the treatment of spinal myeloma lesions (SML) refractory to analgesia, byphosphonates or radiation therapy. Methods:42 patients with SML, from 2 centers were eligible. Vertebral fracture or collapse was confirmed by computed tomography or magnetic resonance imaging. PV of more than one vertebra was performed if feasible. Pain re-

sponse was evaluated by a qualitative scale at 24 h, one and six months after PV. Complications were considered secondary to PV during the following 30 days. Results:110 PV were performed in 49 procedures. The number of vertebrae treated in each procedure was: 1 in 14 cases, 2 in 15 cases, 3 in 15 cases, 4 in 4 cases and 5 in 1 case, being the T12 the most frequent localization (16 cases). Cement leakage was observed in 46%. Six out of 42 patients (14%) experimented complications related to PV: two cases of psoas hematoma, one patient with pulmonary insufficiency, two patients suffered a pulmonary embolism (one died because of cement embolism) and one patient presented a subdural hematoma without neurological repercussion. 24 hours after PV, 83% of patients referred a decrease in pain. The evaluation at 1 and 6 months later, showed an improvement of pain in 83% and 70% respectively. Conclusions: PV is effective for pain control in 70-80% of myeloma patients with SML at short and long-term. However, some patients may experience life-threatening effects.

P-88

Should We Define Osteolytic Skull Lesions as Myeloma-related Organ Impairment?

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We planned this study to determine whether only osteolytic skull lesions in patients with MGUS should be defined as myeloma related organ or tissue impairment (M-ROTI). We reviewed the medical records for patients who showed osteolytic skull lesions between 2008 and 2012. Patients with symptomatic multiple myeloma (MM) having additional M-ROTI to osteolytic skull lesions or solid tumor were excluded. Asymptomatic skull osteolytic lesions were identified in 20 patients including 9 MGUS. Among 13 patients with bone densitometry, 6 and 7 showed osteoporosis and osteopenia. In 9 MGUS patients, mean age was 81 (range 60-93) and they had no M-ROTI except asymptomatic osteolytic skull lesions. Median serum M protein was 0.5g/dL (range:0-1.3). 18F-fluoride PET was conducted 6 MGUS patients and 2 patients showed increased metabolic uptakes in skull. 11 non-MGUS patients had various underlying comorbidities including osteoporosis or ostopenia (n=7), localized eyelid amyloidosis (n=2), solitary bone plasmacytoma of spine (n=1). Two non-MGUS cases which also had osteolytic lesions in spine were diagnosed as hemangioma pathologically. All patients had neither development of M-ROTI including new bony lesions, nor progression to MM during the follow-up. Presence of asymptomatic osteolytic lesions limited on skull should be interpreted cautiously especially in patients with MGUS. Association between incidental osteolytic skull lesions and aging or osteoporosis needs to be further investigated.

P-89

Matrix Metalloproteinase 13 (MMP13) Induces Osteolytic Lytic Lesions Independent from Its Catalytic Activity

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We showed that MMP13 is highly expressed in MM cells and induced by IL6 via induction of AP1 binding to the promoter of MMP13. MMP13 strongly increased osteoclast (OCL) fusion and bone resorption. OCL formation assays using MNC from mmp13-/- mice showed significantly decreased OCL fusion and bone resorption, which was reversed by exogenous MMP13. We investigated the effects of silencing MMP13 in MM cells on bone disease using the 5TGM1 intratibial tumor model. Rag2-/- mice were intratibially injected with either 5TGM1-EV or 5TGM1-MMP13 KD MM cells, and lytic lesions were monitored by microQCT. Mice injected with 5TGM1-MMP13 KD MM cells showed less lytic lesions confirming the critical role of MMP13. To determine whether MMP13 protease activity is required for the effects on osteoclasts, we generated an enzymatically inactive MMP13 by mutating E223, in the zinc binding motif. Pro-MMP13 wt and E223A mutant constructs containing a C-terminal his tag were produced in HEK 293 cells, which do not express detectable endogenous MMP13 expression. The enzymatic activity was confirmed by comparison with commercial pro-MMP13 wt protein in the presence of MMP13 activator APMA confirming that the MMP13 E223A mutant totally lost the protease activity. Surprisingly, MMP13 wt and E223A used for OCL cultures showed equal activity in promoting OCL formation indicating that proteolytic activity of MMP13 is not required for induction of osteoclast formation and activity. Our data show that MMP13 independent of its catalytic activity is critical for MMBD and is a potential new treatment target.

P-90

Def124b is Downregulated in Differentiating Osteoblasts by IMiDs Which May Mediate Suppressive Effects on Osteogenesis

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We recently reported a suppressive effect of thalidomide and lenalidomide on osteoblast (OB) development *in vitro*. Similar findings were noted when these IMiDs were combined with bortezomib. Previous studies showed that IMiDs upregulate DKK1 in myeloma cells. Here, we evaluated whether the IMiD induced upregulation of DKK1 accounts for their suppressive effects on osteogenesis via inhibition of the Wnt signalling pathway. DKK1 expression was studied by qPCR in developing OBs derived from hBMSCs *in vitro*. Blocking experiments were performed using antibodies against DKK1. We further used gene expression profiling to identify key factors in IMiD-modulated osteogenesis. Exposure of differentiating OBs with thal or len resulted in enhanced DKK1 expression up to 8.6 fold ($P<0.05$). Neither DKK-1 nor activin A inhibition rescued BMSCs from the OB inhibitory action of the IMiDs, suggesting that other mechanisms are involved in IMiD related suppression of osteogenesis. Microarray analysis revealed deregulation of several OB associated genes including *Runx2, MMP3, COL5A3, PTN and GREM1*, with different patterns depending on the IMiD used. *Def124b*, a poorly characterized member of the family of β-defensins, was the only gene affected by both IMiDs, being downregulated 5-fold. Hence, DKK1 does not seem to be a key factor responsible for IMiD mediated suppression of osteogenesis. Our data point to *Def124b* as a central orchestrator of IMiD induced inhibition of osteogenesis. Modulating its expression might obviate the untoward bone related side effects of these compounds.

P-91

Percutaneous Vertebroplasty (PV) Does Not Alter Stem Cell (PBSC) Collection and Transplant in Multiple Myeloma (MM)

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Vertebral fractures occur in over 50% of MM patients and can cause pain, disability and poor quality of life. MM therapy can lead to symptoms improvement in the majority of the patients, but these positive effects can take time to be perceived. Furthermore, application of radiotherapy prior to PBSC mobilization can severely impair stem cell collection. PV has been proposed as a suitable option to rapidly relieve bone pain from vertebral fractures in patients with neoplastic diseases such as MM, but so far, little is known about the effects of this procedure on subsequent PBSC mobilization, collection and transplant. 17 consecutive patients (9M, 8F, median age 63 yrs) with untreated, symptomatic MM and painful vertebral lesions underwent PV prior to proceed to the planned transplant program at our institution. 30 procedures were performed at C2-L5 levels, 58% of the patients were treated at a single level, a maximum of seven levels were treated in 1 patient. PBSC mobilization regimen consisted of cyclophosphamide + G-CSF in 14 patients and G-CSF + plerixafor in 3 patients; all the patients successfully mobilized PBSC; in a median of 1.8 pheresys, the median number of collected CD34+ cells was 10.8 x 106/kg. All the patients underwent autologous stem cell transplant; hematological recovery averaged 11 days both for PMN >500/mmc) and for platelets (>20000/mmc). In conclusion, PV is useful in MM patients with painful vertebral fractures as it allows rapid and durable achievement of pain control, without interfering with PBSC collection and transplant.

P-92

Urine N-telopeptide across the Plasma Cell Dsycrasias

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Background: Multiple myeloma (MM) is characterized by lytic bone disease and abnormal bone resorption markers such as urinary N-telopeptide (uNTx). Whether abnormal uNTx occurs in earlier precursor states including MGUS and smoldering myeloma (SMM) is uncertain.

Methods: Medical charts of patients (pts) with a plasma cell dyscrasia and uNTx value were reviewed for myeloma-related labs, lytic disease, clinical information including date of diagnosis, comorbidities, concurrent medications, and survival outcomes. MM pts were categorized based on whether they had received anti-myeloma therapy at the time of the uNTx value. Differences in uNTx between diagnostic groups were made using t-tests; linear regression controlled for additional clinical characteristics; log-rank tests were performed for survival analyses.

Results: 402 pts (100 MGUS, 64 SMM, 238 MM) were in-

cluded. Mean uNTx values differed between MGUS, SMM, and untreated MM (40.4 vs 34.4 vs 49.6, p=0.005). uNTx of treated MM pts were lower than those who had not yet begun treatment (p=0.02), even after adjusting for bisphosphonate use (p=0.01). There were no differences in survival when either treated or untreated MM pts were stratified by uNTx (p=0.54-0.70). uNTx did not differ dependent on the presence of lytic disease in MM (p=0.66).

Conclusions: Urinary NTx differs between MGUS, SMM, and untreated MM. Whether this abnormality in bone metabolism is truly a reflection of progressive underlying bone disease or could represent the development of myelomagenesis is unknown, but worthy of prospective investigation.

Section C: Clinical Studies (including Transplantation)

P-93

Higher Incidence of Injection Site Reaction after Subcutaneous Bortezomib on the Thigh Compared with the Abdomen

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Subcutaneous (sc) rather than intravenous administration of bortezomib (Bor) is becoming more common for treating multiple myeloma (MM) because scBor results in lower incidence and severity of peripheral neuropathy and has equivalent efficacy. Bor is an irritant cytotoxic agent when it leaks out; therefore, it is recommended that injections of scBor should be rotated among 8 different sites on the abdomen and thigh. However, detailed information about injection site reactions (ISR) have not been sufficiently documented. We retrospectively analyzed the incidence and severity of ISR following scBor administration in 15 Japanese patients with MM. Grade 1 ISR occurred following 40 of 158 (25.3%) scBor injections in 10 patients, whereas grade 2 ISRs occurred following 7 injections (4.4%) in 5 patients. Five patients did not develop ISR. Of note, grade 2 ISR was documented in 6 of 63 (9.5%) thigh injections but only in 1 of 95 (1.1%) abdominal injections. These data show that grade 2 ISR were more common in the thigh compared with the abdomen possibly because the thigh contains lesser adipose tissue than the abdomen. Grade 2 ISRs resolved without any sequela within a median of 7 days. scBor administration on the abdomen instead of the thigh should be considered, especially for emaciated patients, because ISR rapidly resolves within the interval before the next injection even if it occurs.

P-94

Melphalan 200 mg/m2 vs 140 mg/m2 as Conditioning Regimens for Autologous Stem Cell Transplantation in Multiple Myeloma

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Autologous stem cell transplantation (ASCT) in newly diagnosed myeloma increases progression-free survival (PFS) and overall survival(OS) compared with conventional chemotherapy. Melphalan 200 mg/m^2(MEL200) is considered the standard conditioning regimen for patients aged <65 years. There is limited published data on how to condition older patients or those with comorbidities. We performed a retrospective analysis of 199 ASCTs performed at St Bartholomews Hospital. 142 and 57 patients underwent MEL200 (median age 56) and MEL140 (median age 64) conditioning respectively. Patients were dose reduced on account of renal impairment, age >65 or the presence of comorbidities. Median PFS from ASCT was 21 months in the MEL200 group and 24 months in the MEL140 group (p=0.49). Median OS from ASCT in all patients was 78 months with no difference between the MEL200 and MEL140 groups (p=0.53). There was no significant difference in transplant related mortality and no difference within each conditioning group when analysed by age (<65 vs >= 65 years); p=0.97 (MEL200) and p=0.91 (MEL140). We conclude MEL140 ASCT in patients >65 years, with renal impairment or with comorbidities is an effective consolidation strategy with near equivalence to conditioning with MEL200. This suggests the need for a prospective randomised trial comparing the two conditioning regimens.

P-95

Phase II Study of Sequential High-dose Dexa and Response Adapted PAD or VAD Followed by ASCT for Newly Diagnosed MM

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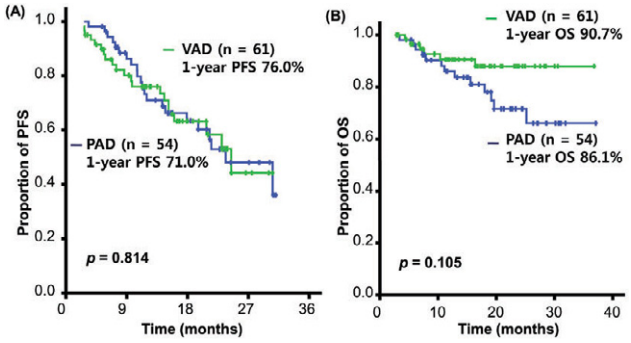
Background: We evaluate the efficacy and safety of the brief course of high dose dexamethasone (HD) and the response adapted PAD (Bortezomib, Adriamycin, Dexamethasone) or VAD (Vincristine, Adriamycin, Dexamethasone) induction chemotherapy in the newly diagnosed younger patients with MM. Methods: Patients with newly diagnosed MM received 2 cycles of HD followed by PAD or VAD according to the response to the HD. PAD 4 cycles were given to nonresponsders and VAD 2 cycles were given to who achieved more than PR to HD. The primary endpoint was CR + nCR rate after ASCT. This trial will be continued until total 210 patients will be enrolled. Results: 155 patients (88 male) were enrolled. CR + PR rate was 53% after 2 cycles of HD. 61 patients (53%) received subsequent VAD chemotherapy and 54 patients (47%) received PAD. CR + PR rate after induction therapy was 83% (79% in VAD vs 89% in PAD). CR + nCR rate after ASCT were 74% (74% in VAD vs 73% in PAD). Among 115 patients in whom VAD or PAD was actually performed, 1 year OS was 88.1%. (VAD 90.7% vs. PAD 86.1% (P=0.105): median follow-up; 16.6 months). Conclusion: PAD re-induction therapy after failure of initial steroid induction treatment might overcome the inferior results in the high risk MM patients. Almost half of the patients who responded to HD can be saved of novel agents during induction treatment, and PAD can successfully rescue the other half who are not sensitive to HD. Therefore, initial steroid response adapted strategy might be the more cost-effective approach in the newly diagnosed ASCT eligible MM patients.



P-96

A Comparison of Next-generation Sequencing and ASO-qPCR for Minimal Residual Disease (MRD) Detection in Multiple Myeloma

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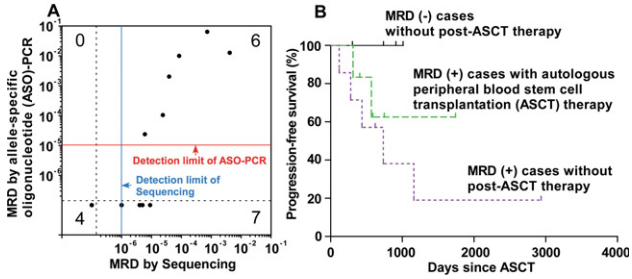
Background: Although molecular CR in multiple myeloma (MM) can be assessed by ASO-PCR, this technique requires preparation of clonotype-specific primers for each individual which is both laborious and time-consuming. The usage of the LymphoSIGHT™ method, a next-generation sequencing (NGS)-based platform, may overcome these challenges and further increase sensitivity and specificity. Therefore, we compared the LymphoSIGHT™ approach with ASO-qPCR for MRD detection in autografts in the ASCT setting. Patients and Methods: Seventeen Japanese patients with newly diagnosed MM who received various induction regimens prior to ASCT were retrospectively analyzed. All patients had achieved a PR or CR after ASCT. BM slides from 13 MM patients and fresh BM cells from 4 MM patients at diagnosis as well as autografts were obtained for DNA extraction. Results: MRD in autografts was detected in 6 of 17 (35%) by ASO-qPCR and 13 of 17 (76%) by NGS (Fig. 1A). When MRD was assessed by NGS, 6 MRD (+) cases received post-ASCT therapy while 4 MRD (-) cases and 7 MRD (+) cases were followed without post-ASCT therapy. The MRD (-) cases tended to show a better PFS than the MRD (+) cases with post-ASCT therapy (P = 0.26) and those without post-ASCT therapy (P = 0.09) (Fig. 1B) although OS rates were comparable among the three groups. There was no difference in PFS between MRD (-) and MRD (+) cases when MRD was assessed by ASO-qPCR (P = 0.6). Conclusions: MRD-negativity in autografts revealed by NGS may be more closely associated with durable remission of MM than that revealed by ASO-qPCR.

Fig.1 MRD detection in autografts by next-generation sequencing



P-97

Bendamustine and Prednisone in Combination with Bortezomib in Patients with Relapsed/ Refractory Multiple Myeloma

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Introduction: Bortezomib (Velcade) is a proteasome inhibitor that has shown important clinical efficacy either as a single agent or in combination with other cytostatic agents in multiple myeloma (MM). In the present protocol, bortezomib was combined with other active substances like bendamustine and prednisone (BPV), in order to assess the efficacy and toxicity of the combination therapy in patients with relapsed or refractory MM. Methods: Between January 2005 and December 2011, 78 patients with relapsed or refractory MM were treated with bendamustine 60 (-120) mg/m2 on day 1 and 2, bortezomib 1.3 mg/m2 on day 1, 4, 8 and 11, and prednisone 100 mg on day 1, 2, 4, 8 and 11. 33 patients had pre-existing severe thrombocytopenia and/or neutropenia. Results: A median number of two (range 1-7) BPV cycles were given to the patients. The majority of the patients (n = 54) responded after at least one cycle of chemotherapy with 3 CR, 10 nCR, 10 VGPR, and 31 PR. Median PFS and OS for patients without severe hematological toxicities due to previous treatments (n = 45) were 11 months and 50 months, respectively. Outcome for these patients was significantly better than that for patients with severe hematological toxicities (n = 33) with a PFS, and OS of 3 months ($p < 0.05$) and 5 months ($p < 0.001$), respectively. The regimen was well-tolerated in patients without

severe hematological toxicities due to previous treatments. Summary: These results indicate that the combination of bortezomib, bendamustine and prednisone is well tolerated in patients with relapsed or refractory MM

P-98

Treatment of Newly Diagnosed Multiple Myeloma with Advanced Renal Failure Using Bortezomib, Bendamustine and Prednisone

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Purpose: Renal failure is a frequent complication of multiple myeloma (MM) and, if present at diagnosis, a considerable risk factor for outcome. Treatment with chemotherapy and/or new agents may result in recovery of renal function in up to 50% of patients. The window of opportunity to reverse renal impairment is however rather small, making an immediate and highly active treatment strategy mandatory. Bortezomib as well as bendamustine have been demonstrated to be potent drugs in the treatment of MM. Methods: A total of 18 patients with newly diagnosed/untreated MM and renal insufficiency (GFR <35 ml/min) were treated with bendamustine, prednisone and bortezomib (BPV). Results: The majority of them (n=15; 83%) responded after at least one cycle of chemotherapy with three sCR, five nCR, five VGPR, and two PR. With a median follow up of 17 months, PFS at 18 months was 57% and OS was 61%. The myeloma protein decreased rapidly, reaching the best response after the first cycle in four and after the second cycle in additional seven patients. 13 patients (72%) improved their renal function after treatment. Conclusion: The combination of bortezomib, bendamustine and prednisone is an effective and well tolerated treatment protocol in patients with newly diagnosed/untreated MM and light chain induced severe renal failure. The haematological and renal response was very rapid and occurred within six weeks in the majority of patients. The high efficacy and the favourable toxicity profile of BPV therapy warrant further evaluation in clinical trials.

P-99

Successful Stem Cell Mobilization and Autologous SCT after Bendamustine Pretreatment in Patients with Multiple Myeloma

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Bendamustine is a bifunctional alkylating agent with promising activity in lymphoid malignancies and multiple myeloma. Unfortunately, the previous development of this agent did not provide sufficient information on stem cell toxicity and mobilization of stem cells for autologous SCT after Bendamustine therapy. A retrospective analysis of peripheral blood stem cell mobilization and autologous SCT was performed in 63 patients with multiple myeloma who had received Bendamustine pretreatment at the University Hospitals Leipzig and Heidelberg. The cumulative dosis of Bendamustine per patient was median 960 (range 120 - 2400) mg/qm. The mobilization regimen consisted of Cyclophosphamide 4g/qm (n=41) or 7g/qm (n=4) and G-CSF (2x5ug/kg). Alternative regimens such as CAD and others were also used in the remaining patients. Stem cell mobilization and harvest was successful in 60 of the 63 patients. In 19 of 60 patients a single apharesis was sufficient to reach the target. The median number of aphareses was two (range 1-7) and the median CD34+ cell-count/kg was 5.9 (range 1.7-20.4) x106. Information on autologous SCT is available from all 60 patients with successful harvest. Engraftment was successful in 59 of 60 patients. The median time to leucocytes count >1 × Gpt/l was reached after 12 days and the time to platelet count of >50 × Gpt/l was 14 days. 54 patients responded after the autologous SCT with 6 CR, 4 nCR, 12 VGPR, and 32 PR. In conclusion, the stem cell mobilization and autologous SCT is feasible in multiple myeloma patients who have received Bendamustine pretreatment.

P-100

Revlimid, Bendamustine and Prednisolone in Relapsed/Refractory Multiple Myeloma: Results of a Phase I Study; OSHO #077

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Purpose: While the role of lenalidomide monotherapy in the treatment of relapsed/refractory patients with multiple myeloma (MM) is well established, combination therapies with lenalidomide are still under investigation. In the current dose finding study, a combination therapy of lenalinomide (Revlimid), bendamustine and prednisolone (RBP) was tested in patients with advanced MM. Methods: The first cohort of patients received a starting dose of 10 mg/d d1-21 lenalidomide, 60 mg/qm/d d1-2 bendamustine and 100 mg/d d1-4 prednisolone. Escalation steps in cohorts of three (-six) patients increased the dose of lenalidomide to 15, 20 and 25 mg and after reaching 25 mg/d lenalidomide to increase bendamustine to 75 mg/qm. Results: 21 patients (3 at each of the first three dose levels and 6 at each of the last two dose levels) were enrolled in this phase I study and all completed at least 2 cycles. Two patients developed dose-limiting hematoxicity: one patient at 25 mg/d lenalidomide combined with 60 mg/qm bendamustine and one patient at the highest dose level (25 mg/d lenalidomide in combination with 75 mg/qm bendamustine). The maximum tolerable dose was not reached. Sixteen patients (76%) responded after at least two cycles of RBP with 1 sCR, 1 nCR, 5 VGPR and 9 PR. After a median observation time of 16 months, PFS at 18 months was 48% and OS was 64%. Conclusions: RBP with a dose of 25 mg lenalidomide d 1-21 and 75 mg/qm bendamustine d 1-2 is well tolerated in patients with relapsed/refractory MM.

P-101

Pre-transplant Treatment Goal in Multiple Myeloma

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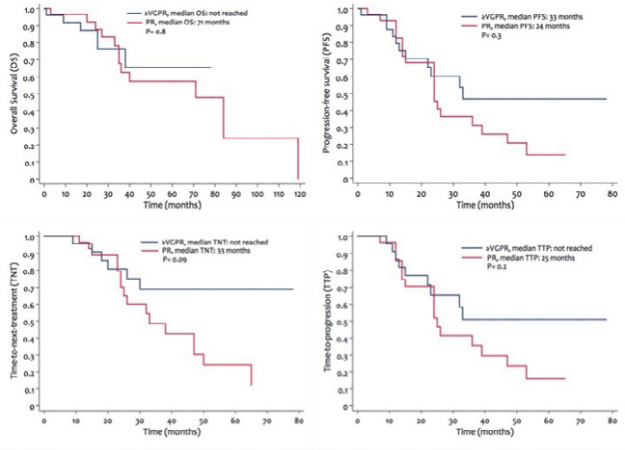
Background: There are several prospective and retrospective studies exploring the impact of pre-transplant response status on disease outcomes in patients with multiple myeloma (MM). While a half claims that it has a prognostic impact on myeloma endpoints, others found no association. We aimed to investigate the impact of pre-transplant response depth on MM outcomes. Methods: We retrospectively analyzed the data of a total of 56 patients with MM who underwent autologous stem cell transplantation (ASCT) between 2000 and 2010. Primary endpoint was time to progression (TTP). Secondary endpoints were progression-free survival (PFS), time-to-next-treatment (TNT), and overall survival (OS). Results: Time-to-transplantation, median follow-up, and treatment-related mortality were 12 (6-36) months, 32 months, and 3.6%, respectively. Median PFS, TTP, TNT, and OS were 25, 32, 47, and 84 months respectively. 5- and 10-year OS were 60.9%, and 26.6%. Pre-ASCT response >partial response (PR) was 41.9%. Proportion of post-ASCT response >PR estimated to be 75.8%. There were no significant differences between patients with a pre-ASCT response >PR and partial response (PR) in terms of PFS (median 33 vs 24 months, p= 0.3), TTP (not reached vs 25 months, p= 0.2), TNT (not reached vs 33 months, p= 0.09), and OS (not reached vs 71 months, p= 0.8) (Figure 1). Conclusion: Patients with MM who achieve PR or >PR before ASCT have similar disease outcomes. Since only 30% of patients will have a >PR with novel agents, at least PR is a reasonable pre-ASCT treatment goal.



P-102

Lenalidomide in Combination with Low-dose Dexamethasone in Relapse/Refractory Multiple Myeloma: a Retrospective Study

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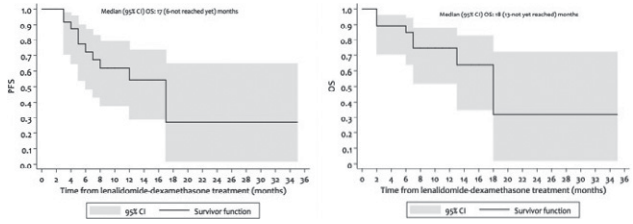
Background: Two randomized controlled trials, MM009 and MM010, demonstrated that lenalidomide in combination with dexamethasone was superior to placebo plus dexamethasone in relapse/refractory multiple myeloma (rrMM). We aimed to investigate the efficacy and safety profile of this combination in rrMM in a small-sized post-marketing analy-

sis. Material and methods: Primary end-point was overall response rate (ORR); secondary end-points included progression-free survival (PFS) and overall survival (OS). Treatment (Rd) consisted of lenalidomide (25 mg on days 1 to 21) and dexamethasone (40 mg on days 1, 8, 15, 22) in repeating 4-week cycles. Dose modifications were implemented accordingly, if needed. Results: A total of 28 (19 male) patients were included into the study. Median age was 65 (range: 44-86) years. Only four patients were older than 75 years of age. Median number of prior therapies was 3 (3-6). Proportions of patients with prior thalidomide use, autologous hematopoietic stem cell transplantation (ASCT), and plasmocytoma were 39%, 39%, and 21%, respectively. ORR and complete response rates were 75% and 43%, respectively. Older age, prior thalidomide use, ASCT and plasmocytoma did not have an impact on response rates. Median follow-up, PFS, and OS were 7 (2-35), 17 (6-not reached), and 18 (13-not reached) months (Figure 1). Grade III-IV adverse events included neutropenia (21%), anemia (28%), thrombocytopenia (28%), deep vein thrombosis (3%), infections (18%), and fatigue (7%). Conclusion: Rd is highly active in patients with rrMM.



P-103

Salvage Autologous Stem Cell Transplantation for Multiple Myeloma Relapsing after Up-front Autologous Transplantation

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Limited data are available regarding the value of salvage therapy with a second AHCT (AHCT2) in multiple myeloma (MM) patients who relapse/progress after AHCT1. We analysed MM patients who underwent salvage AHCT2 at our institution between 1994 and 2011. The patient population is derived from a multi-ethnic community of approximately two million in an equal-access healthcare system. A total of 404 MM patients underwent AHCT1. Of those, 83 patients received AHCT2 for relapse/progression following AHCT1. Median time to progression after AHCT1 for patients who received AHCT2 was 21.5 months (range, 3-86). Median interval between AHCT1 and AHCT2 was 35.4 months (95%CI: 9-93). Median age at AHCT2 was 60.9 years (range, 32-73). Most patients who underwent AHCT2 (77%) had received treatment with novel agents between AHCT1 and AHCT2, and 28% of patients were from ethnic minority groups. Median overall survival (OS) from AHCT2 was 31.5 months (95%CI: 22 - 41). In multivariate analysis, only disease status (at least PR) at AHCT2 was associated with better OS. The 3-year OS rates from AHCT2 for patients receiving AHCT2 in VGPR/CR and PR were 85.9% (95%CI: 61-96) and 51.3% (95%CI: 34-68), respectively. Median progression-free survival (PFS) from AHCT2 was 15.5 months (95%CI: 11-20). In multivariate analysis, disease status (at least PR) and time to progression after AHCT1 of at least 21.5months were associated with better PFS. In summary, salvage AHCT2 is an effective treatment option in patients with chemosensitive relapse/progression and prolonged remission after AHCT1.

P-104

The Ideal Dose Setting and the Possibility of Therapeutic Drug Management of Lenalidomide in Multiple Myeloma

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Introduction: Although the initial Lenalidomide (LEN) dose can determined on the basis of renal function and peripheral blood cell counts, dose adjustments, particularly after drug administration, were necessary in some cases because of interindividual differences in pharmacokinetics. We aimed to develop an equation for the predicted total area under the observed plasma concentration-time curve (AUC) of LEN and to set the ideal LEN dose in patients with myelomas by using only 2 sampling points. Methods: Plasma concentrations of LEN from samples obtained after oral administration were analyzed using HPLC. Results: The plasma concentrations of LEN at 2 and 4 h after its administration were highly correlated with the $AUC_{0\text{-}24}$ value for LEN. In patients for whom the drug was discontinued or administered at a lower dose

because of the development of hematologic toxicity in a subsequent course of therapy, the measured AUC_{0-24} values were significantly higher than the corresponding values in patients who continued to receive LEN. Moreover, the results of ROC analysis showed that the ideal AUC_{0-24} of LEN could be set to avoid hematological toxicity. Conclusion: The predicted AUC_{0-24} value might be a new indicator for the management of LEN therapy. It is possible to adjust the ideal dose by using the equation for AUC_{0-24} with the C_{2h} and C_{4h} values in a test before LEN therapy is actually initiated. Therapeutic drug management of LEN can be performed by establishing the minimum effective concentration and the maximum toxic concentration in a large prospective study in the future.

P-105

Bortezomib Based Chemotherapy Combined HDT/ASCT could Improve IgD Multiple Myeloma Outcome

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Bakeground: To investigate the treatment response, survival of patients with IgD MM. Method: we have retrospectively analyzed 17 patients diagnosed with IgD MM over 17 years. Result: When compared with other type MM, we found that IgD MM was marked by higher level of serum ALP, LDH, and C4 . Six patients were treated with regimen containing bortezomib(Btz) and four of them underwent HDT/ASCT at CR. Another eleven patients were treated with conventional chemotherapy, and one received allo-SCT. After initial chemotherapy, nine (52.9%)CR, one (5.9%) VGPR, and four(23.6%) PR. The ORR was 82.4%. In Btz group, 100% patients achieved CR ,compared with that of 27.3% in patients treated with conventional chemotherapy(P =0.009). Date cut-off was Oct.20, 2012, a median follow up of 23 months. The median OS and PFS were 37.0 and 12months. we excluded the allo-SCT pts for survival analysis below. The median OS for the HDT/ASCT patients has not yet been reached and the chemotherapy(CT) patients was 27 months. Patients who received ASCT had a median PFS of 28 months significantly longer than that of patients prescribed only CT(6 months,P = 0.049) .In addition, compared with the Btz group, the patients prescribed other chemotherapy had a trend towards poorer median OS (not reach versus 46.7 months) and shorter median PFS (8 versus 28 months). Conclusion: IgD MM was a rare and invasive MM. Although there was a good treatment response, the IgD MM patients easily progressed and die with short OS . Bortezomib and HDT/ASCT could further deepen remission degree , prolong survival.

P-106

Reduced-dosage of CyBorD Retains High Response Rate with Less Toxicities in Elderly Patients with Multiple Myeloma

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Background: Once-weekly bortezomib induction therapy with CyBorD (modified-CyBorD) has shown less toxicity with high response rate equal to original regimen. However, more than half of the patients developed bortezomib induced PN (BiPN). Here, we introduced the reduced-dosage of CyBorD regimen (reduced-CyBorD) in the transplant ineligible patients with MM. Methods: The protocol consisted of bortezomib given intravenously at a dose of 1.3 mg/m^2 once a week on days 1, 8, 15, cyclophosphamide orally at a dose of 50 mg daily on days 1-21, and dexamethasone orally or intravenously at a dose of 20 mg daily on days 1,2,8,9,15,16 in 4-week cycles. Total of 32 pts, including 20 newly diagnosed and 12 refractory, were enrolled and evaluated its efficacy and safety. Results: The median age was 72 y.o. (62-88). 21 pts were more than 70 y.o. (66%). According ISS, 4 pts were classified in stage I, 10 were in II, and 18 were in III. The overall response was 90.6 % with 43.8 % of CR/nCR (6 CR, 8 nCR, 7 VGPR and 8 PR). Hematological adverse events were anemia (G1/2 n=7), neutropenia (G1/2 n=10, G3/4 n=2), lymphocytopenia (G1/2 n=10, G3/4 n=4), thrombocytopenia (G1/2 n=1, G3/4 n=3). Non-hematological adverse events were pneumonia (G2 n=2, G3 n=2), VZV infection (G1/2 n=5), cerebral infarction (G2 n=1). Importantly, only 6 pts (18.8%) developed grade 1 PN, and no patient reduced or discontinued bortezomib due to PN. Conclusions: Our results suggested that reduced-CyBorD might be safe and effective approach to the transplant ineligible patients, especially elderly frail patients with MM.

P-107

Once-weekly Bortezomib with Low-dosage Thalidomide and Dexamethasone might be Promising Therapy for Multiple Myeloma

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Introduction: Three-drugs combinations, including one novel agent, were well known to be superior to VAD or MP as part of induction regimen in for the patients with multiple myeloma (MM). Recently, the most promising results with a triplet combination consisting of bortezomib, thalidomide and dexamethasone (VTD) were reported overseas. However, twice a week of bortezomib with thalidomide might be associated with the high risk of developing severe peripheral neuropathy (PN), resulting in discontinuation of further treatment. Here, we introduced once-weekly schedule of bortezomib combined with very low-dosage of thalidomide and dexamethasone for less toxicity. Methods: The protocol consisted of bortezomib given intravenously once a week at a dose of 1.3 mg/m^2 on days 1, 8, 15, thalidomide orally at a dose of 50 mg daily on days 1-21, and dexamethasone intravenously at a dose of 20 mg daily on days 1, 8, 15 in 4-week cycles. Results: Total of 8 patients were enrolled in this study and evaluated its efficacy and safety. The median age was 68 years. 4 were female. 4 were previously untreated patients. According ISS, 4 patients were classified in stage I, 2 were in II, and 2 were in III. Result: 7 out of 8 patients (87.5%) achieved objective response (1 CR, 2 nCR, 1 VGPR, 3 PR, and 1 SD). Neither hematological nor non-hematological grade 4 adverse events were observed. 2 patients developed PN, and one had to discontinue because of G3 PN. No thrombotic event was observed. Conclusion: Reduced-VTD was effective and well tolerated as induction therapy for MM patients.

P-108

Lenalidomide in the Treatment of First Relapsed Multiple Myeloma Patients with Severe Renal Impairment

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INTRODUCTION Patients with multiple myeloma (MM) and severe renal impairment ((S)RI) had a short survival and they were excluded from most of the trials. In these patients the use of Lenalidomide (Len) is based in pharmacokinetics models and they experienced an increased toxicity. METHODS Retrospective unicentric study (Oct08 to Dec12). Analysis of the outcome of seven consecutive patients, in first RMM and SRI (Cr Cl<30 ml/min). The treatment was LenDex: low doses of Dex and Len doses 25mg/d to 5mg qod. We evaluated the efficacy (response rate (RR) and response duration (RD) and the relevant toxicities. Median follow-up was 22,3m. RESULTS RR was 71% (5/7) and the two pts with progressive disease had prior exposure to thalidomide. Median RD was 21m and in 57% (4/7) the response was long than 2 years. 43% had renal improvement but 2 pts persisted in dialysis. No treatment interruption occurred. In long responders a continuous dose adjusted was required mainly because of mielo/neurotoxicity and the Dex dose was reduced until 16mg/cycle. There was no critical infection or second primary tumors. CONCLUSIONS Cr Cl<60 ml/min is a cut-off for Len reduction. After initial therapy with dose-adjusted we should tried a continuous process of dose-adapted to the individual tolerance, even without additional RI. LenDex dosing adjusted according to Cr Cl does not negatively impact in response or in the rate of side effects; it achieves a potential for reversal RI and it ´ s able to induce long duration response. LenDex is an effective regimen for first RMM complicated by SRI.

P-109

Comparison Traditional Regimen and 8Gy Total Marrow Irradiation plus 140mg/m2 Melphalan in Multiple Myeloma

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Purpose: Autologus stem cell transplantation with conditioning regimens of 200mg/m2 melphalan has become a common treatment for myeloma. The objective of this retrospective study was to compare the conventional conditioning regimen with 8Gy total marrow irradiation (helical tomotherapy, TMI) plus 140mg/m2 melphalan in newly diagnosed symptomatic myeloma patients. Patients and Methods: We enrolled 9 consecutive myeloma patients with auto-SCT in Far Eastern Memorial hospital (diagnose between 2007 and 2010). The patients received 3 cycles of vincristine-adriamycin-dexamethasone (VAD) as induction chemotherapy and if patients get partial response, peripheral blood stem cell were collected. In arm A, 6 patients received the common conditioning regimens of 200mg/m2 melphalan. In arm B, 3 patients received the new regimen of 8Gy TMI plus 140mg/m2 melphalan. All the patients received thalidomide for maintenance therapy after stem cell transplantation. Results: Baseline characteristics and disease response to VAD and auto-SCT were identical in the 2 arms. In arm B, the neutropenic duration was significantly longer. However, hematologic recovery (except neutrophil), transfusion requirement, median duration of hospitalization and the dose of G-CSF was similar in the 2 arms. The median duration of overall survival and event-free survival were similar in the 2 arms. Conclusion: We conclude that 8Gy Total marrow irradiation (helical tomotherapy) plus 140mg/m2 melphalan is a toxic manageable

and at least as effective conditioning regimen when compared with 200mg/m2 melphalan.

Response to induction VAD regimen and high dose therapy (HDT)

	Arm A	Arm B	p
Median no. of course of VAD (range)	3 (3-4)	3 (3)	1.000
Response to VAD			1.000
CR	1	0	
VGPR	1	1	
PR	4	2	
Median no. of CD34 (10^6/kg) infused (range)	6.75 (3.6-9.14)	4.9 (4.12-6.21)	0.167
Response to HDT			1.000
CR	1	1	
VGPR	4	1	
PR	1	1	
Toxic death	0	0	1.000
Death due to disease progress	1	1	1.000
Overall survival, d (median)	1223 (709-1659)	1566 (737-2160)	0.515
Progression free survival, d (median)	982 (607-1456)	1101 (677-1475)	0.387

P-110

Combination Therapy with Novel Agents and Stem Cell Transplantation Improve Survival of MM Patients Aged 65-70 Years

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Novel agents (NA) such as thalidomide, lenalidomide, and bortezomib have dramatically changed the treatment paradigm of multiple myeloma (MM). However, it is not clear whether these agents improve outcomes of elderly patients undergoing autologous stem cell transplantation (SCT). We retrospectively analyzed the outcome of 318 patients aged 65-70 years. As initial therapy, 192 patients were treated with conventional chemotherapy (CC), 88 with NA-containing regimens, 21 with CC plus SCT, and the remaining 17 with NA plus SCT. The median progression-free survival (PFS) for these cohorts was 19.1, 24.5, 26.8, and 35.2 months, respectively. PFS was significantly improved in the NA-containing regimen group (p=0.006) as well as in the NA plus SCT group (p=0.032) compared with that of the CC group. The 5-year overall survival (OS) was 40%, 62%, 63%, and 87%, respectively, and OS was significantly improved in the NA-containing regimen group (p=0.001), the CC plus SCT group (p=0.02), and in the NA plus SCT group (p=0.02) compared with that of the CC group. In a multivariate analysis using a stepwise selection model, IgG and IgA type (p=0.013), normal serum albumin (p<0.0003), ISS 1-2 (p=0.004), and the use of NA (p<0.003) were independent prognostic factors significantly associated with extended OS. These results indicate that induction therapy with NA has a major impact on OS prolongation comparable to that of SCT and that combination with NA and SCT has further improved outcome in this subgroup of patients with MM.

P-111

Secondary MGUS is Frequently Associated with Superior Survival and High Depth of Response in Multiple Myeloma

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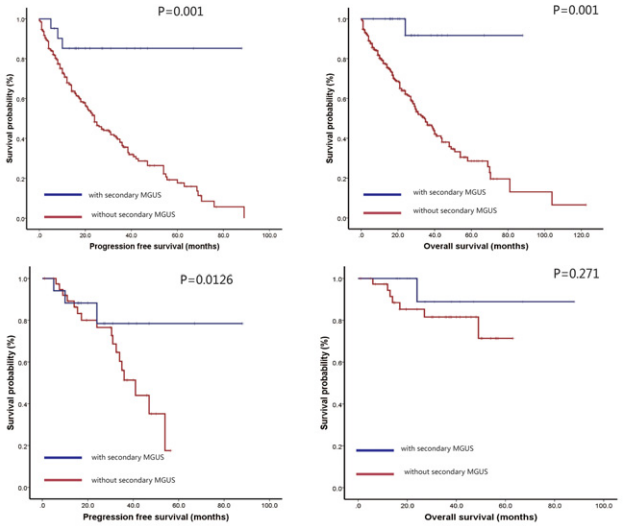
Secondary MGUS is a special phenomenon during the treatment of multiple myeloma (MM). The incidence, clinical features, cytogenetic characteristics and prognostic value of secondary MGUS remain undefined. We explored the prevalence, clinical characteristics and prognostic significance of secondary MGUS in 438 consecutive cases of patients with myeloma. Secondary MGUS was more common in patients with myeloma who had undergone SCT than in those who had not (17 [29.8%] of 57 patients versus 5 [1.4%] of 352, respectively; P＜.001). For the cohort as a whole, despite its low incidence, secondary MGUS predicted for significantly prolonged survival. Median PFS was not reached in patients with secondary MGUS (n=22) versus 24.0 months (95% CI: 20.2-27.8) in the rest of the cohort (P=0.001). Patients with MGUS also had a much longer OS, and median OS of this group was not reached compared with 34.5 months (95% CI: 28.1-40.9) in patients without secondary MGUS (p=0.001). In multivariate Cox regression model, the presence of secondary MGUS retained independent prognostic value of OS (HR 0.108 [95% CI 0.015-0.777], p=0.027) and PFS (HR 0.242 [95% CI 0.077-0.763], p=0.015). However, when analysis was restricted to patients undergoing stem cell

transplantation, no statistical difference in PFS and OS was found between patients with and without secondary MGUS. Secondary MGUS is frequently observed in MM patients after transplantation and confers a more favorable prognosis. The favorable survival could be explained by higher depth of response especially after myeloablative therapy.



P-112

t(11;14) Myeloma: a Unique Subtype Associated with Distinct Clinical Characteristics

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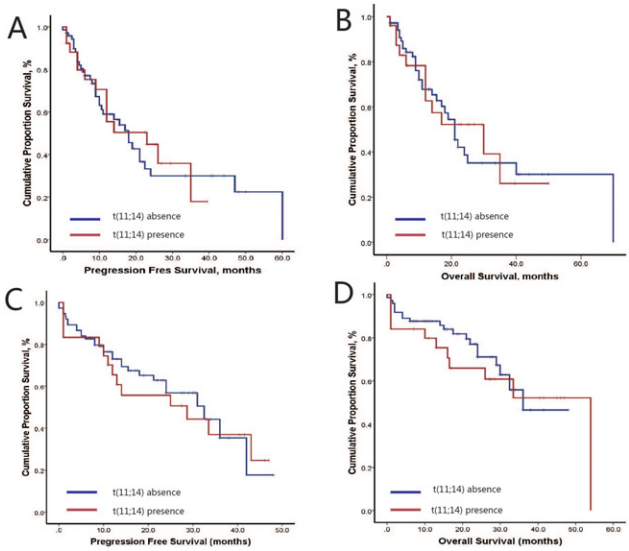
t(11;14)(q13;q32) is the most common chromosome translocation in multiple myeloma (MM) , but a consensus of clinicopathological features and impact on survival is yet to be reached. We analyzed a cohort of 350 patients with various plasma cell malignancies, including newly diagnosed MM (NDMM, n=253), relapsed/refractory MM (RRMM, n=77), as well as primary and secondary plasma cell leukemia (PCL, n=10 and n=10, respectively). A remarkably higher frequency of t(11;14) was observed in the PCL than in the NDMM. A high incidence of t(11;14) was detected in the IgD, IgM, and nonsecretory MM. The t(11;14) MM group was associated with a significantly higher positive rate of B-lineage associated antigens CD20 and CD79a as well as the lack of CD56 expression. A strong correlation between t(11;14) and the absence of 13q14 deletion was observed, and fewer patients displaying t(11;14) were identified as belonging to the high-risk cytogenetic group due to the extremely low incidence of t(4;14) and t(14;16). Patients exhibiting t(11;14) had a comparable outcome with the control cohort in NDMM and RRMM, but a small proportion of patients with extra cytogenetic aberration rapidly progressed to sPCL. Our findings suggest that the t(11;14) plasma cell disorder is a unique entity with distinct biological, clinical and laboratory features. t(11;14) has no impact on survival of NDMM and RRMM.



P-113

Chromosome Aberration in Chinese Patients with Multiple Myeloma: More High-risk MM was Found

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While cytogenetics abnormalities in Western patients with myeloma have been well documented, there are quite few reports from Chinese patients. The objectives of this study was to define the general patterns of cytogenetic abnormalities in Chinese patients with MM and to assess the prognostic value of each of the chromosome aberration by panel FISH detection in a large cohort of patients. Purified CD138+plasma cells were obtained from 306 patients with newly diagnosed MM. 261of the 306 (85.4%) newly diagnosed patients had more than one molecular cytogenetic aberrations. 13q deletions, 17p deletions, illegitimate IGH rearrangement, 1q amplification, t(11;14), t(4;14), t(14;16) were seen in 46.8%, 7.9%, 59.6%, 50.2%, 22.7%, 22.7%, 3.9% of all cases. According to Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) model, 33.2% patients were indentified into high-risk group. The newly diagnosed patients with t(4;14) (p=0.042), 1q21 gain(p=0.00), or 17p-(p=0.00) had shorter progress survival (PFS) and over survival (OS).

del(13)/del(13q) detected only by FISH was not an independent higher risk factor. t(11;14) did not predict superior or poor outcome. Our study demonstrated that genetically more high-risk MM were found in Chinese patients with multiple myeloma, and a direct comparison between Western and Asian patients is relevant. The prognostic value of cytogenetic aberration was similar to the reports from the Western country.

P-114

Prognostic Value of Serum LDH in Multiple Myeloma: a Revaluation in the Context of Cytogenetic Information Available

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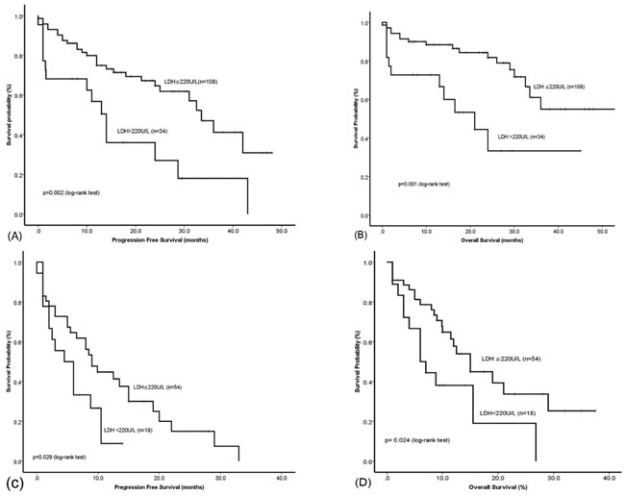
There are limited data about whether high serum lactate dehydrogenase (LDH) levels could maintain independent prognostic value in multiple myeloma (MM) in the presence of genetic-based testing. We retrospectively analyzed a consecutive cohort of patients with newly diagnosed MM (n=238) and relapsed MM (n=72) for whom pretreatment serum LDH values and complete fluorescence in situ hybridization (FISH) data were available. The distribution of chromosomal aberrations analyzed by FISH was similar between patients with and without elevated LDH, but a higher incidence of karyotype abnormalities was detected in patients with increased LDH. High LDH has no impact on survival of patients assigned to thalidomide-based chemotherapy group. Elevated LDH was associated with a negative impact on progression free survival (PFS) and overall survival (OS) with highly significant P values in both NDMM and RRMM treated with bortezomib-based chemotherapy, and increased LDH was able to maintain its significance in RRMM for PFS (HR 2.567 [95% CI 1.206-5.461], p=0.014) and OS (HR 2.553 [95% CI 1.160-5.622], p=0.020) in a multivariate analysis. But it lost independent prognostic value in NDMM in the presence of genetic information. In summary, we validated that increased LDH values could identify a group of patients with poor prognosis and aggressive disease characterized by high tumor masses and proliferative activity. A revaluation in the context of cytogenetic aberration information available indicated that elevated LDH was able to maintain its independent prognostic value in RRMM.



P-115

Prognostic Factors in Relapsed Multiple Myeloma: Role of Genetic Abnormalities

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The validity of most genetic abnormalities has been tested predominantly in the new diagnosis setting, prognostic value of cytogenetic alteration in relapsed myeloma is rarely described. Genetic progression events are likely to arise and the value of different prognostic factors possibly changes with advancing stages of MM. Purified CD138+plasma cells were obtained from 80 patients with relapsed MM. Of the 80 relapsed patients, 77 (96.3%) cases hand one or more molecular cytogenetic aberrations. 13q deletions, 17p deletions, illegitimate IGH rearrangement, chromosome 1q amplification, t(11;14), t(4;14), t(14;16) were detected in 61.3%, 22.5%, 68.9%, 75.6%、18%, 32.9%, 2.8% of all patients. 53.8% patients could be grouped into high-risk group according to mSMART model. However, only 13q deletion (p=0.009) and17p-(p=0.00) suggested worse survival, whereas t(4;14) and 1q21 gains lost prognostic values in this group of relapse/refractory patients. Our study demonstrated that genetically more high-risk MM were found compared with the newly diagnosed MM. The value of different cytogenetic abnormalities might change with advancing stages of the disease.

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A Phase I Study of Weekly Bortezomib for Japanese Patients with Recurrent or Refractory Myeloma.

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OBJECTIVE: We conducted a phase I study of weekly bortezomib to assess the safety, and to identify the maximaum tolerated dose in Japanese patients with myeloma. PATIENTS AND METHODS: Patients with recurrent or refractory myeloma, age 20-85 years, were eligible. Additional eligibility requirements included performance status of 0-2; neutrophil count =>1000/ μl; platelet count =>50,000/ μl; neuropathy <=grade (Gr.) 2; and adequate major organ functions. Patients previously treated with bortezomib were ineligible. This study consisted of two cohorts (level 1; bortezomib 1.3mg/m^2 i.v.: day 1, 8, 15, 22; Q5wks and level 2; bortezomib 1.6mg/m^2 i.v. scheduled similarly with level 1). A dose-limiting toxicity (DLT) was defined as any of the followings during the first cycle: Gr. 4 hematologic toxicity and Gr. =>3 non-hematologic toxicity per CTC criteria. A modified Fibonacci method was used for dose-escalation. This study was approved by the institutional review boards at all participating sites. RESULTS: Nine patients (age, 62-82 years old, median 71; M:F=3:6) were enrolled (level 1, n=3; level 2, n=3+3). None of the DLT was seen at level 1, and two out of six patients at level 2 experienced DLTs as follows: Gr. 3 diarrhea, Gr. 3 skin rash, and Gr. 4 thrombocytopenia. CONCLUSION: This study demonstrates tolerability of weekly bortezomib when given at 1.6mg/m^2 in Japanese patients with recurrent or refractory myeloma. We thus consider that weekly schedule of bortezomib given at 1.6mg/m^2 should be considered as a possible option in future trial of myeloma.

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Clinical Characteristics of 90 Multiple Myeloma Patients with Extramedullary Disease

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Background: In multiple myeloma(MM), plasma cell is usually restricted to the bone marrow. But a number of patients will develop extramedullary disease (EMD) at diagnosis or during the follow-up, showing a different clinical characteristics and a dismal prognosis. Methods: We studied 834 consecutive MM patients in a single center in China and compared clinical features of patients with and without EMD. Results and Conclusions: In general, the prevalence of EMD was 8.6% at diagnosis, and 3.4% during follow up, with significant increase in recent years. Patients with EMD at diagnosis had remarkably lower age, higher hemoglobin(HB) and lactate dehydrogenase (LDH), more ISS stage Ⅰ and more p53 deletion or mutation in bone marrow or tissue biopsies. EMD during follow-up was significantly correlated with EM presentation at diagnosis (HR 8.709,P<0.001), IgD subtype(HR 5.107,P=0.002)and light chain type of λ (HR 3.645,P=0.012). Precedent treatment of bortezomib (HR 0.697) , thalidomide (HR 1.112)or auto-transplant after high dose therapy (HDT) (HR 1.232) showed no correlation with the EMD. In the aspect of prognosis, EMD was associated with shorter overall survival(29 versus 40 months, P=0.01) and time-to progression(15 versus 25 months, P<0.001). In patients received HDT, EMD showed no negative effect in survival, suggesting this method may be beneficial in the survival of the EMD population.

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High Frequencies of Response after Limited Primary Therapy for Multiple Myeloma

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Recent bortezomib combinations have induced remission in approximately 90% of newly diagnosed patients but with frequent side effects. In order to reduce toxicity, and to prepare qualified patients for early intensification, we assessed the anti-myeloma effect and toxicity of 3 different bortezomib combinations in 40 patients between 1/2010 and 5/2012. Each treatment included bortezomib twice weekly x 4 with high-dose dexamethasone for two 4-day courses over an 11-day period; oral cyclophosphamide for the first 4 days was included in the first program (BCD); lenalidomide (25 mg/d) for 11 days and liposomal doxorubicin (30 mg/m^2) on day 4 in the second program (BLDD); and lenalidomide and cyclophosphamide in the third program (BLCD). Prophylactic acetylsalicylic acid and famciclovir were given to all patients. Response rates were high with BLDD and BLCD (92% PR+CR). Side effects were infrequent, mild, reversible, and without grade 3 neuropathy or DVT; the median nadir for neutrophils was 2.5 x10^9/L, and for platelets was 148 x10^9/L. Onsets of remission were usually rapid so that no more than 2 courses of therapy were required before early HDT (after median 4.4 months) was given to those who qualified, or providing a maintenance program for those who did not. Our

combination of novel agents avoided the need for protracted primary treatment of myeloma, and with less toxicity and cost, prior to HDT or maintenance therapy. The combination of BLCD was an effective program with low toxicity that should be evaluated further in more patients.

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Rational Selection of Patients with Multiple Myeloma for Intensive Therapy

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Among 274 patients with multiple myeloma treated from 2000-2011 with primary thalidomide or bortezomib-based combinations, 70% received intensive therapy (high-dose melphalan, HDT) supported by autologous stem cells within the first year. After excluding 21 patients who died (18) or were lost to follow up within 1 year (3), significantly longer survival times after landmark of 1 year were observed for those with CR (median 8.9 years) or PR (median 4.9 years) in comparison with NR (median 10 months) (p<.01). Survival of those with CR or with persistent PR was not prolonged by HDT. Pretreatment disease stage did not correlate with survival, but survival was shorter for those >65 (median 4.3 years) than for younger patients (median 5.5 years) (p=.01). Early HDT converted primary resistant disease to PR in 20 of 26 patients, with survival similar to that of patients with primary PR. HDT converted disease from PR to CR in 42% of 103 patients with pre-transplant serum myeloma protein ≤1.0 gm/dl, or with only Bence Jones protein <0.2 gm/d, but in none of 32 patients with higher levels (p<.01); survival of those converted to CR was similar to that of patients with primary CR. Early HDT prolonged survival only among patients with NR that converted to PR or with PR that converted to CR. Restriction of HDT to the two-thirds of patients most likely to benefit regardless of age would avoid the toxicity and cost of intensive therapy for other patients.

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Impact of Donor KIR Haplotype on Survival after Allogeneic Hematopoietic Stem Cell Transplantation

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We investigated natural-killer (NK) cell allo-reactivity determined by donor killer-cell immunoglobulin-like receptors (KIRs) in 118 patients with multiple myeloma who underwent allogeneic stem cell transplantation (SCT) from unrelated donors (n = 81) or HLA-identical sibling (n = 37). After a median follow-up of five years, the estimated progression-free (PFS) was not influenced by KIR-ligand mismatch or KIR-receptor ligand-mismatch but was significantly better for KIR haplotype B donors in comparison to KIR haplotype A donors (30 vs. 14 %, p = 0.009). The PFS benefit for KIR haplotype B was mainly seen in HLA-matched patients (4y DFS: 39 vs. 18 %, p = 0.005), while in HLA mismatch transplantation the difference according to KIR haplotype did not reach statistical significance (26 % vs. 18 %, p = 0.5). In a multivariate Cox model KIR haplotype A remained a significant factor for worse PFS (HR: 1.82, p = 0.008) and overall survival (HR: 1.69, p = 0.042). Other significant factors for survival in the multi¬variate analysis were female donor sex (HR: 1.67, p = 0.04) and chemo-refractory disease at transplantation (HR: 1.76, p = 0.03). In multiple myeloma a male donor harboring. KIR-haplotype Bx should be considered as donor for allogeneic SCT.

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Lenalidomide Maintenance after Toxicity-reduced Allograft Salvage Therapy for Refractory/Relapsed Myeloma Patients

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We investigated a myeloablative toxicity-reduced allograft (aSCT) consisting of intravenous busulfan (12.2 mg/kg) and cyclophosphamide (120 mg/kg) followed by lenalidomide maintenance therapy in 33 patients with multiple myeloma (MM) who relapsed to an autograft. The median duration remission after autograft was 12 months . The cumulative incidence of non-relapse mortality at 1 year of 6% (95% CI: 0-14). After a median interval of 168 days after aSCT 24 patients started with a median dose of 5 mg (r: 5-15) lenalidomide without dexamethasone and a median of 6 cycles (r: 1-30). During follow-up 13 patients discontinued lenalidomide due to progressive disease (n=6), graft-versus-host disease (GvHD n=3), thrombocytopenia (n=2), or fatigue (n=2). Major toxicities of lenalidomide were GvHD II-III (28%), viral reactivation (16%), thrombocytopenia (III-IV° :16%), neutropenia (III/IV° : 8%), peripheral neuropathy (I/II° : 16%), or other infectious complication (8%). Cumulative incidence of relapse at 3 years was 42% (95% CI: 18-66). The 3-year estimated probability of progression-free and overall survival was 52% (95% CI: 28-76) and 79% (95% CI: 63-95) respectively. Toxicity-reduced myeloablative allograft followed by lenalidomide maintenance is feasible and effective in relapsed patients with multiple myeloma resulting in an acceptable treatment-related mortality, but the induction of GvHD should be considered.

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Dose-finding Study of Lenalidomide Post Allogeneic Stem Cell Transplantation in Multiple Myeloma

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Background: Lenalidomide may prevent relapses after allogeneic stem cell transplantation by promoting the immune-mediated graft-versus-tumor effect. Design and Methods: We performed a prospective phase I/II study to define the dose-limiting toxicity (DLT) as well as the immunological effects of lenalidomide given early (day 100-180) post allograft for 4 cycles in patients with multiple myeloma (MM). Results: According to the Fibonacci design 24 patients with a median age of 53 years were included. Dose limiting toxicity was organ toxicity due to graft-versus-host disease and the maximal tolerable dose was 5 mg. The incidence of graft-versus host disease after lenalidomide was 38%occurring after a median of 22 days and was beside organ toxicity a leading cause to discontinue the study in 29% of the patients. Immune monitoring revealed a significant increase in peripheral γ -interferon-secreting CD4+ and CD8+T cells within the first week of lenalidomide treatment followed by a delayed increase in T regulatory cells . Furthermore, natural killer (NK) cells isolated from the peripheral blood of patients evidenced a significantly improved anti-myeloma activity after lenalidomide treatment. Conclusion: The DLT of lenalidomide early post allogeneic SCT in MM is 5 mg, however GvHD remains a significant factor evenat doses of 5 mg. The immune effect might have contributed to the increased CR rate from 24% to42% after lenalidomide treatment since non-responding patients did show significant less NK and T cell activation. (Study registered under: NCT 00778752)

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Lenalidomide Offers a Survival Advantage in Myeloma Patients When Administered after Allogeneic Transplantation

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Lenalidomide (Len) is an effective drug against multiple myeloma (MM), with several effects, including immunomodulation. This property is attractive in the setting of allogeneic stem cell transplantation (AlloSCT), since Len may interact favorably with the graft-versus-MM effect. To verify this issue, we conducted a case-matched analysis comparing

Len after autologous SCT (AutoSCT) vs. Len after AlloSCT. The matching criterion was the number of treatment lines received before Len. Baseline characteristics between Auto and Allo patients (pts) were similar, except for age at diagnosis (55 years, range 39-70, in Auto pts; 47 years, range 29 - 62, in Allo pts). Median time from transplant to Len start was 50 months (range 7-159) in Auto, and 21 months (range 6-134) in Allo pts. In all cases Len dosage was 25 mg, and it was always combined with dexamethasone. Best responses for Auto and Allo patients were as follows: 5 vs. 3 CR, 6 vs. 8 VGPR, 12 vs. 13 PR, 9 vs. 8 SD, 8 vs. 8 PD. With a median follow-up from of 22 months (range 2-60+), 3-years progression-free survival (PFS) was 13% in the Auto, and 43% in the Allo group (p=0.03). Median PFS was 9 months in Auto, and 16 months in Allo pts. Median OS was 22 months in the Auto group, and was not reached in the Allo group (p=0.05). Hematological and extra-hematological toxicities were mild and similar among the 2 groups. In the Allo group 3 pts had a worsening of a pre-existing extensive cGVHD. In conclusion our study suggests that Len is more active when given after AlloSCT, still retaining a favorable toxicity profile.

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Lenalidomide and Dexamethasone in Overtreated Multiple Myeloma Patients: a Monocentric Experience

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Background. Lenalidomide is a therapeutic option for pretreated patients with multiple myeloma, especially in association with steroids. Methods. Oral daily lenalidomide (Len) for 21 days every month (median courses 9.7) and weekly dexamethasone (Dex) were administered until progression in 41 pretreated patients (median age 66.2 yrs) observed between June 2008 and January 2013. Past therapy included alkylants, anthracyclines, IFN-a, IMIDs and autograft. Twentyfive patients were evaluated after 6 courses of therapy and prospectively followed-up; two patient weren't considered because of early death. Treatment response was assessed according to IMWG uniform response criteria. Results. ORR was 56% (14/25 pts) with a median duration of response of 13 months: 1 patient reached CR, 1 VGPR, 12 PR, 10 SD and 1 PD. Among responder patients, 4 died due to progression disease after a median of 16.5 courses, while 9 are in continuous treatment (3 with over 33 courses each) and 1 in salvage therapy; among non responder ones, 7 died for PD, while 3 are in continuous treatment and 1 in salvage therapy. The median PFS was 14.8 months. The reported side effects included pneumonia, anemia, neutropenia, DVT, diarrhea, peripheral sensitive polyneuropathy, headache, transient liver failure, cutaneous rash, transient aphasia, all resolved with brief therapy discontinuance and specific support therapy. Conclusions. This study shows that Len-Dex combination is an effective oral salvage therapy with good response rate and manageable side effects for relapsed and refractory multiple myeloma patients.

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Myeloma in Scar: an Under-reported Phenomenon or an Emerging Entity in the Novel Agents' Era?

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Tumor relapse in scar tissue is uncommon but well-described in cancer patients. However, extramedullary plasmacytoma (EMP) relapse in scar tissue in the setting of multiple myeloma (MM) has rarely been reported. We report a series of three MM patients whose disease relapsed as EMP in a wound site of previous invasive procedures. All relapses were confirmed histologically.The three patients were treated for the relapsed disease with different treatment modalities, including combination therapies and/or localized radiotherapy. All three patients failed to respond adequately to the various treatments administered and died 3, 6 and 10 months after relapse. At diagnosis, all had advanced stage disease (stage IIIA) with no evidence of extramedullary disease. The three patients were treated with novel agents with or without autologous hematopoietic stem cell transplantation and achieved either complete or very good partial response. We suggest that these treatments, which have become the standard of care in MM, enable predominance of myeloma subclones which are independent of bone marrow microenvironment. These myeloma subclones then gain survival advantage in the active scar tissue niche, allowing for their uncontrolled proliferation. This small but largest to date case series might represent an under-reported phenomenon and might therefore indicate an emerging and difficult to treat resistant disease in the era of targeted therapies in MM. Physicians treating MM patients should be aware of this phenomenon, especially when referring them to invasive surgical procedures.

Table: Clinical Characteristics of 7 Cases of Multiple Myeloma Recurrence in Scar

Patient (Ref)	Paraprotein	Stage*	Prior treatments	HSCT	Type of invasive procedure	EMP Localization	Treatment given for EMP	outcome
Case no 1 (current series)	IgG kappa	IIIA	MP(R), len-dex	no	Internal fixation of humerus fracture	arm	Radiotherapy, VDT-PACE, bendamustine	PD, died 10 months after recurrence
Case no 2 (current series)	IgG kappa	IIIA	VDT-PACE, VD(T), BRd	autologous	Debulking of para-sacral mass	Sacral region	radiotherapy	PD, died 6 months after recurrence
Case no 3 (current series)	IgG lambda	IIIA	(VDT-PACE, VD, len-dex, CTX-prednisone, bendamustine	autologous	Tooth extraction	Gingiva	radiotherapy	PD, died 3 months after recurrence
Cotter 2003[1]	IgG lambda	n/a	radiotherapy	no	cardiac surgery	sternotomy scar	Radiotherapy, MP	PD, died
de Larrea 2010[2]	IgG lambda	IIIA	VBCMP/VBAD, prednisone IFNa2b, VCD+radiotherapy,	autologous	osteosynthesis	humerus	CTX+dex	PD, died soon after recurrence
Rosenblum 2003[3]	IgG kappa	IIIB	VAD	autologous	CVC insertion, hemodialysis catheter, SC injection	Supraclavicular, leg, triceps/deltoid	Lenalidomide	PD, died one month after recurrence
Trullemans 2000[4]	Kappa light chain	IIIA	standard chemotherapy**, radiation	syngeneic	Trauma to leg	leg	radiotherapy	CR, "progression-free with a follow-up of 24+ months"

* According to Durie-Salmon staging system
** No further details.
Abbreviations: HSCT= hematopoietic stem cell transplantation; IgG=immunoglobulin G; n/a=not available; MP(R)=melphalan, prednisone, (lenalidomide); PD=progressive disease; VBCMP/VBAD=Vincristine, carmustine, melphalan, cyclophosphamide and prednisone alternating with vincristine, DCNU, adriamycin and dexamethasone; IFNa2b=interferon a2b; VCD=bortezomib, cyclophosphamide, dexamethasone; VAD= vincristine, adriamycin, dexamethasone; CVC=central venous catheter; SC=subcutaneous; CR=complete remission; len-dex=lenalidomide, dexamethasone; (VDT-PACE= (bortezomib), dexamethasone, thalidomide, cis-platinum, adriamycin, cyclophosphamide, etoposide; VD(T)=bortezomib, dexamethasone, (thalidomide); BRd=bendamustine, lenalidomide, dexamethasone; CTX=cyclophosphamide

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Outcomes of Second Autologous Transplantation Prepared with IV Busulfan and Bortezomib for Relapsed Multiple Myeloma

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Second autologous hematopoietic stem cell transplantation (ASCT) is effective for some patients with relapsed multiple myeloma (MM) after first ASCT. This prospective, multicenter Phase II study tested safety and efficacy of a conditioning regimen using intravenous busulfan (IV Bu) with bortezomib (Vel) in that setting. IV Bu dosing was individualized based on a pre-conditioning pharmacokinetics using a small test dose. Median 3.4 mg/kg (range: 2.0-4.7) of IV Bu was daily administered from Day -5 through Day -2, followed by Vel (1.3 mg/m2) on Day -1. 30 patients were enrolled at 11 centers in the US and Canada. ECG at screening and Day -1 showed no significant changes. There were no instances of seizure, worsening neuropathy or hepatic veno-occlusive disease meeting the Baltimore criteria. The most common grade 3 or 4 adverse events were febrile neutropenia (50.0%) and stomatitis (43.3%). One transplant-related death occurred due to pulmonary complications. Whereas no patient was in complete response (CR) at enrollment, two patients (6.7%) achieved CR at 6 months. Additionally, out of 9 patients with progressive disease (PD), five who had undergone 1st ASCT more than 2 years ago had improved disease status: 1 CR, 1 Very Good Partial Response, 1 Partial Response and 2 Stable Disease as best response. As the remaining four whose interval was less than two years had no improvement from PD, 2nd ASCT apparently benefited patients with PD only when 1st ASCT was done more than 2 years ago. In conclusion, a combination of IV Bu and Vel prior to 2nd ASCT was safe and efficacious.

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Azacitidine with Lenalidomide and Low-dose Dexamethasone (Rd) in Relapsed or Refractory Myeloma (RRMM): Phase I Results

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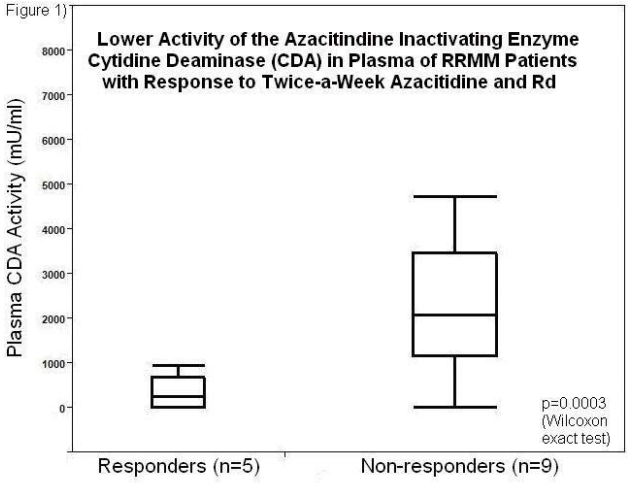
Background: Azacitidine (aza) may overcome MM refractoriness by reactivation of pathways required for senescence, terminal differentiation, cell death, and immune attack. Methods: Aza was escalated from 30mg/m^2 SC weekly to 50mg/m^2 SC twice-a-week (BIW) with fixed Rd (25mg d1-21/40mg weekly). Results: 21 patients (pts) with relapsed (n=1) or re-

fractory (n=20) MM and GFR >= 60ml/min were enrolled after a median of 4 (1-13) prior regimens. 18 pts were refractory to lenalidomide (len), 17 to bortezomib and/or carfilzomib, and 15 to len and proteasome inhibitors. One DLT (neutropenic fever) was observed at dose level (DL)4 (40mg/m^2 BIW), none at the target DL5. Grade 3/4 adverse events consisted of neutropenia (n=9), thrombocytopenia (n=4), neutropenic fever (n=2), diarrhea (n=1), depression (n=1), deep venous thrombosis (n=1), and pleural effusion (n=1). Weekly aza yielded one MR (EBMT) in 6 pts. With BIW dosing responses increased to >= PR (Uniform) in 4 (27%) and to >= MR in 5 (33%) of 15 pts including 1 VGPR at DL5 and responses in 3 len refractory and 2 sPCL pts. The main aza inactivating enzyme, plasma cytidine deaminase (CDA), was measured in 14 BIW aza pts and found significantly lower in responders (p=0.003, fig.1). Conclusions: Azacitidine (aza) together with standard Rd was well tolerated up to target 50mg/m^2 SC twice a week which will be used for phase 2 extension. So far, responses to Rd/azaBIW in refractory MM are in the range reported for pom/dex or carfilzomib. Lower plasma CDA activity in responders suggests longer aza half-life enabled response.

Figure 1)



P-128

Treatment for Refractory/Relapsed Multiple Myelom with Thalidomide-based Regimens; a Single Institutional Analysis

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To assess effects and safety of thalidomide-based regimens for refractory/relapsed multiple myeloma, we retrospectively analysed patients treated between Aug. 2006 and Dec. 2012 in our hospital.Results: 46 patients were followed-up for 105 d - 11y 1mo (median 3y 10 mo), male 23/female 23, age 37-82(70), subtype: IgG 27, IgA 15, IgD 1, BJP 3, ISS stage: I:6, II:18, III:17, unknown: 5, Chromosome abnormality:12/40, 13q- (FISH): 6/10, prior regimen number: 1-5(2), auto-PBSCT:8. T dose 100 mg/d, T alone: 17, T+/-dexamethasone(d): 23, MPT:11, aspirin: 6, treatment following T in 29 patients: lenalidomide +/- d :15, bortezomib +/- d :8, MP: 3, others:2, best response, response just after T and at the final follow-up; ORR(PR≦): 20, 16, 20, CR:0, 0, 2, VGPR: 4, 4, 2, PR:16, 12, 16, SD: 20, 20, 12, PD: 6, 10, 14, respectively. 34 patients were alive at the final follow-up. OS: 4.58y(95% CI: 4.16-), PFS: 4.16y(3.04-), Time to next treatment (TNT) : 2.00y(1.41-3.00). Adverse effects(AE) (grade 3≦): 6, PN:1, anemia:1, neutropenia:2, thrombocytopenia:2, VTE:2. Reason to discontinue T: SD 6, PD 9, AE 13(PN 9, eruption 2, dizziness 1, drowse 1, anorexia 1, nausea 1, anemia 1, thrombocytopenia 1, pancytopenia 1). OS, PFS, and TNT are not statistically different between patients younger or older than 65y or 75 y, and ISS stage does not predict OS, PFS, and TNT. Conclusion: Thalidomide - based regimens, followed by lenalidomide, bortezomib, are effective and feasible therapy for RRMM for durable disease control.

P-129

Transition of Second Primary Malignancy of Myeloma in Era of New Therapeutic Agents

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【Introduction】 After new therapeutic agents for multiple myeloma are used commonly, subsequent secondary primary malignancies(SPMs) may have been changed in various aspects. We analyzed such kind of SPMs in Kyushu Cancer Center, for thirty two years, throughout both eras. 【Patients and Methods】 1) There were twenty SPMs(20/225;8.9%) including six synchronous ones(6/20;30%). 2) M/F; 13/7 3) Among fourteen metachronous SPMs mean latent period was 74.5 months. 4) SPMs consisted of 12 solid tumors and 8 hematologic malignancies as follows; GI tract 6, HCC 2 and so on for solid tumor, and RA 1, RAEB 3, CMMoL 3 and so on for hematologic malignancy, respectively. 5) Five patients are alive, while 15 patients died. 6) Fifteen patients of SPMs have been treated with alkylating agents but never with new therapeutic agents namely, Bortezomib, Lenalidomide and Thalidomide. Rest of 5 patients have been given at least one of the three drugs. Simple primary incidence of SPNs before and after new therapeutic agents were 15/112(13.4%) and 5/62(8.1%). MST from the diagnosis as SPMs of the former and of the latter was 16 months and not reached, respectively. 5-y OS of the former 10.0% and 53.3%, respectively.

【Discussion】 Not only an incidence of SPMs of myeloma are reduced , but also the results of therapy-related SPMs improved. This depends on many factors, such as length of follow-up period, mechanism inducing SPMs, improvement of supporting therapies and so on. Even if a risk of SPMs is taken account of, prognosis of multiple myeloma becomes far better for the new therapeutic agents.

P-130

Daratumumab, a CD38 Monoclonal Antibody in PTS with Multiple Myeloma (MM) - Data from a Dose-escalation PH I/II Study

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Background

Daratumumab (DARA) is a human CD38 monoclonal antibody (mAb) with broad-spectrum killing activity. In this first-in-human dose-escalation study of DARA in pts with relapsed or refractory (RR) MM the safety profile has been acceptable and preliminary efficacy data has been favorable. Here, we present updated phase I safety, efficacy, immunogenicity (ADA) and complement titer CH50 results.

Objectives

To establish the safety profile and maximum tolerated dose and assess efficacy, PK and ADA.

Methods

Pts ≥18yrs with RR MM after at least 2 prior lines of therapy and ineligible for ASCT were enrolled. The study design was 3+3 dose-escalation. DARA was administered over an 8wk period as 2 pre- and 7 full doses, ranging 0.005-24mg/kg. Efficacy was evaluated according to IMWG guidelines. ElectroChemiLuminescence was used for ADA detection. CH50 titer was analysed by liposome immunoassay.

Results

32 pts were enrolled. Median age was 61yrs. Median number of prior treatment lines was 6. For groups ≥4mg/kg, 9/12 pts achieved a reduction in paraprotein of which 7 pts had a 50-100% concomitant reduction in bone marrow plasma cells. No detectable ADA was seen. CH50 data are currently in process. Most common AEs were infusion related (IREs); two of the IREs were grade 3 and the remaining grade 1-2. Six SAEs were assessed related to DARA.

Conclusion

Marked reduction in paraprotein and bone marrow plasma cells was seen in the higher dose cohorts suggesting anti-myeloma activity of DARA not previously demonstrated with a single-agent mAb. No ADA was seen and toxicity proved manageable.

P-131

Comparative Effectiveness of Lenalidomide plus Dexamethasone versus Bortezomib Subcutaneous for the Treatment of RRMM

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Objective: To evaluate the comparative effectiveness (CE) of lenalidomide plus dexamethasone (LEN/dex) versus bortezomib subcutaneous (BTZ SC) for the treatment of relapsed/refractory multiple myeloma (RRMM). Outcomes of interest were time to progression (TTP) and overall response rate (ORR). *Methods*: A systematic review (SR) was conducted to identify randomised controlled trials (RCTs) investigating the clinical efficacy of topical RRMM therapies. In the absence of head to head trials, data from included studies were analysed to determine the CE of LEN/dex vs. BTZ SC utilising a mixed-treatment comparison (MTC) methodology. Results for TTP are reported as hazard ratio (HR) and 95% confidence interval (CI); results for ORR are reported as odds ratio (OR) and 95% CI. Advantage to treatment is denoted by HR/OR >1 with statistical significance represented by positive CIs. *Results*: 16 original RCTs met the inclusion criteria; 12 and 6 of which were able to be connected to form a network of evidence for MTC analysis of ORR and TTP respectively. Two trials directly investigated the efficacy of LEN/dex (N = 353) and one trial directly assessed the efficacy of BTZ SC (N = 148). TTP analysis was statistically significant and favoured LEN/dex over BTZ SC (table). ORR analysis was also statistically significant in favour of LEN/dex over BTZ SC (table). *Conclusions*: MTC analysis demonstrated superiority in clinical efficacy to LEN/dex compared with BTZ SC for the treatment of RRMM. This superiority was shown to be statistically significant for both clinical outcomes of TTP and ORR.

Table: MTC results for TTP & ORR analyses

	Time to progression		Overall response rate	
	HR	95% CI	OR	95% CI
Lenalidomide/dexamethasone vs. bortezomib subcutaneous	1.86	1.08, 3.23	1.96	1.01, 3.79

P-132

Weekly Bortezomib plus Dexamethasone Therapy for Elderly Patients with Relapsed or Refractory Myeloma (JMSG-0902)

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Bortezomib is a proteasome inhibitor with a marked antitumor effect in patients with newly-diagnosed and in patients with refractory multiple myeloma (MM). However, twice-weekly administration of bortezomib has been reported to have severe adverse effects (e.g., peripheral neuropathy) that could result in treatment discontinuation. Therefore, we have evaluated the efficacy and feasibility of treatment with weekly bortezomib plus dexamethasone in patients aged 60-85 years with relapsed and/or refractory MM. A total of 39 patients (17 males and 22 females) who had received more than one previous therapy were enrolled. There were 29, 5, 1, and 4 patients with IgG, IgA, IgD, and light chain MM, respectively. There were 9, 17, and 13 patients with International Staging System stage I, II, and III disease, respectively. Previous treatment included conventional chemotherapy and radiation in 30 patients, IMiDs in 7, and autologous stem cell transplantation in 4. Bortezomib (1.3 mg/m2) and dexamethasone (20 mg/body) were given on days 1, 8, and 15 in a 4-week cycle. Among 27 evaluable patients, 2 (7%) attained a stringent complete response, 1 (4%) very good partial response, 6 (22%) partial response, and 14 (52%) stable disease. The most common adverse events were diarrhea (30%), constipation (22%), and thrombocytopenia (22%). Peripheral neuropathy occurred in 4 patients (1 Grade 1, 2 Grade 2, and 1 Grade 3) but was manageable. Thus, once-weekly administration of bortezomib plus dexamethasone is considered a reasonable option for elderly patients with relapsed and/or refractory MM.

P-133

Lenalidomide is Effective for the Extramedullary Disease in Patients with Multiple Myeloma: Report of 5 Cases

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The presence of extramedullary(EM) disease of multiple myeloma(MM) is the poor prognostic factor. Few studies have been reported about appropriate treatment of patients with EM disease of MM. Bortezomib has been mentioned to be the preferred choice of treatment for EM disease of MM. There is little information about the effect of lenalidomide on EM disease. We report 5 cases of refractory MM with EM disease that were successfully treated with lenalidomide-based regimens. Median age of 5 patients(3 men and 2 women) was 73 years(59-90 years). A chromosome 13 deletion was observed in 1 patient. EM disease of MM occurred at primary diagnosis in 2 patients, other was occurred during the disease. EM diseases were shown at pleural lesion in 3 patients, cervical lesion in 1 patient and paravertebral lesion in 1 patient. 4 patients received bortezomib-based regimens before lenalidomide therapy. All patients received dexamethasone combined with lenalidomide.1 patient received BiRD (clarithromycin/,lenalidomide/ dexamethasone) combination therapy.All patients showed some response in the EM disease including complete disappearance in 1 patient and reduction in size in 4 patients.2 patients were still alive(1 in CR,1 in PR) from 2 to 13 months after therapy with lenalidomide and 3 were died due to disease progression. These cases suggests that lenalidomide could be a useful agent for treating bortezomib-resistant EM disease in patients with refractory MM.

P-134

Bortezomib-melphalan-prednisone-thalidomide Followed by Continuous Bortezomib-thalidomide (VMPT-VT) Improved Survival

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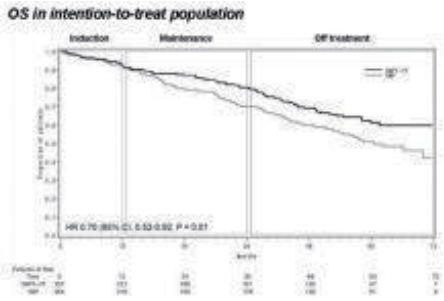
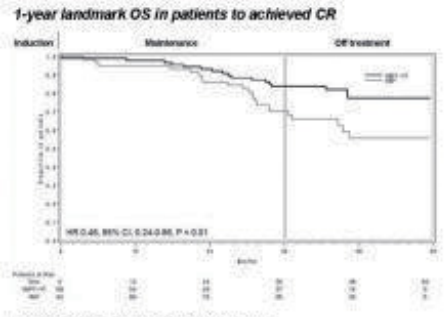
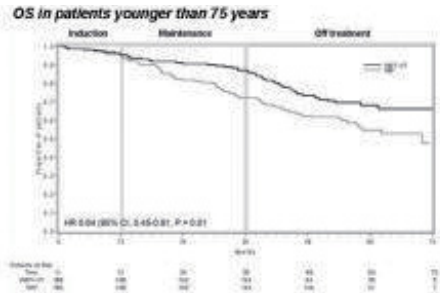
Background: In a multicenter phase 3 trial, VMPT-VT was superior to VMP for response rates, PFS and TNT. Here we report an updated analysis on OS after 54 mos of follow-up. Methods: Pts (N=511) were randomly assigned to receive nine 6-week cycles of VMPT-VT (induction: bortezomib 1.3 mg/m2 d 1,4,8,11,22,25,29,32 cycles 1-4, d 1,8,22,29 cycles 5-9; melphalan 9 mg/m2 d 1-4; prednisone 60 mg/m2 d 1-4; thalidomide 50 mg d 1-42; maintenance: bortezomib 1.3 mg/m2 every 14 days and thalidomide 50 mg/d up to 2 years) or VMP alone. After the inclusion of 139 pts, the protocol was amended: both VMPT-VT and VMP induction were changed to nine 5-week cycles and bortezomib schedule was modified to weekly administration (d 1,8,15,22). Results: The median PFS and TNT were longer with VMPT-VT (35.3 and 46.6 mos, respectively) than with VMP (24.8 and 27.8 mos, respectively; HR 0.58 and 0.52; P<0.0001). The 5-year OS was greater with VMPT-VT (61%) than with VMP (51%; HR 0.70; P=0.01). The OS benefit was mainly noticed in pts < 75 years (HR 0.64; P=0.01), with ISS I/II (HR 0.66, P=0.04) or with CR after treatment (HR 0.45; P=0.01). In the landmark analysis, median OS from start of maintenance was greater in pts who received VT (4-year OS 67% vs 55%; HR 0.63; P=0.006).During maintenance 7% of pts experienced grade 3-4 peripheral neuropathy, 5% hematological toxicity, 3% infection and 12% discontinued due to adverse events. Conclusions: VMPT-VT improved OS in pts not eligible for transplantation.The benefit was greater in pts < 75 years, pts with good prognosis or with chemosensitive tumor.







P-135

Bendamustine, Velcade and Dexamethasone (BVD) is Effective in MM Patients Pre-treated with Bortezomib and Lenalidomide

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Bendamustine seems to be effective in relapsed-refractory Multiple Myeloma (rrMM). We evaluated the efficacy and toxicity of the combination Bendamustine (70 mg/m2 days

1, 8), Bortezomib (1.3 mg/m2 days 1, 4, 8, 11) and Dexamethasone (20 mg day and day after Bortezomib) administered every 28 days for 6 cycles and every 56 days for further 6 cycles in patients with rrMM treated with less than 5 prior lines of therapy and not refractory to Bortezomib. Primary end-point of the study was ORR after 4 cycles. Seventy-three patients have been enrolled. Median age was 68 years (range 41-85), 26% had ISS stage III and 31% LDH above normal. Prior treatments were 1-2 and 3-4 in 83% and 17% of patients, respectively. All patients had received new-drugs (55% Thalidomide, 44% Bortezomib, 53% Lenalidomide, 15% Bortezomib+Lenalidomide) and 33% were refractory to the last treatment. After 4 cycles of BVD, ORR was 71% (CR: 16%, VGPR: 19%, PR:35%) while 19% of patients achieved SD and 10% had PD. ORR was significantly higher in patients not pre-exposed with bortezomib (87% vs 63%; p=0.023). After a median follow-up of 10 months, median TTP was 17 months and 1-year OS was 78%. Factor adversely affecting TTP were platelets < 100 x 109/l (p=.028) and 3-4 prior therapies (p=.035). Main grade 3-4 side effects were thrombocytopenia (33%), neutropenia (18%), infections (13.5%; grade 5:5.5%) and neuropathy (8%). BVD regimen was tolerated and effective particularly in early relapsed MM patients even if pre-treated with Lenalidomide and/or Bortezomib.

P-136

Lower Plasma miR-92a Levels in Newly Diagnosed Symptomatic Multiple Myeloma Patients with Poor-risk Cytogenetics

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Purpose: Cytogenetic abnormalities (CAs) are important factors for the prognosis of multiple myeloma (MM). Plasma miRNA profiling has showed considerably lower plasma miR-92a levels in MM patients (Yoshizawa et al. Blood Cancer Journal 2(1):e53, 2012). Here, we evaluated a possible association between plasma miR-92a levels and cytogenetic classification. Methods: We measured plasma miR-92a levels (miR-92a/miR-638) by qRT-PCR in 61 patients recently diagnosed with symptomatic MM; 48 of these were evaluated for evident CAs by using fluorescence in situ hybridization (FISH) and conventional cytogenetic studies. We also analyzed the clinical relevance of plasma miR-92a levels with respect to CAs. Results: Chromosomal aberrations were noted in 21 (44%) MM patients after diagnosis, including 9 patients with t(4;14), 5 with t(11;14), 3 with t(14;16), 1 with del(17p), and 1 with del(13q). Between MM patients with and without poor CAs, there were no significant differences in β2M and albumin levels (P = 0.791 and 0.314, respectively), International Staging System stagings (P = 0.2963). The plasma miR-92a level was significantly lower in the newly diagnosed MM patients with poor-risk CAs than in those with good-risk CAs (P = 0.0155). Conclusion: The plasma miR-92a values vary across poor- and good-risk cytogenetics in newly diagnosed MM patients. Our study indicates that plasma miR-92a levels may not only function as novel biomarkers for diagnosis, but may also be helpful for prognostic stratification, even in patients with inadequate cytogenetic results.

P-137

Consolidation with VTd Improves the CR Rate Following VTd Induction and Single Autotransplantation in Multiple Myeloma

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Background. Studies have demonstrated the impact of VTd (Bortezomib-Thalidomide-dexamethasone) on response and PFS upfront in Myeloma; but no data is available regarding VTd consolidation in a VTd induction regimen followed by single auto (VTd-auto-VTd). We assessed efficacy and safety of VTd-auto-VTd regimen as compared to VTd-auto without consolidation. Method. 121 newly diagnosed MM across 9 IFM centers were eligible for the VTd-auto-VTd regimen and 96 for the VTd-auto without consolidation in the same period of time. Results. In the whole study, the median age was 56 years, 50% had ISS 2 and 3, 22% had adverse FISH (similar across groups). The ORR was identical across cohorts at completion of therapy, 92.5% and 94%. Nevertheless CR rate

was significantly greater in VTd-auto-VTd, 52% vs. 34%, respectively (p=0.003). CR rates were identical after induction and after ASCT across cohorts. With median follow-up of 30 months, the relapse rate was lower in the cohort VTd-auto-VTd, 21% and 45%, respectively (p=0.001); consequently improving the median TTP, not reached and 35 months, respectively (p=0.034). The expected 4-years TTP was 85% and 53% in either cohort, respectively. The safety profile of VTd-auto-VTd was superimposable to VTd-auto without consolidation. Conclusion. This study showed an impressive increase in CR rate in relation to the consolidation that translated into a prolonged TTP. VTd-auto-VTd compared very favorably to the other upfront protocols, and may become in the near future a standard of care in newly diagnosed patients with Myeloma.

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Phase 1/2 Study of Carfilzomib Replacing Bortezomib for Multiple Myeloma (MM) Pts Refractory to a BTZ-containing Regimen

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Data has suggested single-agent carfilzomib (CFZ) can produce response for MM pts refractory to prior bortezomib (BTZ)-containing regimens. This Phase 1/2 trial investigated CFZ as a replacement for BTZ in the most recent BTZ-containing regimen on which pts have progressed. CFZ IV over 30 min replaced BTZ in each regimen on D1, 2, 8, 9, 15, & 16 of each 28-day cycle. CFZ doses were escalated in each of the first 4 cycles from 20 to 27, 36, and 45 mg/m^2 or until MTD was reached for that regimen. Aside from CFZ replacing BTZ, regimens were identical to the most recent BTZ-containing regimen. To date 33 pts were treated with CFZ in 13 different combination regimens containing ascorbic acid, bendamustine, clarithromycin, cyclophosphamide, dexamethasone, lenalidomide, melphalan, methylprednisolone, pegylated liposomal doxorubicin, and/or thalidomide. Pts completed a median of 3 cycles with 7.8 months of median follow up. To date one regimen has reached MTD. Clinical benefit was seen in 19 (65.5%) pts: CR = 6.9%; VGPR = 17.2%; PR = 20.7%; MR = 20.7%; SD = 27.6%. Eight pts have progressed on study, with 6 progressing after initial response. Median PFS is 8.3 mo with median DOR at 8.5 mo. Common > G2 adverse events include thrombocytopenia, lymphopenia, neutropenia, leukopenia, pneumonia, fever, UTI, sepsis and, tumor lysis syndrome. Fifteen pts experienced serious adverse events. Ten pts experienced dose-limiting toxicities. These results suggest that CFZ is an effective and tolerable replacement for BTZ for pts refractory to a variety of BTZ-containing regimens.

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BVD in Elderly MM Progressive after 1st Line Therapy (IFM 2009-01 Trial): Predictive Factors of Defavourable Outcome

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Background: We conducted a phase 2 study of Bendamustine, Bortezomib and Dexamethasone (BVD) in elderly patients with RRMM. The present analysis aimed to determine predictors of defavourable outcome at 6 months. Methods: IFM 2009-01 trial was dedicated to pts > 65 years in 1st relapse or refractory to 1st line therapy. Inclusion criteria were measurable disease, PS ECOG 0-2, ANC > 1.5x109/l, platelets > 100x109/l, serum creatinine level < 250 mcmol/l, AST and ALT < 3xULN. Pts with prior exposure to bortezomib were excluded. Treatment regimen was 6 28 days cycles of B 70 mg/m2 D1-8, V 1.3 mg/m2 D1-8-15-22 and D 20 mg D1-8-15-22. Responders were assigned to receive maintenance treatment with 6 additional cycles given 1 month out of 2. Pts with favourable outcome at 6 months were defined as achieving sustained PR or better and beginning maintenance treatment without major toxicity or unrelated event. Results: 73 pts were included (median age 75.8 years). Best response was PR or better: 49 pts , MR: 6, SD: 4, progression: 13, early discontinuation: 1. At 6 months, PFS was 67.1% and OS 80.8%. Defavourable outcome was observed in 36 pts (49.3%): failure to achieve sustained PR in 24, treatment toxicity in 6, unrelated adverse event in 4, patient refusal or lost to follow-up 1 each. Predictive factors of a defavourable outcome were beta 2 microglobulin (B2M) level > 3.5 mg/l (p=0.0029), 17p deletion (p=0.025) and male sex (p=0.04). Conclusion: In the IFM 2009-01 trial, elevated serum B2M level, presence of deletion 17p and male sex correlated with defavourable outcome.

P-140

Pomalidomide + Dexamethasone + Pegylated Liposomal Doxorubicin in Relapsed/Refractory Multiple Myeloma

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Pomalidomide (POM) has shown efficacy in combination with dexamethasone (DEX) for patients (pts) refractory to bortezomib (BTZ) and lenalidomide (LEN). Our recent trial evaluating LEN in combination with DEX, pegylated liposomal doxorubicin (PLD), and BTZ (DVD-R) showed that both efficacy and tolerability was improved by changing the dose and schedule of these drugs. We conducted a Phase 1/2 trial investigating POM in combination with DEX and PLD using a modified dose and longer 28-day schedule for relapsed/refractory (RR) multiple myeloma (MM) pts. Phase 1 pts had progressive MM at enrollment and had relapsed on an anti-MM regimen. Phase 2 pts were refractory to LEN (single-agent or combination). During Phase 1, POM was administered orally (2, 3, or 4 mg daily D1-21) along with IV DEX (40 mg) and IV PLD (5 mg/m^2) on D1, 4, 8, & 11 of each 28-day cycle. POM doses were escalated by cohort until a maximum-tolerated dose (MTD) was reached. Eleven pts were enrolled, all during Phase 1. Pts received a median of 4 prior treatments and completed a median of 3 cycles with a median follow up of 3.6 mo. (range: 1-6.7). We enrolled all three cohorts with MTD declared at 4 mg POM. Best overall response rate was 40%: 4 PR; 4 SD; 2 PD. Four pts progressed on study, 1 after initial response. Common > G2 adverse events (AEs) included neutropenia, lymphopenia, anemia, hyponatremia, fever, and fatigue. There were 3 SAEs with no DLTs. The combination of POM with DEX and PLD on a 28-day cycle appears to be an effective treatment option with acceptable tolerability for R/R MM patients.

P-141

A Phase 1 Study of ARRY-520 with Bortezomib (BTZ) and Dexamethasone in Relapsed or Refractory Multiple Myeloma (RRMM)

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ARRY-520 is a novel kinesin spindle protein inhibitor with encouraging activity in patients (pts) with RRMM. Preclinical synergy of ARRY-520 and BTZ provides the rationale to combine these drugs in the clinic. This Ph 1 study evaluates the safety of ARRY 520, BTZ and dexamethasone (dex). Eligible pts had RRMM with ≥ 2 prior lines of therapy, including a proteasome inhibitor and an IMiD. ARRY 520 is given intravenously (IV) on D1,2,15,16; BTZ as an IV bolus, and oral dex on D1,8,15 in a 28-day cycle. 34 pts were treated to date at various dose levels of both ARRY-520 and BTZ. Pts had a median of 5 prior regimens (range 2-10). The dose escalation cohorts to date are shown in the attached table. ARRY-520 (1mg/m2/d) with BTZ (1.3 mg/m2/d) and dex was not tolerated (2/3 DLT). Addition of GCSF allows ARRY-520 and BTZ to be combined at 1.5 and 1.3 mg/m2 respectively, the maximum planned dose of both drugs. The most commonly reported adverse events include neutropenia, diarrhea, anemia, thrombocytopenia, and pyrexia. Preliminary evidence of pharmacodynamics and clinical activity was seen at higher dose levels including BTZ refractory pts still on study for >10 cycles without steroids. To date, ARRY-520 +BTZ appears well tolerated with G-CSF and has demonstrated evidence of activity including responses in BTZ refractory pts. These data support further exploration of this combination including alternative schedules of ARRY-520. Updated data will be presented.

Cohort	N	mg/m²/d		Dex	G-CSF	DLT
		ARRY-520	BTZ			
1	3	1	1.3	Y	N	2
2	3	0.5	1	N		0
3A	3	0.5			Y	0
3B	3	0.75				0
3C	6	1				1
3D	2	1.25				0
4A	3	0.75	1.3			0
4B	3	1				0
4C	3	1.25				0
4D	5	1.5				-

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Clinical Features of Myeloma in Patients Aged 80 Years and Over

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Object: Elderly myeloma cases are often times excluded from clinical trials because of their poor performance status, complications, and socio-economic reasons. The purpose of this study is to explore the characteristics of elderly myeloma. Methods: 333 multiple myeloma patients treated in JRCMC between Apr/1987 and Aug/2012 were enrolled. Patients were grouped according to age, over and under 80 years. We compared the laboratory findings, prognosis, response to treatment, and early death rates between the two groups retrospectively. Results: The median age of diagnosis in ≧80 years was 83.8 (80-90), while that of <80 was 62.0(29-79). Rates of patients with Hb<10g/dl, β2microglobrin>3.5mg/dl and ISS 3 were significantly higher in patients ≧80. Rates of patients who's prognosis was PR or better was 83% vs 95% in patients ≧80 and between 66 and 80 respectively(P=0.038). Mean OS were 29.6 vs 44.7 months respectively(P=0.047). Early death rate was higher in patients ≧80, but not significantly. (14%vs7% P=0.25) Conclusion: Myeloma patients ≧80 years were likely to be anemic and have advanced ISS stage, leading to poorer prognosis. Response to treatment in ≧80 years group was poorer, however, this rate was better than that in the other studies. Since the mean OS of myeloma patients in ≧80 years group is less than half of the life expectancy at age 80, we considered that the temporary goal of treatment should be to achieve that.

P-143

Bortezomib, Melphalan, Prednisolone for Newly Diagnosed Korean Myeloma Patients Who are Not Eligible for Transplantation

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Efficacy of VMP for newly diagnosed myeloma patients was well-documented by phase 3 study. However, Efficacy and toxicities in Asian patients has not well documented. Thus we conducted retrospective study to observe the efficacy and toxicity of VMP treatment in Korean myeloma patients outside of clinical trial. Data were collected retrospectively from medical record from 25 hospitals. Sixty five patients who started VMP as first line from 2011 Feb to Aug were included. Median age was 70.5 and 48% were male sex. IgG type was most common (52.3%) and IgA 23.1%. ISS stage I is 10.8 and III is 50.8%. Creatinine less than 30ml/min comprised of 23.1%. Patients with high risk FISH (Del17p, t(4;14), t(4;16)) were 15.4%. Median 4 cycles (range 1-9) were given.Overall response rate(RR) was 75.48% and VGPR or more was 39.5%. RR was not different according to the Ccr, age, high-risk FISH or ISS stage. Median PFS and OS was not reached yet. One year PFS was 68.3% and one year OS was 82.8%. Most common toxicity was cytopenias, peripheral neuropathy, and gastrointestinal toxicities such as nausea and diarrhea. The onset of peripheral neuropathy was early and most of them started within 3 cycles. Dose intensity of bortezomib decreased for the first 4 cycles due to neuropathy and infection. Efficacy of VMP regimen was good in Korean patients. With relatively high mortality due to pneumonia preventative measure for prophylaxis need to be developed. Considering early onset of peripheral neuropathy, close observation and intervention are needed to prevent aggravation of neuropathy.

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Single Centre Experience on the Efficacy and Quality of Stem Cell Mobilization among Myeloma Patients

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Introduction: Autologous stem cell transplantation (ASCT) is still remained the standard treatment for myeloma patients who are transplant-eligible in the era of emerging novel agents. We would like to evaluate the efficacy and quality of stem cell mobilization among myeloma in our centre for the last 11 years. Method and results: We retrospectively analyzed a total of 118 myeloma cases between January 2001 and December 2012 who underwent peripheral blood stem cell (PBSC) mobilization, using high dose cyclophosphamide of 3g/m2 follow by G-CSF stimulation. Majority of our patients are IgG subtype (IgG Kappa 43% and IgG Lambda 28%). There was no significant gender different in our cohort with the median age of 54 year old. The induction chemotherapy prior to stem cell collection has evolved from VAD regimen (30%) to Thalidomide-based regimen (48%) then Bortezomib-based regimen (22%) with time. We successfully collected a minimal target cell dose of 2x10^6 cells/kg among 89% of our myeloma patients and majority of them just required one session of apheresis (62%). The collected PBSC were immediately sent for cryopreservation using 5% DMSO. The mean of stem cells viability prior cryopreservation was 99.45% (range: 92.72%-100%) and post thawing was 96.88% (range: 91.0%-99.0%) respectively. A total of 102 patients underwent (97%) ASCT with one incidence of documented TRM (1%). Both the median day of neutrophils and platelet engraftment was Day+10 days. Conclusion: We managed to achieve promising and successful stem cell mobilization and storage program among our myeloma patients.

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A Phase II Trial of Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma Patients

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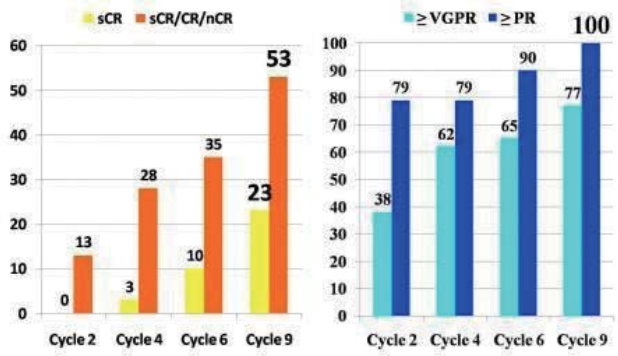
Background: Carfilzomib is a novel, irreversible proteasome-inhibitor. Here we evaluated efficacy and safety of the combination carfilzomib-cyclophosphamide-dexamethasone (CCd) in elderly newly diagnosed MM pts. Methods: Pts received oral cyclophosphamide (300 mg/m2 d 1,8,15), oral dexamethasone (40 mg d 1,8,15,22) and iv carfilzomib (20 mg/m2 d 1,2 and 36 mg/m2 d 8,9,15,16 cycle 1; 36 mg/m2 d 1,2,8,9,15,16, cycles 2-9) every 28 days for 9 cycles, followed by maintenance with iv carfilzomib (36 mg/m2 d 1,2,15,16) every 28 days until progression. Results: Enrollment was completed (54 pts): median age was 71, 28% of pts was > = 75 years, 40% had ISS stage III, and 35% had unfavorable FISH [t(4;14) or t (14;16) or del17p]. The median duration of treatment was 5 cycles. Responses improved with the duration of treatment reaching after 9 cycles: 100% PR, 77% VGPR, 53% CR/nCR, including 23% stringent-CR. Responses were rapid with the median time to PR of 1 month and the median time to CR of 2 months. After a median follow-up of 7.5 months, the 1-year PFS was 87% and the 1-year OS was 88%. Grade (G) 4 hematologic toxicities included neutropenia (2 pts, 5%). G3-4 non-hematologic toxicities were infections (4 pts, 10%), cardiac (2 pts, 5%) and gastrointestinal complications (1 pt, 2.5%). Five pts (12%) discontinued treatment and 7 pts (17%) required carfilzomib dose reductions due to adverse events. Conclusions: CCd showed encouraging activity in patients with newly diagnosed MM and was well tolerated with limited need for dose modification. Results will be updated at the meeting.



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Lenalidomide-dexamethasone vs Melphalan-prednisone-lenalidomide vs Cyclophosphamide-prednisone-lenalidomide in NDMM

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We designed a multicentre phase III trial comparing lenalidomide plus low dose dexamethasone (Rd) with melphalan-prednisone-lenalidomide (MPR) and cyclophosphamide-prednisone-lenalidomide (CPR) to evaluate the best combination in multiple myeloma patients >= 65 years old or not eligible to autologous stem cell transplantation. Between October 2009 and October 2012, 663 patients were enrolled and randomized to receive nine 28-day induction cycles of Rd (lenalidomide 25 mg/day for 21 days; dexamethasone 40 mg on days 1, 8, 15 and 22 in patients 65-74 years old and 20 mg in those >= 75 years) or MPR (lenalidomide 10 mg/day for 21 days; melphalan orally 0.18 mg/Kg for 4 days in patients 65-74 years old reduced to 0.13 mg/Kg in >= 75 years patients; prednisone 1.5 mg/Kg for 4 days) or CPR (lenalidomide 25 mg/day for 21 days; cyclophosphamide orally 50 mg/day for 21 days in patients 65-74 years old reduced to 50 mg eod in >= 75 years patients; prednisone 25 mg eod). After induction, all patients were randomized to receive maintenance therapy with Lenalidomide 10 mg/day on day 1-21 alone or in com-

bination with prednisone at the dose of 25 mg eod. Each cycle was repeated every 28 days, until disease progression (PD). Median age of the study population was 73 years, 49% were male, 27% had a ISS stage 3 and 17% had at least one bad prognostic cytogenetic abnormality. Patients characteristics were well balanced in the three arms. Database were locked in December 2012. Efficacy and safety data will be available at the meeting.

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Use of sFLC in Combination with an M-protein in the β-region to Measure Response

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Quantification of M-proteins can be performed by protein electrophoresis (sPEP) and the sFLC. If an M-protein migrates into the β-globulin fraction quantification is often difficult.Twelve percent of MM patients, particularly with IgA M-proteins, present with a sPEP spike in the β-region. We evaluated whether sFLC had an additional value in response assessment. All patients in a 3-year time period with an M-protein in the β-region and a simultaneously sFLC measurement (n=21, 125 measurements, group 1) were included. These patients were compared with a second cohort of randomly selected patients with an M-protein in the γ-region and a simultaneously sFLC measurement (n = 30, at least one quantifiable M-protein (>5g/L) to exclude oligosecretory disease, 228 measurements, group 2). When analysing the 2 groups separately the percentage of unquantifiable M-protein by sPEP was higher in group 1 (54.4% vs 33.8%). When using the border for quantifiable sFLC (>100 mg/L), we found significantly more measurements in group 1 with an unquantifiable M-protein and an elevated sFLC, (30.9% vs. 7.8%, p-value 0.000). This is possibly explained by a more accurate measurement by sFLC which is underestimated in patients with a sPEP spike in the β-region. In conclusion, in this retrospective study we found that an unquantifiable band in the β-region is accompanied by a relevantly high sFLC (> 100 mg/L) in one third of all measurements. Implementing the sFLC assay in response assessment of patients who have a M-protein in the β-region may therefore have additive value

	γ -region (33.8%*)	ß-region (54.4%*)	p-value
FLC elevated	46 (59.7%)	30 (44.1%)	0.049+
FLC normal	31 (40.3%)	38 (55.9%)	
FLC > 100	6 (7.8%)	21 (30.9%)	0.000+
FLC < 100	71 (92.2%)	47 (69.1%)	

P-148

Transplant for MM 1995 -2010-Survival Improvement in All Age Groups and Across Induction/Maintenance/Post-Relapse Phases

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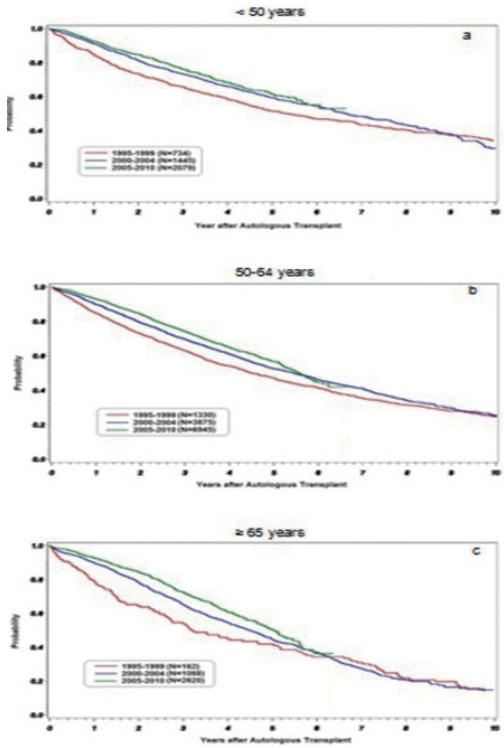
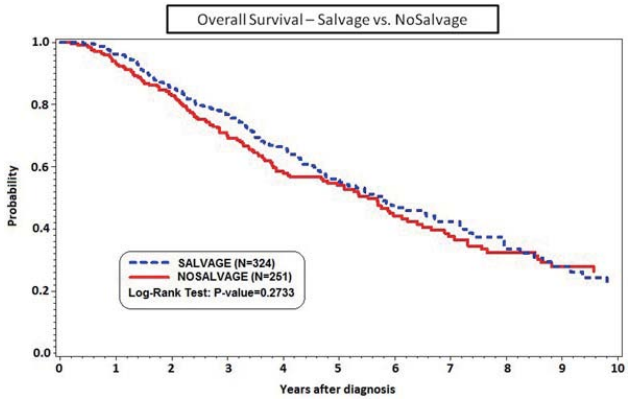
Impact of novel drugs (thalidomide/lenalidomide/bortezomib) on outcomes post AHCT is unknown. We analyzed outcomes of 20,278 AHCT recipients (within 12 months of diagnosis) in the N. America across 3 cohorts based on year (yr) of AHCT: 1995-99 (n=2226), 2000-04 (n=6408) and 2005-10 (n=11644), reflecting increasing availability of novel drugs. Five yr survival after AHCT progressively improved over the 3 eras from 47% to 53% and 56%. In multivariate analysis, AHCT in later cohorts (2000-04 or 2005-10) and younger age were associated with better survival. Induction therapy with VAD-like regimens declined (83% in 95-99 to 11%). Novel agent induction increased to 74% by 2005-10 resulting in a higher proportion in complete/partial remission pre-AHCT. Planned maintenance changed from interferon/steroid use in 95-99 to steroids, and novel agents in the later cohorts. Successive cohorts had superior progression free survival after AHCT (50% vs. 55% vs. 57% at 24 months) and post-relapse survival (58% vs. 65% vs. 72% at 24 months after relapse). Survival benefits accrued to all age groups (Figure). For <50 yr olds treated in 2000-2004 and 2005-10 the HR for death was 0.88 and 0.76 respectively compared to 1995-99. For 50-64 yr olds, corresponding HR for death was 0.81 and 0.67 in 2000-04 and 2005-10. Similarly for those above 65 years HR of death declined to 0.80 and 0.58 in 2000-04 and 2005-10. Integration of novel agents and AHCT has a complementary effect on the natural history of transplant eligible MM with outcomes improving in all phases of therapy and across all age groups.



(p=1.0), relapse (p=0.2), Progression free (p=0.2) or overall survival (p=0.5) were no different between cohorts. On multivariate analysis, a higher creatinine at diagnosis predicted for higher NRM (p=0.008) and inferior OS (p=0.003), while the use of novel anti-MM agents predicted for lower risk of NRM (HR = 0.37, P=0.04). A left-truncated multivariate analysis performed to reduce potential waiting time bias also indicated similar outcomes irrespective of whether salvage regimens were used (Fig). In the setting of upfront AHCT, no additional benefit was demonstrated for salvage regimens to upgrade response pre-AHCT.



P-149

Non-response to Initial MM Induction-is There Benefit to Additional Therapy to Upgrade Response Pre-transplant (AHCT)?

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The benefit of additional salvage therapy to upgrade response pre-AHCT in patients (pts) with a less than partial/complete response (PR/CR) to first line induction therapy is not clear. Between 1995 -2010, 575 pts received upfront AHCT (within 12 mo of diagnosis) for MM after failing to achieve a PR/CR to initial induction therapy. We compared outcomes after dividing these pts into 2 cohorts - those who received additional salvage therapy (SALVAGE; n=324); and those proceeding to AHCT immediately without any additional therapy (NOSALVAGE; n= 251). More pts in NOSALVAGE received VAD as first line therapy and had a higher base-line creatinine. In the SALVAGE cohort, 75%, 20% and 4% received one, two and three salvage regimens respectively resulting in a response upgrade to CR/PR in 55%. In NOSALVAGE, 93% were in a minimal response or stable disease state and 7% with progressive disease. Median follow-up for survivors was > 5 years. Non-relapse mortality (NRM)

P-150

Lenalidomide with Dexamethasone Treatment for Relapsed/Refractory Myeloma Patients in Korea

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Efficacy of Lenalidomide for relapsed and/or refractory(RR) myeloma has been well-documented by phase 3 studies in Europe and North America. However few data has been reported on Asian patients. We gathered data on the lenalidomide with dexamethasone for Korean RR myeloma patients. Data were retrospectively collected from 110 patients of 20 hospitals treated between 2008 and 2012. Median age was 62 and 53.6% were male.Time from diagnosis to lenalidomide treatment was 3.1 years (0.2-9.6) and number of previous treatment were 4(1-11) and 66.7% received prior transplantation. Most of the patients exposed to thalidomide (79.3%) and bortezomib (93.2%) and considerable proportion of them were refractory to thalidomide (48.7%) or bortezomib (55.5%). Lenalidomide 25mg D1-21 (83.6%) and Dexamethasone 160mg per cycle (63.8%) was most commonly used dose. Median 4 cycles (1-34) were administered and overall response rate was 43.6% and response more than VGPR was 15.4%. Median TTP was 9 months and 2Y OS was 63.7%. Most common toxicities were cytopenias and fatigue, neuropathy, and anorexia were common non-hematologic toxicities. Only ECOG performance was significant factor to TTP in univariate analysis, but pretreatment creatinine clearance, previous transplantation, high risk cytogenetics, ECOG PS, pretreatment leukocyte, hemoglobin and platelet were significant for OS. In multivariate analysis creatinine clearance and previous exposure to bortezomib were significant. For heavily pretreated Korean myeloma patients lenalidomide showed considerable efficacy and manageable toxicities.

P-151

Efficacy and Safety of High-dose Chemotherapy with Autotransplantation for Symptomatic Multiple Myeloma (JMSG-0901)

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Objective: The additive effect and safety of bortezomib + dexamethasone (BD) as induction therapy in patients who were non-responsive to initial vincristine + doxorubicin + dexamethasone (VAD) induction therapy followed by high-dose chemotherapy with autologous peripheral blood stem cell transplantation (APBSCT) was evaluated in patients with previously untreated symptomatic multiple myeloma. Patients and methods: Forty-one patients were enrolled to receive two cycles of VAD followed by two to four cycles of BD if VAD did not achieve at least a VGPR. After cyclophosphamide was administered, PBSCs were harvested and APBSCT was performed with melphalan (Mel) 200. The effects were evaluated according to IMWG response criteria. The survival rate was measured with Kaplan-Meier method. Results: The data of 37 patients (22 males; median age, 58 years [range, 38-65]) were analyzed. The M-protein types were IgG, IgA, and BJ in 28, 7, and 2 patients, respectively. There were 16, 12, and 9 patients in ISS stage I, II, and III, respectively. The response rate after BD was 78.4% (CR, 8.1%; VGPR, 18.9%; PR, 51.4%). The median number of CD34+ cells harvested was 3.96 × 106/kg (1.92-54.5 × 106/kg). The response rate at 100 days after APBSCT was 87.1% (sCR, 6.5%; CR, 22.6%; VGPR, 35.5%; PR, 22.6%). The 1-year progression-free survival was 75.4%, and the 1-year overall survival was 96.7%. Conclusions: The response rate after BD as induction therapy was high. BD therapy enabled the harvest of a sufficient number of CD34+ cells, suggesting that BD is useful as induction therapy before APBSCT.

P-152

Bortezomib-doxorubicine-dex/Bortezomib-cyclophosphamide-dex for Primary Plasma Cell Leukemia: a Phase 2 Study by the IFM

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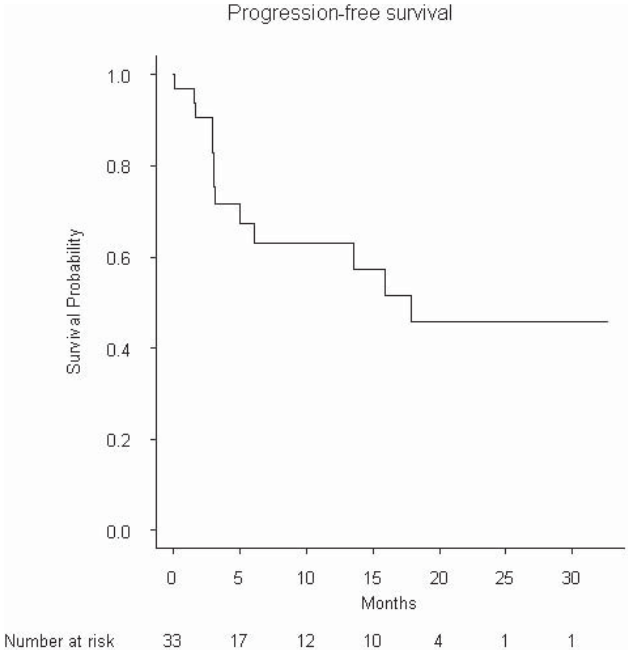
Introduction: Primary plasma cell leukemia (pPCL) has poor prognosis. We report here a prospective phase 2 trial of pPCL treated with PAD/VCD as induction before high dose Melphalan/autologous stem cell transplantation (HDM/ASCT) followed by allo or 2ndASCT + consolidation. Patients and method: Patients (pts) with pPCL were included. PAD (Bor 1.3mg/m2+Dex 40mg D1 4 8 11+Doxo 30mg/m2 D4) and VCD (Bor+Dex+Cyclo 300mg/m2 D1 8) were administered alternatively each 21 days, 4 cycles. For responding pts double HDM/ASCT was performed followed by consolidation with VRD (Bor+Dex+Len 15mg/day 1-15) on months 1 4 7 10 and Len 15mg 21/28 D on others months for 1 year or tandem HDM/ASCT-reduced intensity conditioning-allograft if they were <66yrs. Primary end-point was PFS, secondary included responses rates, OS, toxicity. Results: 27 are evaluable after induction, 6 on current treatment. Median age was 58yrs (27-71). Median number of circulating plasma cells was 5.2G/L (1.2-73). 24% had CrCl < 50ml/mn, 15% <30ml/mn, 43% ISS 2, 43% ISS 3. After induction 17/27 (63%) responded: VGPR+CR 37%, PR 22%, SD 4%. 10/27 (37%) did not respond and were discontinued. On 17 responding pts, 16 underwent HDM/ASCT, 1 allo. 15/17 are evaluable at 3 mos: VGPR+CR 80%, PR 13%, PD 7%. 2ndHDM/ASCT was performed in 5 pts (conso is ongoing) and allo in 8. Median follow-up was 10.4 mos, PFS 17.8 mos. Toxicities were cytopenia/infection. 3 pts died of sepsis. Conclusion: PAD/VCD + HDM/ASCT is feasible and induces high responses rates in pPCL pts. Allo or 2nd HDM/ASCT + VRD-Len as consolidation are currently being



P-153

The Choice of Regimens Based on Bortezomib for Patients with Newly Diagnosed Multiple Myeloma: Experiences from China

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Introduction: There are few prospective randomized trials even the retrospective reports that compared the response of combinations with bortezomib in multiple myeloma (MM). Here, we report four bortezomib-based therapies in newly diagnosed MM patients in the Chinese population from three hematology centers. Methods: In the initial eight 28-day cycles, newly diagnosed symptomatic patients were treated with combination therapy including bortezomib plus dexamethasone (PD) and the triplet combinations of PD with adriamycin (PAD), cyclophosphamide (PCD), thalidomide (PDT) . Results: The ORR of patients in PTD, PCD, PAD and PD groups are 86.7%, 95.4%, 91.4 and 78.8%, respectively. The rate of VGPR and better in these groups are 53.3%, 65.2%, 62.9% and 33.3%, respectively. The ORR and the rate of VGPR and better in PCD group were superior to PD. The median PFS was 16.0 months, 23.0 months, 23.9 months and 21.8 months in PDT, PCD, PAD and PD with no sig-

nificant differences between. The median OS for PD arm was 41.8 months while other arms were not reached, but the median OS for PTD, PCD and PAD was significant longer than PD. Peripheral neuropathy was more frequently reported in PTD group without routine anti-viral therapy. The incidence of neuropathy was extremely higher in PTD regimen than other groups, especially grade 2 and 3. Conclusions: Our experience indicated that bortezomib-based regimens were active and well-tolerated in the Chinese population, triplet combinations PCD, PAD regimens were superior to PTD or doublets, especially the PCD regimen.

P-154

Detection of Patient-specific MRD with Quantitative RT-PCR in the Patients with Multiple Myeloma

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Introduction: Among several technique, the PCR by using patient-specific primers for individual IgH VDJ region is considered to be most sensitive method to detect MRD. Methods: This study was approved by IRB and started from Dec, 2011. After an informed consent, patient-oriented PCR primers were designed from sequence information of IgH variable region of myeloma cells from each patient. We quantified the PCR levels of mRNAs in BMMNCs and PBMNCs as well as cell-free DNAs in plasma every six month during the treatment. We have analyzed 13 MM cases registered until May, 2012. Results and Discussion: The median age in this cohort was 70.5 (55-78); the ratio of male to female was 6:7; and the numbers of IgG, IgA, and BJP type patients are 8, 3, and 2, respectively. We successfully designed the primers for IgG- or IgA-type patients, but not for BJP cases. PCR fragments were amplified in all BMMNC samples. The amount of PCR products reduced in parallel to that of M proteins during the treatment. The longer follow-up would definitely prove the significance of MRD monitoring by using quantitative RT-PCR. Interestingly, we could detect the PCR products in mRNA of PBMNCs from 2 cases, DNA from plasma from 2 cases, and mRNA of CD20+38- cells from 1 case before the treatment. The patient whose PCR products were detected in PBMNCs and BM CD20+38- cells showed resistance to chemotherapies. To clarify how the detection of the PCR products in PBMNCs and/or CD20+38- cells is related to treatment response and prognosis, further analysis using more patients will be required.

P-155

A Phase 1 Study of Tabalumab and Bortezomib (BTZ) in Patients (pts) with Previously Treated Multiple Myeloma (MM)

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B-cell activating Factor (BAFF) is elevated in some pts with MM, can increase resistance to dexamethasone (dex)-mediated apoptosis in vitro, and is associated with decreased survival. Tabalumab is a human IgG4 monoclonal antibody that neutralizes serum and membrane-bound BAFF and has anti-tumor activity in pre-clinical models of MM. We conducted a Phase 1 study to find a safe and potentially efficacious dose of tabalumab to combine with BTZ. Pts with MM who had measurable disease, good performance status, and had received at least 1 prior therapy were enrolled (n=48). The median age was 65.7 and pts had a median of 3 prior therapies (BTZ in 75%, IMiD in 88% and stem cell transplant in 52%). The study had 2 parts; tabalumab dose escalation (Part A, n=20) and dose expansion (Part B, n=28). In Part B, 12 pts received standard oral dex (20 mg po day of and day after BTZ). The most common Grade 3/4 adverse events were thrombocytopenia, pneumonia, neuropathy and neutropenia; one death occurred due to acute respiratory distress syndrome. The median B-cell count declined 65% after cycle 4, consistent with BAFF neutralization. The maximum median decrease in uninvolved serum IgG was 14%. A partial response or better was confirmed in 22 pts. Nine pts with baseline serum BAFF levels >1500 pg/mL did not respond. We conclude the combination of tabalumab and BTZ warrants further investigation, and a higher dose of tabalumab may be necessary. A phase 2 study is underway randomizing pts to placebo, tabalumab 100 mg, or tabalumab 300 mg in combination with standard doses of BTZ and dex.

P-156

Prolonged Overall Survival with Pomalidomide and Dexamethasone in Myeloma Characterized with End Stage Diasease

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Background. Myeloma (MM) refractory to bortezomib (Bort) and to immunomodulatory drugs has a median overall survival (OS) of 9 months. We investigated whether treatment with pomalidomide (Pom) plus dexamethasone (Dex) prolongs survival in this population. Method. The purpose of the IFM2009-02 study was to determine the impact of the combination Pom; orally 4 mg, either 21 days (arm 21/28) or continuously (arm 28/28) of a 28-days cycle, plus Dex in refractory MM to lenalidomide (Len) and Bort. The analysis was performed on the ITT population and combines data from both arms. Results. 84 patients (pts) enrolled across both arms. The median age was 60 yrs. Median time from diagnosis was 70.5 months and median number of prior lines 5. 84.5% were refractory to their last prior line and 77% were refractory to both Len and Bort. With a median follow up of 28 months, 74 pts discontinued treatment and 53 pts have died, primarily due to myeloma (similar across arms). In the ITT population, the median duration of response was 7.3 months, and TTP was greater on Pom than on any other therapy accessible to pts in France. The median OS was 14.9 months with 44% of pts who survived greater or equal 18 months (similar across arms). All survival endpoints were significantly more prolonged in responders when compared to pts with SD. Importantly, 10 patients (12%) remain on treatment after 30 months. Conclusion. This study provides further evidence that Pom-Dex can provide longer benefit for pts who have relapsed after other novel therapies.

P-157

Lenalidmide Therapy in Our Hospital

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Introduction: It has been reported that the treatment of novel agents, such as lenalidomide (Len), could prolong OS and improve QOL. Objectives: We tried to assess the prognostic factors, which is associated with 1) ORR and 2) OS, based upon the retrospective analyses of the patients treated with Len.Methods: 31 patients were evaluated. Different patient characteristics were examined for prognostic factors associated with ORR and OS. Basic demographics included age, the term from diagnosis to the onset of Len-treatment, the number of prior therapies, hematological parameters, the presence of abnormal plasma cell in peripheral blood, serum chemistry and chromosomal abnormalities.Results: 31 patients were evaluated. The best response during the treatment was 73.9% and the ORR was 56.5%.1) Among examined patient demographics, the presence of abnormal plasma cell in peripheral blood (0% vs. 36.4%) and PLT number (160,000 vs. 100,000) were significantly associated with ORR and LDH level (167 vs. 241) had a tendency to be associated with ORR.2) All patients, who have had response to Len-treatment, are alive at the present time. Conclusion: Three prognostic factors associated with the proliferation of myeloma cells. These results indicate that the efficacy of Len could be reduced in the patients, in whom multiple myeloma cells are aggressively proliferating, irrespective of disease stages and it is required to change treatment regimen in relapsing patients, who had efficacy of Len.

P-158

Bortezomib, Reduced-intensity Transplantation Followed by Lenalidomide for Newly Diagnosed Elderly Myeloma Patients.

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In elderly newly diagnosed MM patients(>= 65 years old) association of novel agents with Melphalan-Prednisone are considered standard regimens. We designed a multicenter phase II trial that evaluated a sequential approach including ASCT in this MM setting. 102 patients were enrolled and received 4 cycles of bortezomib-pegylated doxorubicin-dexamethasone (PAD), tandem melphalan (100 mg/m2) followed by ASCT (MEL100-ASCT), 4 cycles of lenalidomide-prednisone consolidation (LP), and lenalidomide-maintenance (L) until progression. In intention to treat analysis, complete response (CR) rate was 33% after MEL100-ASCT , 49% after LP and 54% after L. After a median follow-up of 66 months median time to progression (TTP) was 55 months, median progression free survival (PFS) was 48 months, median overall survival (OS) was not reached, and OS at 5 years was 63%. The achievement of CR correlated with longer TTP (median 70 months) PFS (median 63 months) and OS (83%at 5 years). Median survival from relapse was 28 months. Overall, the main grade 3-4 toxicities included thrombocytopenia, neutropenia, infections, peripheral neuropathy, gastrointestinal AEs, dermatologic toxicity and thromboembolism. The incidence of second cancer (skin cancer excluded) was 0.5% per year of follow-up. Death related to adverse events (AEs) occurred in 8/102 patients (only during induction or transplantation) and were higher in patients >70 years than in younger patients (19%vs5%, P=0.024).In conclusion, this sequential approach may represent a valid alternative for selective MM patients < 70 years old

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Lenalidomide Maintenance Improves Progression Free Survival in Newly Diagnosed Young Multiple Myeloma (MM) Patients.

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Background: The incorporation of new drugs into induction, consolidation and maintenance therapy is changing the treatment paradigm in newly diagnosed MM pts. Aims: To compare maintenance with lenalidomide with no maintenance in pts receiving melphalan-prednisone plus lenalidomide (MPR) or tandem high-dose melphalan (melphalan 200 mg/m2 with stem-cell support; MEL200) in the prospective randomized trial RV-MM-PI-209. Materials and Methods: Four hundred and four patients were enrolled. Two-hundred and two were randomly allocated to MPR [six 28-day cycles of melphalan (0.18 mg/kg days 1-4), prednisone (2 mg/kg days 1-4) and lenalidomide (10 mg days 1-21)] followed by maintenance with lenalidomide (10 mg, days 1-21; N=98) or no maintenance (N=104). The 200 other pts were assigned to receive MEL200, followed by maintenance with lenalidomide (10 mg, days 1-21; N=100) or no maintenance (N=100). Results: Patients characteristics were well balanced. Lenalidomide maintenance did not significantly increase response rate: CR rate was 19% after MPR and 22% after maintenance, while it was 24% after MEL200 and 32% after maintenance. The 3-year PFS from the start of maintenance was 54% for patients randomized to maintenance and 27% for the no-maintenance arm (HR 0.50; p<.0001). The 3-year OS survival was similar: 83% with lenalidomide maintenance and 77% without maintenance (HR 0.68, p=0.08). The rate of second primary malignancies was 2% in both maintenance arms. Conclusions: Lenalidomide maintenance significantly reduced the risk of progression in newly diagnosed young MM pts.

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Carfilzomib plus Melphalan-prednisone Induces Very High Response Rates in Elderly Patients with Newly Diagnosed Myeloma

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MP+thalidomide (MPT) and MP+bortezomib (MPV) have shown significant PFS and OS benefits in NDMM

pts >65 years (y) but are associated with periph neuropathy (PN). CFZ, a novel proteasome inhibitor, has shown promising activity+favorable toxicity profile with low PN rates. This PhI/II study in NDMM <65y was designed to determine maximum tolerated dose (MTD) of CMP and assess safety and efficacy. In PhI, CFZ was started at 20mg/m2, then escalated to 27, 36, and 45mg/m2, given IV in 42-day (D) cycles (C) on D1/2/8/9/22/23/29/30 for 9C. Melphalan 9mg/m2 and prednisone 60mg/m2 were given PO D1to4. MTD was based on dose-limiting toxicity (DLT) in C1 defined as any grade (G) 4 hematologic AE, any hematologic AE preventing >2 C1 CFZ doses except G4 thrombocytopenia w/o bleeding or G4 neutropenia <7D, >G3 febrile neutropenia, or any >G3 nonhematologic AE. As of Jan 6, 2013, 24 pts have been enrolled in PhI: 6 for each dose level. There were 2 DLTs at 45mg/m2 (fever, hypotension) resulting in a MTD of 36mg/m2. In PhII, 45 additional pts received CMP at 36mg/m2 CFZ for N=69 (median age 74y). ORR was 89% with 51% >VGPR. With median f-up of 12 mo, the projected 2y OS was 90%. CMP was well tolerated w/o PN >G2. These results compare favorably to those of MPV, MPT, MP+lenalidomide (R), and R+dex in similar pts (ORR 71% SanMiguel NEnglJMed2008, 76% Facon Lancet2007, 80% Palumbo JClinOncol2007 and 85% Rajkumar LancetOncol2010, respectively). CFZ 36mg/m2+MP is tolerable and effective in elderly NDMM pts. Treatment is ongoing. Final safety and efficacy data will be presented.

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Subcutaneous Versus Intravenous Administration of Bortezomib in Patients with Multiple Myeloma: a History Control Study

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Peripheral neuropathy (PN) always limited the intravenousinjection of bortezomib (Btz). Subcutaneous administration is an important alternative. We compared the efficacy and safety of subcutaneous versus intravenous Btz in patients with multiple myeloma (MM). This history control study was undertaken at a single center in China. Patients with newly diagnosed or relapsed/refractory MM (n=51)were received up to eight 21-day cycles of PAD (Btz 1.3 mg/m^2, subcutaneous injection on days 1, 4, 8, 11; adriamycin and dexamethasone). Then the efficacy and safety of subcutaneous Btz were compared with those of intravenous Btz (n=69) which were history used with PAD regimen. Patients received a median of three cycles (range 1 to 6) in both groups. Overall response rate (>=PR) was 100% and 97.5% in these two groups. Most of any grade adverse events (AE) were less common with subcutaneous than those with intravenous administration. The incidence of the common AEs were thrombocytopenia (26.2% vs 19.5%), neutropenia (15.5% vs 20.2%]), anemia (18.4% vs 25.3%) and PN (12.2% vs 48.6%; p=0.012). Grade 3 or worse AE were reported in 19.4% patients in the subcutaneous group versus 40.4% in the intravenous group. Importantly, PN of any grade (12.2% vs. 48.6%; p=0.012), and grade 3 or worse (0% vs. 15.7%; p=0.006) was also significantly less common with subcutaneous than that with intravenous administration. The efficacy of subcutaneous Btz was comparable with standard intravenous administration. Subcutaneous administration significantly decreased the incidence and serious of PN.

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Outcome of Bortezomib-based Combination Regimens in Newly Diagnosed Chinese Patients with Multiple Myeloma

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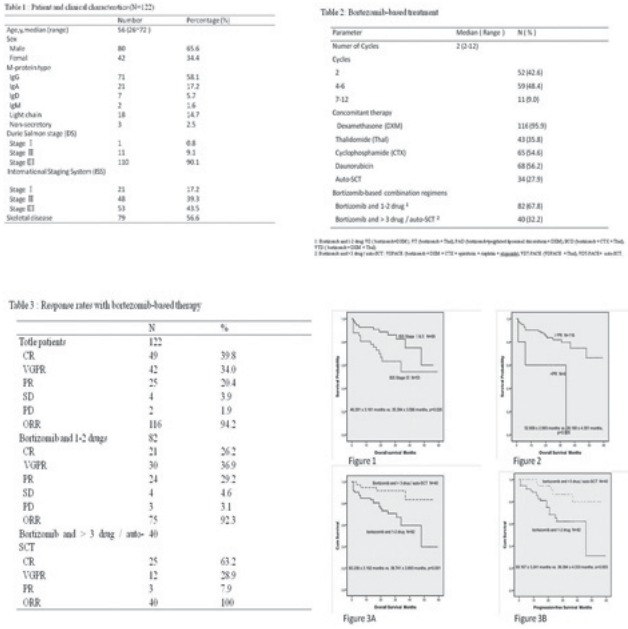
Background: Multiple myeloma (MM) is a malignant plasma cell disorder. Although the efficacy of bortezomib in MM was already demonstrated in many international clinical trials, it is still necessary to confirm in Chinese patients. Methods & Results: A total of 122 newly diagnosed MM patients were enrolled between Feb. 2002 to Dec.2011. The clinical characterstics of the patients showed in Table 1. Bortezomib was administered intravenously at a dose of 1.3 mg/m2 on days 1, 4, 8, 11 every 21 day. 34 of patients received auto-stem cell transplantion (auto-SCT) after induction therpay (Table 2). The overall response rate (ORR) was 94.2% (Table 3). The ORR in patients who received bortizomib with >3 agents or auto-SCT was higer than that in patients without (100% vs. 92.3%, p=0.000). The median follow-up was 22 months by July 30, 2012. The median progression-free survival (PFS) was 46.746 ± 3.248 months, the median overall survival (OS) was 49.386 ± 2.964 months. The difference in OS between stage Ⅰ, Ⅱ and stage Ⅲ evaluated by ISS was statistically significant (p=0.026, Figure1). The median OS for patients who achieved a PR or better was longer than the others (p=0.005, Figure 2). The median OS and PFS were improved for the patients received bortezomib with more intensive chemotherapy or auto-SCT than the patients who did not (p=0.003, Figure 3). Conclusion: Bortizomib-based combination regimens were the effective therapies for newly diagnosed multiple myeloma, and bortezomib with more in-

tensive chemotherapy or auto-SCT after induction therapy could improve the OS and PFS.



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Allogeneic Stem Cell Transplantation for Multiple Myeloma Improved Bortezomib Sensitivity: a Case Report

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Background: Although Multiple myeloma (MM) remains incurable, the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib has improved clinical outcomes. Allogeneic stem cell transplantation (allo-SCT) is thought to be the only treatment option that has curative potential, while it has the problem of high rate of relapse. We here report a MM patient who regained bortezomib sensitivity after allogeneic stem cell transplantation. Case: A 44-years-old man was diagnosed with BJ- λ type MM in July 2009. He received five courses of BD (bortezomib and dexamethasone) and rapidly relapsed. We conducted VAD, VMP (bortezomib, melphalan and prednisolone), ASCT and lenalidomide treatment in turn, but the patient became refractory. He was treated with a reduced intensity-conditioning regimen using fludarabine and Melphalan. Although he once achieved VGPR, the disease progressed around day 180. At the same time he suffered from aGVHD (mainly gut, maximum grade3) and chronic renal failure. His disease states become worse and we diagnosed him as plasma cell leukemia nine months after allo-SCT. We conducted one course of BD following high dose dexamethasone and surprisingly plasma cells disappeared from peripheral blood and bone marrow. Conclusion: We treated successfully a refractory MM patient post allo-SCT with bortezomib that once lost its sensitivity.

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Mobilization of Patients with Newly Diagnosed Myeloma Undergoing ASCT : are We Ready to Switch from G-CSF to Peg G-CSF?

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G-CSF is the most common cytokine administered for peripheral blood stem cell mobilization. Studies have hypothesized that Pegylated G-CSF (Peg-GCSF) could be considered for mobilization while reducing the duration of treatment and offering a better control of the leukapheresis process. From May 2006 to November 2011, 68 pts with newly diagnosed MM were included into a phase II randomized trial. Responders to 3 to 4 cycles of induction therapy were randomized to receive filgrastim 10 μg/kg daily administered until last day of leukapheresis (arm A, n= 23) vs a single injection of pegG-CSF 12 mg (arm B, n= 23) vs pegG-CSF 18 mg (arm C, n= 22). Given the narrow mobilization peak observed in previous studies, CD34+ count was required 48 hours post growth factor (GF) administration until a minimum of 10 CD34+/ μL was reached determining the first day of leukapheresis. In 19 patients (28%), the CD34 count 48 hours post GF was missed. The CD 34 peak was reached 72 hours after GF administration in arm A; 96 hours in arms B and C. The optimal yield was considered as a min of 4 x 10^6 CD34/ Kg and the minimal yield a min of 2 x10^6 CD34/Kg. Four patients unable to reach the minimal yield were considered as mobilization failure (Arm A = 1; Arm B = 1 and Arm C = 2) (see table 1). As a conclusion, mobilization by PegGCSF 12 mg and 18 mg was successful. The use of PegGCSF 18 mg showed no additional benefit. In addition, the study showed how difficult it was for the centers to change their habits to plan a CD34+ count 48 hours after the GF injection.

	Table 1 : Leukapheresis data		
	Arm A	Arm B	Arm C
WBC ($x 10^9$/L)	45.25 (9.61 – 94.75)	33 (5.87 – 88.92)	34.8 17.06 – 90.53)
Platelets ($x 10^9$/L)	272 (63 – 565)	192 (56 – 615)	211 (31 – 643)
Peripheral CD34+ (/μL)	45 (0 – 291)	35 (1 – 345)	29 (0 – 166)
< 2 x 10^6 CD34/Kg	0 (0%)	0 (0%)	1 (1.5%)
< 4 x 10^6 CD34/Kg	4 (18.1%)	4 (19%)	2 (9.5%)
CD34+ collected (10^6/Kg)	8.11 (2.09 – 17.07)	7.05 (2.16 – 15.57)	7.21 (1.65 – 13.1)
Number of leukapheresis	1.5 (1 – 2)	2 (1 – 4)	2 (1-4)

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Response Adapted Therapy Using Single Agent Lenalidomide in Newly Diagnosed Standard Risk Multiple Myeloma

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We reported promising outcomes of a retrospective cohort of newly diagnosed (ND) multiple myeloma (MM) pts (pts) treated with single agent (SA) lenalidomide (Len). We conducted this prospective study to evaluate the efficacy of a response adapted approach using SA Len in ND standard risk MM Eligible pts had symptomatic MM without high risk features (b2m<5.5, absence of t(4;14), t(14;16), 17p deletion, aneuploidy or 13q by metaphase cytogenetics) and were not eligible or not willing to undergo high-dose melphalan. Pts received Len 25 mg PO D1-21 every 28 days for 2 cycles. In the event of >MR the pt continued on SA Len until PD. Alternatively, prednisone (pred 100 mg PO D1-5) or Dexamethasone (Dex 40 mg weekly) was added for SD or PD respectively. From 2/2010 and 9/2012, 22 pts were treated. The median age was 75 (64-83) years and 15 (68%) were males. 13 pts (59%) had ISS stage I while 9 pts (41%) had ISS stage 2. By FISH, deletion 13 was noted in 23%, 1q21 trisomy or tetrasomy in 14%, 41% had normal cytogenetics. The overall response rate (>PR) of SA Len was 63.5% and the >MR rate was 81.7%. To date, 5 pts required the addition of Dex and the response was: 1 VGPR, 1 PR, 1 MR, 1 SD and 1 PD; 3 pts required the addition of pred and the response was: 1PR, 1 MR, 1 SD. 6 pts went off study, 2 for PD and 4 withdrew consent (3 were in PR at the time and 1 in SD). The 1 year PFS for Len monotherapy was 77% and for protocol therapy 96%. In this pt population, a response adapted therapy using SA Len is safe and effective sparing Dex toxicities from the majority of pts.

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BSBMT/UKMF Myeloma X Relapse (Intensive) Trial - Challenges Encountered During Recruitment and Randomisation

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Despite the successful early closure of the BSBMT/UKMF Myeloma X relapse trial with 297 patients registered (174 randomised), recruitment to this study has been difficult. Eligible patients with MM relapsing after a prior ASCT were approached for enrolment into this study aimed to examine the clinical utility of a second autologous stem cell transplant. The central trials unit recorded the reason for non-entry from a multiple-choice list, with clinicians being invited to give further details on the reason for non-entry. In total, 392 patients screened for trial participation did not enter the study. 73 patients failed to meet criteria with regard to eligibility while 109 were inappropriately staged for inclusion (35 no previous transplant, 34 early relapse, 25 at diagnosis and 15 in 2nd remission) For patients in whom additional comments were available 85 patients declined to take part in the study, of these 13 patients did not want to undertake the travel to the centre performing the study. 32 patients did not want to have a second transplant; in contrast 15 patients declined as they wished to ensure they did receive a transplant, 3 patients opted to enrol in alternative studies. 15 patients screened for the trial were recommended to not take part and a further 12 were considered too unwell to participate. These data highlight problems in undertaking clinical studies, and serves to underline the importance of careful patient selection, especially in relation to perceived patient choice. Lessons from this analysis will inform future study design and implementation.

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Effect of Pre-transplant Bortezomib Induction in Multiple Myeloma Patients; Single Center Experience

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Up-front autologous stem cell transplantation (ASCT) is a standard of care for younger patients with multiple myeloma. However, in the era of novel therapeutic agents the impact of stem cell transplantation remains to be clarified. We aimed to document the effect of pre-transplant bortezomib on transplantation results. 49 multiple myeloma patients underwent ASCT were retrospectively evaluated . Median age was 56 (29-68). Patients were divided in two groups. In the first group (n:15, only CT induction group) all patients received 2-4 cycles of VAD chemotherapy before ASCT (before the availibility of novel drugs). In second group (n:34 bortezomib-CT induction group) patients received bortezomib / dexamethazone for a median of 4 (3-6) cycles, after two cycles of VAD or cyclophospamide-dexamethasone chemotherapy before ASCT. "Very good partial remission" and "complete remission" rates were 46.7 % and 70.6 % in only CT induction and bortezomib-CT induction groups respectively (p=0,109). Overall response rates, defined as partial remission or better response, were 60 % and 82.4 % in only CT induction and bortezomib-CT induction groups respectively (p=0,094). Despite the better response rates in bortezomib-CT induction group overall and progression free survival (achieved after transplantion) were similar between both groups. Conclusion; pre-transplantation addition of bortezomib to chemotherapy seems to be have a better response rate probably due to its in-vivo purging effect. However, its impact on progression free survival and overall survival is still unclear.

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8-Color Plasma Cell Flow Cytometry with DNA Analysis: A Comparison to 6-Color Flow, Cytogenetic, and Labeling Index

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Highly sensitive clinical assays are needed to characterize the abnormal plasma cells (PCs) of multiple myeloma. A novel, single tube, 8-color flow cytometry (FC) assay including DAPI to simultaneously analyze PC phenotype, DNA content, and proliferation was devised and compared to a combination of 6-color FC, cytogenetics, FISH, and BrDU based PC labeling index in 202 clinical marrow specimens. 8-color FC was highly specific and more sensitive than 6-color FC for PC detection (Table 1). The 17 cases detected only by this method had few abnormal PCs (median 0.00028%); in 11 the PCs were aneuploid, facilitating their detection. 8-color FC was 28% more sensitive than cytogenetics and FISH for detecting PC aneuploidy (Table 2) and was particularly effective in cases with few abnormal PCs (<1%). In addition, hypodiploid PCs were disproportionately represented in the discrepant group, comprising 4 of the 17 cases. The correlation of the PC % S-phase between methods was relatively low (R=0.59). This improved when only including cases with >5% PCs (56 cases, R=0.75), likely due to imprecision of slide-based labeling index with low PC numbers. Furthermore, the methods compared well in discriminating between low and high PC proliferation values (Table 3), and the discrepant cases in this comparison were either near the cut-off or had low PC numbers. 8-color FC PC analysis is a highly sensitive clinical tool which can supplant or augment other methods for characterization of newly diagnosed myeloma and which can also be used for minimal residual disease assessment.

	6-color FC Positive (n=142)	6-color FC Negative (n=60)
8-color FC Positive (n=159)	142 (70%)	0
8-color FC Negative (n=60)	17 (8%)	43 (22%)

Table 1

	Cytogenetic Diploid	Cytogenetic Aneuploid
8-Color FC Diploid	42	0
8-Color FC Aneuploid	17	49

Table 2

	PC Labeling Index Low (n=92)	PC Labeling Index High (n=37)
8-color FC %S-phase<1.5% (n=89)	78	11
8-color FC %S-phase≥1.5% (n=40)	14	26

Table 3

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A Phase I, Dose Escalation Study of BI-505 in Relapsed/Refractory Multiple Myeloma

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The human anti-ICAM-1 mAb BI-505 was identified by a function-first approach and has significant anti-tumor activity in models of multiple myeloma (MM). This multicenter, first-in-human study evaluates the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI-505 in 35 patients with advanced relapsed/refractory MM. BI-505 was given on day 1 and 15 at doses from 0.0004 to 20 mg/kg IV, with a possibility of extended therapy every two weeks until disease progression for patients in cohort 6 and onwards. The results presented in this abstract are based on preliminary data assessed by the Data Monitoring Committee after the last patient was enrolled. The number of AEs was low, with the majority being grade 1-2. Infusion-related reactions (IRRs), such as fever and headache, were limited to the first dose and were managed by premedication and prolonged infusion. In 7 cases, SAEs were assessed as possibly or probably related to BI-505, of these, the majority were IRRs. One patient in the 3 mg/kg cohort experienced a dose limiting toxicity: Headache (grade 3), and premedication was modified in subsequent cohorts. No maximum tolerated dose was identified. BI-505 half-life increased with dose while clearance decreased, indicating target-mediated clearance. The optimal biological dose was defined as 10 mg/kg every two weeks, and additional patients were treated with this regimen. Six patients on extended therapy had stable disease for at least 2 months. In summary, BI-505 has an advantageous safety profile and the 10 mg/kg dose will be used in forthcoming trials.

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Pomalidomide Plus Low-dose Dexamethasone (POM+LoDEX) in RRMM: Analyses Based on Prior Therapy and Renal Function

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Background: The MM-002 phase 2 study evaluated the efficacy and safety of POM +/- LoDEX in relapsed and refractory multiple myeloma (RRMM) patients (pts) who were exposed to most available therapies and have failed lenalidomide (LEN) and bortezomib (BORT). Methods: Pts with >=2 prior therapies and refractory to their last treatment were randomized to POM+LoDEX (POM 4 mg/day, days 1-21 of a 28-day cycle; LoDEX 40 mg/week) or POM alone. Pts were stratified by prior number of treatments, and retrospectively categorized based on baseline creatinine clearance (CrCl): 30-<45, 45-60, and >60 mL/min. Results: 113 pts with a median of 5 prior therapies (range 2-13) were assigned to POM+LoDEX; the overall response rate (ORR) was 33-35%, regardless of prior therapy. Most patients (80%) received >3 prior therapies. ORR was 48% in pts who had received <=3 prior therapies and 30% in pts who had received >3 prior therapies. ORRs were similar regardless of refractoriness to LEN or BORT as last prior therapy. Efficacy (Table) and AEs were generally comparable regardless of baseline renal function. In pts with CrCl 30-<45 (n=21), 45-60 (n=14), and >60 (n=70) mL/min. The rates of grade 3/4 neutropenia, thrombocytopenia, anemia, and pneumonia were 52%, 21%, and 40%; 14%, 14%, and 20%; 29%, 21%, and 19%; and 19%, 21%, and 24%, respectively. Conclusions: Earlier treatment with POM+LoDEX (<=3 prior therapies) achieved better ORR (48%) compared with pts who received POM+LoDEX later (>3 prior therapies; ORR, 30%). Baseline renal function did not appear to impact the efficacy or safety profile.

Table. Efficacy parameters based on baseline renal status in the POM + LoDEX (N = 113) group.

CrCl, mL/min	≥ 30 to < 45 (n = 21)	≥ 45 to ≤ 60 (n = 14)	> 60 (n = 70)
ORR (≥ PR), n (%)	7 (33)	6 (43)	24 (34)
Median DoR, mos	8.3	9.2	8.3
Median DoT, mos (range)	4.2 (0.5–21.6)	5.0 (0.9–24.1)	5.5 (0.1–28.2)
Average daily dose,[a] mg (range)	4.0 (2.3–4.0)	4.0 (2.1–4.0)	4.0 (1.6–4.2)
Median relative dose intensity,[b] (range)	0.9 (0.5–1.2)	0.9 (0.5–1.0)	0.9 (0.2–1.2)
Pts with ≥ 1 dose reduction, n (%)	9 (43)	4 (29)	18 (26)
Median time to first dose reduction, mos (range)	1.2 (0.1–11.3)	2.3 (1.2–15.9)	1.6 (0.9–20.8)

Five patients had CrCl < 30 mL/min, and CrCl data were missing for 3 patients due to incomplete reporting of weight.
[a]Average daily dose = cumulative dose/dose exposure.
[b]Relative dose intensity = dose intensity (cumulative dose/treatment duration)/planned dose intensity.
CrCl, creatinine clearance; DoR, duration of response; DoT, duration of treatment; LoDEX, low-dose dexamethasone; ORR, overall response rate; POM, pomalidomide; PR, partial response; pts, patients.

P-171

Thalidomide, Cyclophosphamide, Dexamethasone in Newly Diagnosed MM Prior to Autologous Stem Cell Transplantation

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Thalidomide, low-dose cyclophosphamide and dexamethasone (TCD) is still widely used in many countries as an induction treatment due to their easy accessibility and the immune modulating effects of thalidomide and low-dose cyclophosphamide. However, it is still an issue of debate whether TCD chemotherapy may have a negative effect on stem cell mobilization. Thus, we retrospectively analyzed 36 patients with newly diagnosed myeloma who underwent TCD induction chemotherapy before ASCT at the Samsung Medical Center between April 2010 and April 2012. The treatment schedule includes thalidomide 100mg per day for 28 days, oral cyclophosphamide 150mg/m_2 and dexamethasone 40 mg on Days 1 through 4. With the median number of four cycles, the overall response rate to TCD was 75.0% (27/36) including 3 CR (8.3%), 13 VGPR (36.1%) and 11 PR (30.5%). The stem cell mobilization was done in all patients with cyclophosphamide plus G-CSF, but two patients required more than 4 days of collection and the other two patients failed to reach the target of CD34-positive cells (4/36, 11.1%). However, all patients underwent high-dose melphalan and ASCT without transplantation-related mortality, and there was no engraftment failure. The overall response rate was increased to 97.2% after ASCT and the quality of response was improved including 15 CR and 12 VGPR. In conclusion, TCD regimen is an effective and feasible induction treatment for newly diagnosed myeloma patients who destined for ASCT although it showed a negative effect on stem cell mobilization in a limited number of patients.

P-172

FLC Evaluation in Monoclonal Gammopathies and Multiple Myeloma Patients

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Background. Identifying patients with optimal response and long term survival is important for clinical guidance because patients with these features are likely not need further therapy. Serum Free Light Chains (sFLC) are used for better assessment of treatment response, thus patients are considered to achieve stringent Complete Response (sCR) by having CR criteria plus normal serum Free Light Chains Ratio (sFLCR) and absent clonal cells in bone marrow. Methods. We have examinated 60 patients (36M and 24F) with Monoclonal Gammopathy (MGUS) (40) and Multiple Myeloma in course of therapy (20). We have assessed serum Free Light Chains (sFLC) and serum Free Light Chains Ratio (sFLCR) for evaluation of progression disease and treatment response in association at Monoclonal Component (MC). Results. We have observed progression of serum Free Light Chains (sFLC) in patients with Monoclonal Gammopathy in evolution with contemporary progression of Monoclonal Component (MC). In Myeloma patients sFLC were assessed for evaluation of the treatment response and we have observed a stringent correlation with Monoclonal Component progression. Conclusions. Role of sFLC and sFLCR is well established and we consider that these assessments represent an important criteria for evaluate progression of Monoclonal Gammopathies and treatment response in Multiple Myeloma.

P-173

A Phase 4, Observational Study of Bortezomib in Chinese Patients with Relapsed or Refractory Multiple Myeloma

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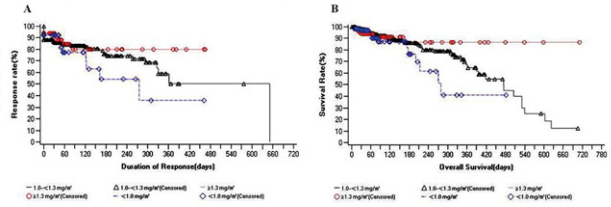
This prospective, observational, multicenter phase 4 study assessed the efficacy and safety of bortezomib in Chinese patients with relapsed/refractory multiple myeloma following at least one prior chemotherapy. The endpoints of this study were; to assess the usage of bortezomib, and the treatment outcome and safety of bortezomib. Of the enrolled patients (N=517; either sex; mean [SD] age: 59 [9.9] years), most had IgG type (46.23 %) and stage IIIa (47.78%) myeloma. Majority used bortezomib as third line treatment (48.16%). The objective response rate was demonstrated in 88.91% of patients (partial response [PR]: 42.26% and complete response [CR]: 24.69%). The proportion of patients exhibiting complete response (strength of response) increased (from 10% to 45%) as the treatment extended. The mean time to response was 36.11 days (95% CI [mean]; 32.57, 39.64). Overall survival rate decreased gradually from 97.15% (by 30 days) to 25.22% (by 720 days). Patients receiving average dosage >1.3 mg/m^2 demonstrated longer duration of response/higher survival rate, and those receiving average dosage <1.0 mg/m^2 exhibited shortest duration of response/lowest survival rate compared with the other 2 dose subgroups (Figure 1). The most frequent treatment-emergent adverse events were decrease in platelet count (14.37%), diarrhea (13.79%), hypoesthesia (10.10%), and peripheral neuropathy (10.68%). Bortezomib was well-tolerated and demonstrated clinical response in majority of patients.

Figure 1: Kaplan-Meier curve of duration of response/overall survival in different subgroups of bortezomib dosage in patients with relapsed/refractory multiple myeloma



P-174

Stem Cell Mobilization and Transplantation is Feasible after ASCT in Heavily Pre-treated Patients with Multiple Myeloma

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Heavily pretreated patients with relapsed/refractory multiple myeloma (MM) are often suffering from cumulative hematotoxicity. The autologous stem cell transplantation (ASCT) has a high potential of long term remission and allows a renewal of the hematopoiesis, but its use is limited by the capacity of stored hematopoietic progenitor cell (HPC) products. Collection of HPC after ASCT was considered difficult due to the stem cell toxicity of melphalan (MEL). However, mobilization and collection procedures improved in recent years. Here, in two MM patients in our department sufficient numbers of HPC were collected despite previous high dose MEL therapy and ASCT. A 63 years old man, achieved VGPR after ASCT in first line. For progressive disease five additional lines of therapy including second ASCT had to be administered. Cyclophosphamide/ etoposide (CE) followed by G-CSF and plerixafor were used for HPC mobilization. Three large volume aphereses (LVL) resulted in sufficient HPC and a third ASCT was performed. A 75 years old female with MM achieved VGPR after initial ASCT. In relapse, three additional lines of treatment were employed. At that time, a second HPC mobilization with CE, G-CSF and plerixafor was started. HPC could be harvested in two LVL apheresis and allowed ASCT. In both patients an ANC>0.5/nL was achieved on day +12. Thus, sufficient HPC mobilization and harvest is feasible in advanced MM patients even after high dose MEL therapy offering an additional treatment option.

P-175

Feasibility and Safety of Lenalidomide Continous Therapy in Multiple Myeloma Elderly Patients

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Background. Lenalidomide represents an important treatment option for multiple myeloma patients either as first line therapy, either in resistant/refractory disease or consolidation/maintenance therapy. In this way Lenalidomide increases the available treatment options. In our Department, Lenalidomide was administered in resistant/relapsing myeloma patients and as continous therapy in elderly myeloma patients. Methods. We treated 47 patients (26M and 21F) with median age of 73 years (range 66-81). We have evaluated 38 patients with a median follow-up of 30 months. These patients were treated with Lenalidomide at variable doses (5-25 mg/die p.o., according to tolerability of each patient, for 21 days every 28 days), in association of very low doses of dexamethasone (10 mg/die p.o. days 1, 2, 3, 4) for first four cycles and then alone in continous treatment. We used Enoxaparin for

prophylaxis of venous thromboembolisms. Clinical restaging was performed after three, six and twelve months, in course of therapy. Results. At present we have not observed any progression of disease and in 25/47 cases we found a good impact on Monoclonal Component (MC). In all patient therapy was well tolerated and were not found significant adverse events or second neoplastic events. Conclusions. Role of Lenalidomide is established as continous therapy in previously treated elderly myeloma patients. This therapy seems to lead an improvement in prognosis of these patients, without causing severe complications.

P-176

Lenalidomide in Patients with Chemotherapy-induced Neuropathy and Relapsed/Refractory MM:Single-centre Prospective Study

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Objectives. Although lenalidomide has been claimed to be less neurotoxic than its analogue thalidomide, formal evidence of this property is still lacking. In this prospective study we assessed lenalidomide safety in multiple myeloma (MM) patients to evaluate whether its administration would modify a previously ensued chemotherapy-induced-polyneuropathy (CIPN). Methods. Thirty consecutive MM patients (13 women, 17 men, mean age 63.7 ± 9.4) previously treated with bortezomib and/or thalidomide and starting on lenalidomide (25 mg/day for 21 day cycles) for relapsed/refractory MM were assessed at baseline, after 6 and 12 months from the beginning of lenalidomide with Total Neuropathy Score clinical version (TNSc). Pain was assessed according to numeric rating scale (NRS). Based on previous studies TNSc >2 was considered significant for CIPN. Changes of TNSc of at least 4 points from baseline value were accepted as clinically-relevant. Results. At baseline 16/30 patients (53.3%) had symptoms and signs of CIPN (mean TNSc 5.8, median 5.5, range 3-15). After 6 months, 13 patients were unchanged, one improved and 2 worsened. After 12 months the patient who had improved persisted stable, while the 2 who had worsened returned to TNSc baseline value. The 14 patients without CIPN at baseline did not develop neuropathy. NRS and ECOG performance status did not modify. Conclusions. Our results confirm the safety of lenalidomide and demonstrate the very low neurotoxicity of lenalidomide also in MM patients with pre-existing CIPN treated for one year.

P-177

A Population Pharmacokinetic-Pharmacodynamic Modeling of Platelet Count to Assist Panobinostat Regimen Design

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Background: Thrombocytopenia (TCP) is the most common dose-limiting toxicity of the pan-deacetylase inhibitor (pan-DACi) panobinostat (LBH589). This adverse event occurs due to a reversible delay in megakaryocyte maturation and rapidly improves with dose interruption. Addressing TCP is particularly important since panobinostat is combined with other TCP-inducing agents, such as bortezomib, in myeloma. Methods: An indirect response model with the tumor type (hematologic vs solid) covariate was used to characterize the relationship between the dose/concentration of panobinostat and platelet count using the data from 14 phase 1 and 2 trials. Results: A total of 441 patients (pts) were included in the model. As expected, pts with hematologic tumors had lower baseline platelet counts and a higher probability of grade ≥ 3 TCP vs pts with solid tumors. Although simulations based on the final model demonstrated considerable variability in platelet response, pts with higher platelet counts at baseline had a lower probability of a grade ≥ 3 TCP event. The simulations also predicted a dose-dependent increase in grade 3/4 TCP and platelet rebound during scheduled dose interruption. Conclusions: The indirect response model adequately characterized platelet dynamics and can be used to help predict platelet response based on tumor type, dose, and schedule. Specifically, the model predicts that TCP is highly responsive to dose interruption and/or reduction, consistent with dose/schedule selection for panobinostat combination therapy in myeloma.

P-178

Ph 1 Trial of Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVD) in Relapsed and/or Refractory Multiple Myeloma

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Background: LEN, BORT, and DEX combinations have shown preclinical synergy and clinical efficacy in newly diagnosed and relapsed/refractory MM (RRMM). POM ± DEX showed promising activity in pts with prior LEN and BORT. MM-005 was designed to identify the PVD dose for a phase 3 trial comparing PVD vs BORT+LoDEX in RRMM.

Methods: Pts with 1-4 prior antimyeloma therapies, progressive disease (PD) during a LEN-containing treatment (Tx) or within 60 days of last dose, and proteasome inhibitor exposure (but not BORT-refractory) were eligible. Maximum tolerated dose (MTD) determination followed a 3+3 design in 5 cohorts (Table). Tx continued until PD or unacceptable toxicity. Dose-limiting toxicities (DLTs) were assessed during cycle 1. Endpoints included MTD (primary) and safety, overall response rate (ORR; ≥ partial response), duration of response, and time to response (secondary).

Results: All 15 pts had prior LEN and BORT; 73% had PD on LEN as last Tx. As of Oct 15, 2012, no DLTs have been observed. MTD confirmation is ongoing. Grade (G) 3/4 AEs included thrombocytopenia (27%) and neutropenia (27%). Peripheral neuropathy (none painful) occurred in 4 pts (G1 and 2, n=2 each). No thromboembolism occurred. 3 pts discontinued, none due to AE. The ORR was 73% at data cut off. Median time to response was rapid (1 cycle) with promising activity seen in pts with adverse cytogenetics.

Conclusions: PVD is well tolerated in RRMM, with no DLTs or Tx discontinuations due to AE to date. PVD has encouraging activity with 73% ORR. Best response is expected to improve with longer follow-up.

3+3 Design (21-day cycles)			
Cohort*	POM (D1-14)	BORT (D1, 4, 8, 11†)	LoDEX (D1-2, 4-5, 8-9, 11-12‡)
1 (n = 3)	1 mg/day	1 mg/m²	20 mg§
2 (n = 3)	2 mg/day	1 mg/m²	20 mg§
3 (n = 3)	3 mg/day	1 mg/m²	20 mg§
4 (n = 3)	4 mg/day	1 mg/m²	20 mg§
5 (n = 3)	4 mg/day	1.3 mg/m²	20 mg§
Expansion cohort (n = 6) at MTD/MPD			

*All pts received thromboprophylaxis (aspirin or low-molecular-weight heparin) and herpes zoster prophylaxis (acyclovir). †For cycles 1-8, then D1, 8 for cycles 9+; ‡For cycles 1-8, then D1-2, 8-9 for cycles 9+; §10 mg for pts aged > 75 yrs. MPD, maximum planned dose, MTD, maximum tolerated dose.

P-179

30-min Infusion of High Dose Carfilzomib plus Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma

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Background: Carfilzomib (CFZ), when infused over 2-10 min up to 27 mg/m², has shown favorable efficacy and safety in patients (pts) with relapsed and/or refractory multiple myeloma (RRMM). Subsequent results from a phase 1b dose-escalation study (PX-171-007) in RRMM of CFZ when infused over 30 min showed a maximum tolerated dose of 56 mg/m² with an ORR of 60%. An expanded cohort of 007 assessed the tolerability and efficacy of CFZ doses of 45 or 56 mg/m² combined with low-dose dexamethasone (dex); the results are reported herein. Methods: CFZ was administered as a 30-min infusion on Days (D) 1, 2, 8, 9, 15, and 16 of a 28-D cycle (C). C1D1-2 doses were 20 mg/m², followed by escalation to either 45 or 56 mg/m². Dex 20 mg was administered prior to each CFZ dose; 40 mg was administered during week 4 of the cycle. Safety assessments were evaluated according to CTCAE v 3.0 responses were determined according to IMWG Criteria. Results: As of October 2012, 22 pts have enrolled and started a median of 6 (1-10) C; CFZ dose was reduced in 1 pt and discontinued in 1 both due to an AE. The most common AEs regardless of drug relationship were thrombocytopenia and fatigue (40.9% each) and the only AEs >= Grade 3 in at least 10% of total pts were hematologic. Of 20 pts evaluable for efficacy, overall response rate (>=PR) was 55.0% with 5 VGPR and 6 PR. Conclusions: The combination of CFZ 30-min infusion with low-dose dex was well tolerated with compelling preliminary efficacy results. The regimen, with a CFZ dose of 20/56 mg/m², is being evaluated in the phase 3 trial ENDEAVOR.

P-180

Pharmacokinetics (PK), Safety & Efficacy of Lenalidomide+Dexamethasone (LEN-DEX) in Myeloma Patients with Renal Failure

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Introduction: LEN dose should be adjusted to glomerular filtration rate (GFR). Current dosing recommendations are based on PK data obtained in non-malignant patients (pts) and on modelling/simulations. We conducted a prospective study evaluating PK, safety and efficacy of LEN-DEX in multiple myeloma (MM) pts with various degrees of renal impairment (RI), as estimated by MDRD (GFR/MDRD) or Cockcroft-Gault (CG) equations (GFR/CG). Methods: 38 pts with stable GFR, previously treated for symptomatic MM, were divided in 5 groups according to baseline GFR/CG. Pts received at least 3 28-day cycles of LEN (days 1-21, dose defined according to GFR/CG) + DEX (40 mg/week). Results: As in pts with non malignant conditions, LEN clearance was highly correlated to GFR/CG and GFR/MDRD. The average daily area under curve values for groups 2-5 were 103-149% of that for group 1 (1742 h*ng/mL). No difference was found in plasma LEN levels at 2h post-dose between day 9 (LEN alone) and day 15 (LEN-DEX) across groups. Hematological response rate (PR or more) was 81% in the whole cohort, and 82% in pts with GFR/CG <50ml/min. The frequency of adverse event of grade 3/cycle was 0.6/pt, similar across the 5 groups. Renal function improved in 6 pts. Conclusion: The effect of RI on LEN PK in MM pts treated with LEN-DEX was similar to that in non-malignant pts receiving LEN alone. The recommended adjustments in starting dose achieved appropriate plasma exposure with similar efficacy/safety in the different renal function groups. MDRD and CG equations may be interchangeable for determining the LEN dosage.

P-181

Molecular Radiotherapy with a Y-90 Labeled Anti-CD66 mAb Prior to Allogeneic SCT for MM: Results of a Phase I Trial.

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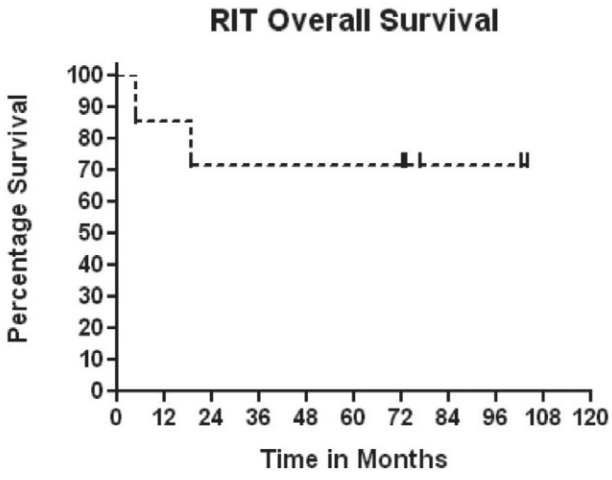
We report the use of a yttrium-90 (Y-90) labelled anti-CD66 monoclonal antibody (mAb) incorporated in the allogeneic stem cell transplant conditioning (alloSCT) protocol fludarabine, melphalan and Campath as part of a phase I study. CD66 is expressed by normal myeloid cells and plasma cells (1) making it an excellent target antigen for molecular radiotherapy. Dosimetry was performed prior to transplantation using the same anti-CD66 labeled with indium-111 (In-111). Seven patients with MM received Y-90 anti-CD66+Flu/mel/campath conditioning prior to alloSCT. 6 of 7 patients had relapsed disease after autologous SCT, one patient was in CR post autoSCT. Two patients received an infused Y-90 dose of 10MBq/kg body weight, three patients 37.5MBq/kg, two patients 45MBq/kg. At 45MBq/kg the estimated dose delivered to the bone marrow was 38Gy; 4.3Gy to liver, 16.5Gy to spleen, 2.8Gy to kidneys and 2.4Gy to lungs. Peripheral blood stem cells were used in all patients; 5 sibling and 2 unrelated donors. Median age 52.9 yrs (45-56), transplant related mortality zero at days 100 and 180, median follow-up 73.3 months (4.9-104.0 m). Toxicity was not increased. The actuarial probability of overall survival was 71.4% at 104 m. 5/7 patients are alive in CR (EBMT criteria). We have shown in this small study that a Y-90-anti-CD66 mAb can deliver significant radiation to sites of disease in patients with myeloma without additional toxicity. This may result in improved outcome following alloSCT in MM and warrants testing in a Phase II study. 1. Lee C et al, Br J Haematol. 2010 Jun;149(5):795-6.



P-182

Oligoclonal and Monoclonal Bands after Single Transplantation in Myeloma in the Era of Novel Agents

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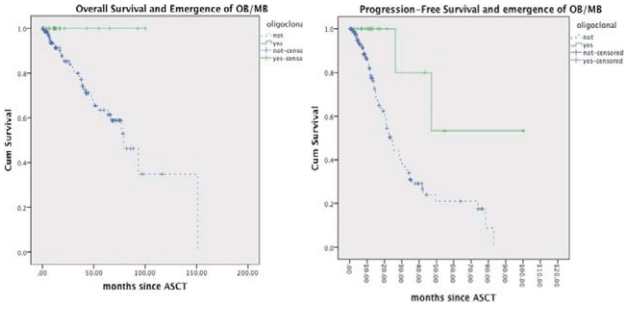
Patients (pts) with multiple myeloma (MM) post-autologous stem cell transplant (ASCT) can develop oligoclonal and monoclonal bands (OB/MB) that are associated with a good prognosis. In this study, we aimed to assess the impact of OB/MB occurrence on overall survival (OS) and Progression Free Survival (PFS) for MM pts undergoing single ASCT who had received novel agent induction-based regimens. Methods: All consecutive pts with MM undergoing single ASCT from 01/07 to 09/12 who had novel induction therapy were evaluated. OB/MB were defined as per the secondary MGUS criteria (Kyle RA, et al., 2004) Results 184 pts were identified. CyBORD was used in 48.9% cases, Thalidomide plus dexamethasone in 27.2% and Lenalidomide and Dexamethasone in 8.2%. Twenty-one out of 184 pts (11.4%) were found to have developed OB/MB. OB and IgG kappa were seen in 28.5% each. Nineteen (90%) pts who developed OB/MB had achieved at least VGPR at day-100 post-ASCT. Median overall survival for pts who did not develop OB/MB at day-100 post ASCT was 78 months (CI 95%; 73.0-81.5) versus not reached for those who did (p=0.04); PFS was 71 months (CI 95% 41-101) compared to 33 months for those who did not not develop OB/MB (p=0.006) (Fig. 1) Multivariate analysis showed emergence of OB/MB as the major independent prognostic factor for OS and PFS (p=0.002, and p=0.01, respectively) In conclusion, OB/MB occurrence is an important prognostic factor in MM pts who undergo ASCT in the era of novel agents, the biological significance and its impact on clinical outcomes should be prospectively validated.



P-183

Consistency of LEN+DEX Efficacy across Prior Treatments in Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: Newer MM agents have improved clinical outcomes. This post-hoc analysis assessed whether the effect of LEN+DEX on time to progression (TTP) is modified by prior treatment history, particularly bortezomib (BORT).

Methods: Data from 704 patients from 2 phase-III trials (MM-009/010) comparing LEN+DEX vs dexamethasone (DEX) in RRMM were classified based on prior therapies ([PT] 1 [35%] vs ≥2 [65%]), including doxorubicin, thalidomide and melphalan. All patients had previously used DEX. Effect modification by PT was assessed in Cox regression models by adding an indicator for PT, along with an interaction term between the treatment group and PT indicators. This measures the difference in the effect of LEN+DEX for each prior PT (eg, BORT) users and non-users in the 1 and ≥2PT subgroups. It was not possible to assess the impact for prior BORT use in the 1PT group, which included only one patient.

Results: LEN+DEX was associated with a 70% reduction in risk of progression among patients with 1PT (HR=0.31; CI:0.22-0.44), and a 63% reduction for those with ≥2PT (HR=0.37; CI:0.29-0.47). In the 1PT group, HR for LEN+DEX vs DEX was similar across all PT (except BORT, which was not evaluable). The HR was identical (0.38), for prior BORT users (CI:0.2-0.7) and non-users (CI:0.3-0.5) in the ≥2PT group. No interaction estimate reached statistical significance.

Conclusions: The findings suggest the effect of LEN+DEX on TTP is unaffected by prior treatment history. LEN+DEX had equivalent efficacy regardless of prior BORT use in patients with multiple PTs.

P-184

Bortezomib-based Induction Therapy Followed by Iv Busulfan-melphalan as Conditioning Regimen in Newly Diagnosed MM

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We have previously reported the safety and efficacy of intravenous (iv) busulfan and melphalan (BUMEL) as conditioning regimen for autologous stem cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma (MM) after induction with conventional chemotherapy. In this pro-

spective study we show the results of this preparative regimen in 49 patients (22 M/27 F; median age 61 years, range 33-67) with newly diagnosed MM who received bortezomib (Bz)-based combinations as induction therapy (Bz-dexamethasone (BzD): 68%; VBMCP/VBAD x4 + BzD x2: 18%;BzD + pegylated liposomal doxorubicin: 10%; BzD + thalidomide: 4%). Complete response (CR), near CR, and very good partial response rates pre-and post ASCT were 22/2/14% and 46/20/10%, respectively. A normal hematopoietic recovery was achieved in every patient. Mucositis (88%) and febrile neutropenia (71%) were the most common non-hematologic toxicities observed. Mild liver toxicity was detected in 16% of patients but no patient developed sinusoidal occlusive syndrome. Other toxicities (gastrointestinal (12%), pulmonary (2%), and cardiac (2%)) were mild. Median duration of hospitalization was 17 days (range, 1-52). There were no transplant-related deaths. After a median follow-up of 19 months, 10 patients have progressed and 2 have died. Median PFS and OS have not been reached. Our results show that the use of pre transplant ivBUMEL conditioning regimen in patients with newly diagnosed MM receiving induction therapy with Bz-based combinations is associated with an acceptable toxicity and a high anti-myeloma efficacy.

P-185

Bortezomib, Melphalan and Prednisone (VMP) in Refractory/Relapsed Multiple Myeloma

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INTRODUCTION The standard treatment for untreated patients with MM who are not candidates for high-dose therapy is the combination VMP. PATHIENTS In our exploratory experience 2 patients with "relapsed MM" and 3 patients with "refractory MM" were treated with VMP. The first patient with "relapsed MM" was retreated once again with the same combination after 18 months because of both the very good haematologic response previously obtained and severe cardiac comorbidities that might have rendered the patient more susceptible to the vascular complications of IMiDs. The second patient with "relapsed MM" received VMP as third-line treatment after thal+dexa and VD due to severe renal failure. The patients with "refractory MM" received VMP as second-line therapy because of the progression disease appearance during front-line therapy with RD. V 1,3 mg/m2 was given on days 1, 8, 15, 22, M 9 mg/m2 was given on days 1-4, P 60 mg/m2 was given on days 1-4. Each cycle was repeated every 35 days for a total of 9 courses. RESULTS The dose of bortezomib was reduced in only one patient due to pre-existing peripheral neuropathy; the dose of melphalan was reduced in only one patient due to CrCl < 15 mL/min. Adverse events, mainly thrombocytopenia and neutropenia, were manageable. Two patients achieved a CR, 1 patient a VGPR, 1 patient a PR. One patient interrupted the treatment for progression disease. CONCLUSIONS Our experience suggests that the retreatment with VMP may induce unexpected new clinically significant responses also in patients with refractory or relapsed MM.

P-186

Detection of Multiple Extramedullary Plasmacytomas of Upper Airways by F-18 FDG PET/CT Imaging

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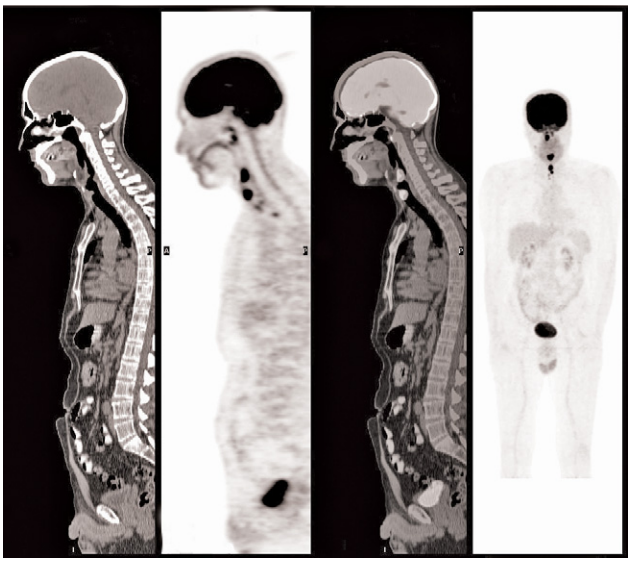
A 42-year-old man had complaints of progressive hoarseness and shortness of breath for 6 months. Examination showed a nasopharyngeal mass and biopsy revealed atypical plasma cells consistent with plasmacytoma. Bone marrow examination showed no evidence of increased plasma cells, however, serum immunofixation electropheresis demonstrated a monoclonal paraprotein of IgG-lambda type. MRI of the neck and nasopharnyx revealed multiple mass lesions of upper airways with polypoid protrusions to the lumen obliterating airway passage. An F-18 FDG imaging obtained to see the extent of the disease demonstrated pathologic increased 18F-FDG accumulations within the posterolateral part of nasopharynx (SUVmax: 19), epiglottis (SUVmax: 17) and trachea (SUVmax: 17). Sagittal view shows pathologic increased 18F-FDG accumulations in these locations (Figure). Solitary extramedullary plasmacytoma is very rare and occurs when there is soft tissue infiltration of clonal plasma cells. There should be no evidence of bone destruction or occult disease elsewhere including bone marrow. The most common site for extramedullary plasmacytoma is the upper aerodigestive tract followed by gastrointestinal involvement. Rare sites of involvement have also been reported in the literature. PET-CT is a successful tool for diagnosis and monitoring of disease status in plasmacytoma.



P-187

Effect of Lenalidomide-dexamethasone Therapy on the Level of Activated and Regulatory T-cells in Myeloma Patients.

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Treatment of relapsed or refractory myeloma (RRMM) with dexamethasone (Dex) and lenalidomide (Len) is an effective anti-tumour strategy. In addition to direct anti-tumour effects, Len exhibits immunostimulatory activity, although this may be compromised by concomitant dexamethasone. *In vitro* coculture of myeloma cell lines (HMCL) with sorted $CD4^+CD25^-$ lymphocytes induced T_{Reg} cell ($CD4^+CD25^{Bright}$*FoxP3*$^+$) differentiation ($p<0.001$), with only minimal T_{Eff} cell ($CD4^+CD25^+$*FoxP3*$^-$) generation. Incubation of HMCL with Len prior to coculture gave rise to a higher T_{Eff}:T_{Reg} ratio through induction of T_{Eff} cells ($p=0.001$). Patients with RRMM ($n=21$) had profound $CD4^+$ lymphopenia ($p=0.027$), compared to age-matched controls, which was not corrected by LenDex therapy. The number of recent thymic emigrants was significantly lower in RRMM than in control subjects ($p=0.0002$). The proportion of activated $CD4^+$ T_{Eff} cells was reduced in RRMM pre-treatment compared to controls ($p<0.001$), but increased with LenDex ($p=0.021$), especially between cycles 4 and 7. T_{Reg} cells were expanded in RRMM ($p=0.005$) but rapidly reduced early in LenDex therapy, returning to baseline with Dex tapering. The level of T_{Reg} cells after cycle 4 correlated with the time-to-progression ($r2=0.669$, $p=0.009$). The T_{Eff}:T_{Reg} ratio was lower in RRMM compared to controls ($p=0.05$), but rose above baseline by cycle 4. Neither baseline ($p=0.29$) nor cycle 4 ($p=0.22$) ratios correlated with TTP. The data demonstrate the *in vivo* immunomodulatory effect of LenDex may redress the imbalance caused by MM.

P-188

Long Term Outcome after Allogeneic Stem Cell Transplantation for Advanced Multiple Myeloma

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We report on the outcome of 42 patients with advanced stage multiple myeloma (MM) treated with allogeneic stem cell transplantation (allo-SCT) between 1988 and 2011, after a myeloablative (MAC, n=16) or reduced-intensity conditioning (RIC, n=26), from a related (n=37) or unrelated donor (n=5). Median age at transplantation was 51y (36-67). Most patients were heavily pre-treated, 16 had a previous autologous SCT, only 7 received novel drugs, 14 were in relapse or progression. The median follow-up for patients alive at time of analysis is 10y. Eighteen patients experienced grade II-IV acute GVHD, and 7 extensive chronic GVHD. Best responses post-transplantation were CR in 21 patients and PR in 15. OS was 50% at 5y, and 25% at 20y. PFS was 50% at 5y, and 3% at 20y. Disease progression occurred in 26 patients, in 7 of them later than 6y post-transplant. Cumulative incidence of relapse/progression was 28% at 1y, 69% at 5y and 86% at 10y. Three out of 13 patients showed at least a PR to DLI. Twenty-six patients have died, 50% of disease progression or relapse, and 50% from transplant-related complications (NRM). Cumulative incidence of NRM was 27% at 1y, 30% at both 5 and 20y. There was no significant difference in outcome between RIC and MAC. Chronic GVHD and achievement of CR after SCT were not significantly associated with better OS or PFS. Our observation suggests that long-term disease control can be expected in a subset of MM patients undergoing allo-SCT, even performed in heavily pretreated, advanced stage MM that fail prior therapy.

P-189

Progression-Free Survival (PFS) and Overall Survival (OS) Advantages with Pomalidomide + Low-Dose Dexamethasone: MM-003

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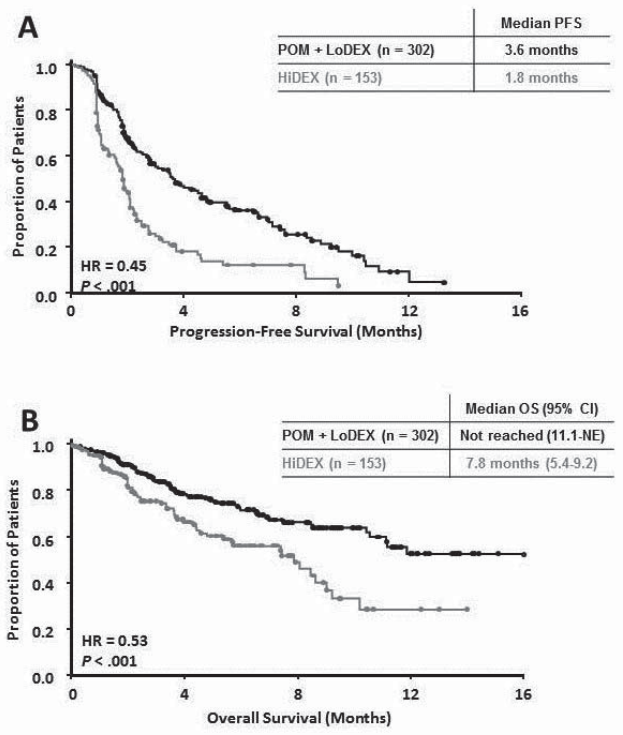
Background: MM pts who have exhausted LEN and BORT therapy (Tx) have short median OS and limited options. High-dose dexamethasone (HiDEX) is commonly used to treat these pts.

Methods: MM-003 compared POM+LoDEX (n=302) vs HiDEX (n=153) in pts who failed LEN and BORT. Pts must have been refractory to last prior Tx (progressive disease [PD] during or within 60 days) and failed LEN and BORT (alone or in combination) after receiving ≥ 2 consecutive cycles of each. Tx was described (Dimopoulos. ASH 2012). The primary endpoint was PFS; secondary endpoints included OS, overall response rate (ORR; ≥ partial response), and safety.

Results: The median number of prior Tx was 5 (1-17); 72% were LEN and BORT refractory. Median follow-up was 4 mos. PFS and OS were significantly longer with POM+LoDEX vs HiDEX (Figure). 29% of HiDEX pts received POM after PD. PFS and OS were significantly improved for POM+LoDEX vs HiDEX in pts refractory to LEN and BORT, with LEN or BORT as last prior Tx, or with normal or moderately impaired renal function (CrCL ≥ or <60 mL/min). After data evaluation, the DMC recommended crossover from HiDEX to POM+LoDEX. With updated data, ORRs were 21% vs 3% for POM+LoDEX vs HiDEX (*P*<.001). The most frequent grade 3/4 AEs for POM+LoDEX vs HiDEX were neutropenia (42% vs 15%), anemia (27% vs 29%), and infections (24% vs 23%). Discontinuation due to AE was low (7% vs 6%). Quality of life analyses are ongoing.

Conclusions: POM+LoDEX significantly increased PFS and OS vs HiDEX in pts who have failed LEN and BORT and should become a new Tx option in these pts.



P-190

Use of Lenalidomide in Relapse/Refractory Multiple Myeloma_Benefits of Earlier Treatment in Overall Survival

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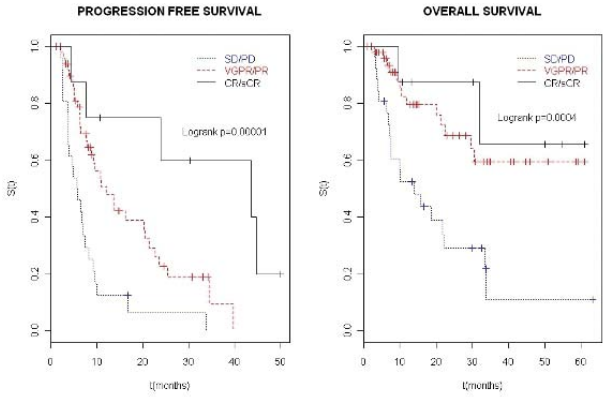
Lenalidomide is an immunomodulator approved for relapsed/refractory Multiple Myeloma (rrMM). We studied the efficacy and safety of lenalidomide in all rrMM patients (pts) treated in our centre with lenalidomide for at least 2 cycles (May/2007 to Sep/2012). We retrospectively reviewed 91 pts: 56% males; median age at diagnosis 58yo; 63yo (29-78) at start of lenalidomide; main subtypes were IgG κ (41%) and IgG λ (20%); 13% high-risk cytogenetics; 37% plasmocytoma; 6% amyloidosis; 81% received lenalidomide 25mg/d x 21d (28/28d) and dexamethasone 40mg/w; median 8 cycles (3-44). Median number of previous lines was 3 (20% had

1 line, 27% had 2, 53% >2). Overall, 65% pts responded (9% CR/sCR, 25% VGPR, 31% PR). Pts with one previous line had significantly better response compared to >1 (ORR 94%vs63%, p=0.016; CR/sCR 12%vs9%, VGPR 41%vs23%, PR 41%vs30%). Response was associated with better progression-free survival (PFS; p<0.0001) and overall survival (OS; p=0.0004). Median follow-up 13.4 months (mo), median PFS was 9.2 mo; (43.7 mo in CR/sCR pts); median OS was 32 mo (was not reached in VGPR or CR/sCR pts). Unadjusted hazard-ratio for PFS in CR/sCR pts compared to pts without response was 0.096 (p=0.0003). Compared to pts without response, CR/sCR pts had 80% reduction in the hazard of death (p=0.031). Toxicity occurred in 71% pts, mainly hematologic (52%; G1/2 in 70%). Thrombotic events in 3%, despite prophylaxis. Lenalidomide/dexamethasone increases OS in responsive rrMM with good tolerability. Results were significantly better when lenalidomide was used earlier.



P-191

High-Dose Lenalidomide plus Melphalan as Transplant Conditioning in Relapsed or Refractory Multiple Myeloma.

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Background: We investigated whether high dose lenalidomide (HDLEN) could be safely added to 200mg/m2 melphalan (MEL200) conditioning in autologous stem cell transplant (ASCT) in a phase 1 study. Methods: 12 patients (pts) with relapsed or refractory multiple myeloma (RRMM) participated in a 3+3 phase 1 study of HDLEN added to MEL200 prior to ASCT. HDLEN was given on days -5 to -1, (day 0 as day of stem cell infusion) at 4 dose levels: 1) 25mg twice daily; 2) 25mg AM, 50mg PM; 3) 50mg AM, 75mg in PM; 4) 75mg AM, 100mg PM. Bone marrow was examined at Day -2, before MEL200 dosing. LEN 25mg for 21/28 days maintenance started at Day 100, continued until disease progression/intolerability. Results: 12 pts with RRMM (8 resistant to LEN), with 4 median prior lines of therapy completed ASCT without DLT. Median days (range) to wbc and platelet engraftment was 11 (10-13) and 12 (9-16). Toxicities were mild and all occurred after MEL200: (Grade 1/2): GI: 83%/17%; Myalgia: 34%/ 0; Rash:8%/0; Dyspnea: 17%/0; Fever: 17%/0. The sole Grade 3 toxicity was cholecystitis at Day +50 in 1 pt. Transplant-related mortality was 0%. Day -2 biopsies showed marked (>50%) and moderate (25-50%) reduction in plasmacytosis in 40% and 30% of pts, respectively. Responses at Day +100 / best with maintenance: PR 55%/18%, VGPR 18%/45%, CR 37%/36%. After median follow-up of 17 months, 83% of subjects are alive, 50% without progression. Conclusions: HDLEN added to MEL200 ASCT in RRMM does not exacerbate expected toxicities. The maximum tolerated dose of HDLEN was not found at dosing up to 175mg daily.

P-192

Coexistent Multiple Myeloma and Increased Bone Marrow Plasmacytosis Define an Equally High Risk Subset of AL Amyloidosis

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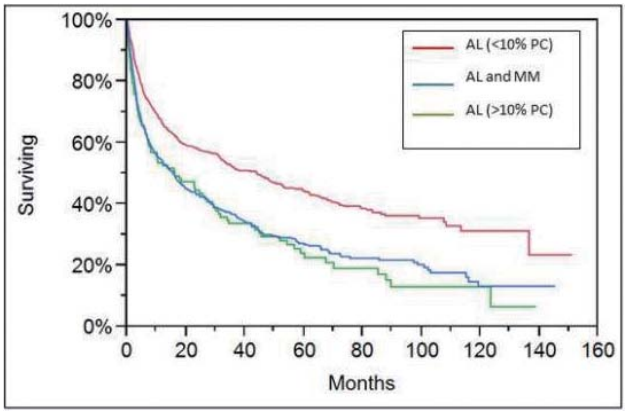
OBJECTIVE: There is consensus that light chain amyloidosis (AL) patients with CRAB criteria (abnormal calcium or renal function, anemia or lytic bone lesions) also have multiple myeloma (MM). There is confusion whether increased bone marrow plasmacytosis in the absence of CRAB affects outcomes in AL. The aim of this study was to examine the spectrum of AL with and without myeloma, with a goal of defining the optimal bone marrow plasma cell number to qualify as AL with MM. METHODS: We identified 1272 patients with AL seen within 90 days of diagnosis, between January 1, 2000 and December 31, 2010. We defined a population of patients with coexisting MM based on the existence of CRAB (AL-CRAB-MM). Receiver operating characteristics analysis determined the optimal BMPC cut-point to predict for one-year mortality in AL patients without AL-CRAB-MM to produce two additional groups, AL-only (less than 10%

BMPC) and AL-PC-MM (more than 10% BMPC). RESULTS: Among the 1272 patients, 117 had AL-CRAB-MM, 476 had AL-PC-MM, and 679 had AL only. Their respective median overall survivals were 16.2, 15.8, and 28.4 months. (figure). Since the outcomes of AL-CRAB-MM and AL-PC-MM were similar, they were pooled for subsequent analyses. On multivariate analysis, AL-CRAB-MM and AL-PC-MM retained negative prognostic value independent of age, cardiac stage, and dFLC. CONCLUSION: AL patients with less than 10% BMPCs have a poor prognosis similar to patients with AL-CRAB-MM and should be considered together as AL with MM.



P-193

Excellent Response in Untreated Myeloma with Low Dose Lenalidomide Followed by Autologous Transplant and Maintenance

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Lenalidomide (len) 25mg with dexamethasone (dex) 40mg weekly is effective in treatment of myeloma. Higher doses may have increased toxicity. Efficacy of low dose len and dex was studied in this phase II trial. Subjects: Newly diagnosed transplant eligible myeloma patients. Induction: Len 15-25 mg D1-21 +/- dex 20mg weekly for 4-6 cycles. Hematopoietic stem cell (HSC) mobilization: cyclophosphamide 2-4 gm/m^2 + G-CSF 10mcg/kg. Transplant conditioning: melphalan 140-200mg/m^2. Maintenance: len 25mg D1-21(minimum 12 cycles) + dendritic cell(DC) vaccination (D1 C1-6) (n=10). 36 patients have completed induction, HSCT and commenced maintenance. Median CD34+cells collected=11.9 × 10^6(4.9-40.6) over median 3(1-6) days. DC for 6(1x10^6(cell) vaccinations generated in 12 patients with median DC yield=165 × 10^6(45-298), purity 84.2 %(72-98). Post induction: overall response rate=94%, partial response(PR)=61%, very good PR(VGPR)=19%, complete response(CR)=6%, stable disease=8% and refractory disease=6%. Improvement seen post autograft with PR=39%, VGPR=31% and CR=22%. At median follow up of 21(11-45) months, best response achieved was VGPR=33% and CR=44%. In responders best response was achieved post induction in 21%, post HSCT in 41% and during maintenance in 38%. 24 patients continue on maintenance with a median of 12(3-39) cycles. Low dose len and dex induction followed by HSCT and maintenance in untreated myeloma patients is associated with high response rates. Depth of response is improved by HSCT and maintenance. Collection of hematopoietic and dendritic cell precursors is unimpaired.

P-194

Melphalan/Prednisolone/Zoledronic Acid Therapy in Newly Diagnosed Japanese Patients with Multiple Myeloma.

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Introduction: Before the introduction of novel agents, melphalan/prednisone (MP) therapy was a standard-of-care in the treatment of multiple myeloma (MM). In Japan, no multicenter clinical study of MP therapy has been reported. Patients and Methods: This is a prospective, open label, multicenter phase 2 trial. The primary endpoint of was to evaluate the incidence of SREs at 1 year, and the secondary endpoints

were to evaluate the incidence of SREs at 2 year, the overall response rate (ORR) , and the change of bone metabolism marker and bone density. Between September 2008 and December 2011, 92 patients were enrolled including 3 patients excluded. Eighty-nine patients [median age 73 (60-88) years; male/female, 31/58; ISS 1 (n=29), 2 (n=31), 3 (n=22), unknown (n=7)] were studied. Patients received oral melphalan 6 mg/m2 and prednisone 40 mg/m2 on days 1-4 of every 28-day cycle until plateau, and received intravenous ZA 4.0 mg/body every month. The response was assessed according to EBMT criteria. Results: SREs were observed only in 4 cases (4.5 %). ORR was 46.9 % (2CR, 36PR, 24MR, 14NC, 5PD, 8NE). Regarding adverse events considered to be related to ZA, osteonecrosis of the jaw (ONJ) was observed only in 1 case (1.1 %). Discussion: The incidence of SREs was very low in this study, so that ZA treatment would be recommended to Japanese MM patients. The oral care before and during the ZA treatment was considered effective to prevent ONJ. The ORR was similar to those in other reports, and this result should be used as the platform data of MP therapy in Japanese MM patients.

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Phase 2 Study of Prolonged Carfilzomib Therapy in Patients Previously Enrolled in Carfilzomib Phase 1 and 2 Trials

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Background: Prolonged treatment with carfilzomib (CFZ), a proteasome inhibitor recently approved in the US for relapsed and refractory multiple myeloma (MM), was investigated in the PX-171-010 (010, NCT00884312) extension study. Updated results are reported herein. Methods: Patients (pts) must have completed a phase 1 or 2 CFZ study within 90 days of entering 010. CFZ dosing was 11-56 mg/m2 and pts could have a regimen change of: 1) CFZ schedule decreased to once every other week, 2) CFZ dose change, 3) addition of other anti-MM agents, or 4) combination of 2 and 3. The primary study endpoint was safety including all adverse events (AEs) >/=Grade (G) 3, serious AEs (SAEs), and AEs resulting in dose modification and discontinuation. Pts were also followed for efficacy. Results: Overall, 100 pts have enrolled in the 010 study (91 MM and 9 solid tumor). Pts have started a median of 10.5 cycles; 63.0% reported AEs >/=G3 (mainly hematologic) and 53.0% reported SAEs (pneumonia and dyspnea most common). AE-related discontinuations were 11.0%, and there were 6 deaths (3 due to AEs and 3 due to progressive disease). Of the patients with MM overall response rate across various regimen changes ranged from 24.2% to 45.2% and for any regimen following progressive disease from 16.7% to 40.0%. Conclusions: Pts were able to stay on CFZ treatment for extended periods with clinically meaningful disease control and no evidence of unique or serious cumulative toxicity. Preliminary long-term tolerability of and responses to prolonged CFZ treatment are promising.

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PANORAMA 2: Panobinostat, Bortezomib, and Dexamethasone in Patients with Relapsed and Bortezomib-Refractory Myeloma

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Background: The oral pan-deacetylase inhibitor panobinostat (PAN) demonstrates potent synergy with bortezomib (BTZ) to inhibit both the aggresome and proteasome pathways in preclinical studies, with promising phase 1 results. PANORAMA 2 evaluated whether PAN recaptured responses in advanced, BTZ-refractory multiple myeloma (MM) patients (pts). Methods: Pts with relapsed and BTZ-refractory MM (at least 2 prior lines of therapy, including an IMiD, and who had progressed on or within 60 days of the last BTZ-based therapy) were treated in this single-arm, phase 2 study with PAN + BTZ + dexamethasone (Dex). Results: Fifty-five pts were enrolled (median age, 61 years). Pts were heavily pretreated: median 4 prior regimens (range, 2-11), and median 2 prior BTZ-containing regimens (range, 1-6). All pts were previously treated with BTZ, Dex, and at least 1 IMiD (le-

nalidomide [98%], thalidomide [69%]). The ORR was 35% (1 nCR and 18 PR, including 3 pts [5%] achieving a VGPR [Table]), and CBR was 53%. The median duration of exposure was 4.6 months (range, < 1-14.8). In pts who achieved response, the median time to response was 1.4 months (range, 0.1-3.9), and the median DOR was 6.0 months. Common grade 3/4 adverse events, regardless of study drug relationship, included thrombocytopenia (64%), fatigue (20%), diarrhea (20%), anemia (15%), pneumonia (15%), and neutropenia (15%). Only 1 pt (2%) experienced grade 3 peripheral neuropathy. Conclusions: PAN, when combined with BTZ and Dex, can recapture durable responses in heavily pretreated, BTZ-resistant pts with relapsed and refractory MM.

	N = 55
Complete response (CR)	–
Near complete response (nCR)	1 (2%)
Partial response (PR)	18 (33%)
Minimal response (MR)	10 (18%)
Stable disease (SD)	20 (36%)
Progressive disease	3 (5%)
Unknown	3 (5%)
Overall response rate (ORR; ≥ PR)	19 (35%)
Median duration of response (DOR; in responders), months (range)	6.0 (1.9-12.2)
Clinical benefit rate (CBR; ≥ MR)	29 (53%)
Very good partial response (VGPR)	3 (5%)
Median progression-free survival (PFS), months (range)	4.9 (0.7-12.9)

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Impact of Bone Marrow Plasma Cell Assessment before Autologous Stem Cell Transplantation on Disease Progression

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Current definition of complete remission (CR) in multiple myeloma (MM) includes a negative serum and urine immunofixation (IFE) and <5% bone marrow plasma cells (BMPCs). Pre-transplantation CR correlates with outcomes following autologous stem cell transplantation (ASCT). Since there is uncertainty in the arbitrary 5% limit in BMPCs in patients with negative IFE, we evaluated the prognostic impact of BMPCs on the patients with MM undergoing ASCT. BM aspiration was performed before peripheral progenitor cell mobilization and BMPCs were assessed after CD138 immunostaining. Forty-eight men and 40 women were included in this study. The median age was 55.5 (33-65) years and the median disease duration prior to ASCT was 6.8 (3.4-40.1) months. Among evaluable 88 patients, 34 patients (38.6%) obtained a negative IFE in serum and/or urine before ASCT while 29 and 21 achieved very good partial response (VGPR) and PR, respectively. Four patients were < PR. Patients with <5% BMPCs had a significantly better progression-free survival (PFS) compared to those with the 5% or more BMPCs (P=0.004). In the patients without a serologic CR, BMPCs <5% was also an independent factor predicting better PFS (P = 0.034). By contrast, in the serologic CR subgroup, BMPCs had no significant impact on PFS (P = 0.944). Pre-transplant conventional BM study with immunostaining constitutes an independent predictor for disease progression in patients with MM undergoing ASCT. In particular, the significant impact of <5% BMPCs was observed in the patients who do not achieve a serologic CR.

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Phase 1 Study of Elotuzumab (Elo) + Lenalidomide/Dexamethasone (Len/Dex) in Relapsed/Refractory Multiple Myeloma (RR MM)

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Background: Elo is a humanized anti-CS1monoclonal antibody that enhances Natural Killer cell-mediated antibody dependent cellular cytotoxicity of CS1 expressing myeloma cells. In a phase 2 study of patients (pts) with RR MM, Elo (10-20 mg/kg) + Len/dex was generally well tolerated with a 84% response rate. Median progression free survival was not reached (10 mg/kg) after a median follow-up of 20.8 mos (Richardson ASH 2012). This study evaluated the safety/tolerability of Elo + Len/dex in Japanese pts with RR MM. Methods: Pts received 28-day cycles of Elo IV (d1, 8, 15, 22 in cycles 1-2; d1, 15 in cycles >=3) + Len 25 mg (d1-21) and dex 28 mg PO + 8 mg IV on Elo dosing days or 40 mg PO on no Elo dosing days. Elo dose was initially 10 mg/kg (cohort 1, n=3) and escalated to 20 mg/kg (cohort 2, n=3) if no cycle 1 dose limiting toxicity (DLT) was observed in cohort 1. Results: Of the 6 pts (median 63.5 yrs; median 1.5 prior therapies), there were no DLTs. Median treatment duration was 82 wks (cohort 1) and 40 wks (cohort 2). Most common grade >=3 adverse events were leukopenia and lymphopenia similar to phase 2 results (Table). Lymphopenia was transient (median duration 14.5 d) and improved while continuing therapy. One serious infection (grade 3 bronchopneumonia [cohort 2]) was reported; there were no on-study deaths. Three pts are ongoing, best overall responses for completed pts are 1 minimal response (cohort 1) and 2 very good partial responses (cohort 2). Con-

clusion: Elo 10-20 mg/kg + Len/dex had an acceptable safety/tolerability profile in Japanese pts with RR MM.

AEs, n	Cohort 1 Elo 10 mg/kg (n=3)		Cohort 2 Elo 20 mg/kg (n=3)		Total (n=6)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Leukopenia	3	1	3	0	6 (100)	1 (17)
Lymphopenia	3	3	3	2	6 (100)	5 (83)
Neutropenia	3	1	2	1	5 (83)	2 (33)
Dysgeusia	2	0	3	0	5 (83)	0
Pyrexia	3	0	1	0	4 (67)	0
Constipation	2	0	2	0	4 (67)	0
Nasopharyngitis	2	0	1	0	3 (50)	0
Insomnia	2	0	1	0	3 (50)	0
Rash	1	0	2	0	3 (50)	0

Table. Adverse events (AEs) occurring in ≥2 pts in either cohort.

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A PrECOG Study of Lenalidomide and Dexamethasone in Relapsed Multiple Myeloma Patients with Impaired Renal Function

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Background: Lenalidomide (len) is a highly effective therapy in relapsed multiple myeloma (MM), but its dosing in patients (pts) with renal insufficiency remains unknown. Objective: To establish the maximum tolerated dose (MTD) of len in three cohorts of pts with impaired renal function: Group A - creatinine clearance (CrCl) 30-60 mL/min, Group B - CrCl <30 mL/min not on dialysis, and Group C - CrCl < 30mL/min on dialysis. Secondary endpoints were response rate, progression free survival (PFS) and overall survival (OS). Methods: Previously treated MM with CrCl < 60 mL/min. All pts received len as described in Table 1 along with dexamethasone (dex) 40 mg orally weekly and daily ASA. Results: 27 pts have been enrolled, all with advanced ISS stage (22% stage 2 and 78% stage 3). MTD has not been reached in any group, as no dose limiting toxicities (DLTs) have occurred to date. Hematological toxicities (grade 3-4) occurred in 62%, mostly neutropenia and thrombocytopenia. Response was seen in 15/25 pts (64%) - CR in 2 (8%), VGPR in 3 (12%), PR in 11 (44%), and SD for the remaining 9 (36%). Median follow-up is 24 months, with PFS 9.8 mos and OS 31.5 mos. Conclusion: Len/dex is an effective and well tolerated regimen in pts with MM and renal insufficiency. MTD has yet to be reached, allowing for higher doses to be given than previously reported. These results will provide needed dosing for len in MM pts with renal insufficiency.

Table 1: Dosing Schedule and Enrollment

Dose level	Patients Enrolled	DLT's
Group A: CrCl 30 - 60 mL/min		
1 (10mg qd)*	6 of 6**	0
2 (15mg qd)	3 of 3	0
3 (25mg qd)***	6 of 6	0
Group B: CrCl <30 mL/min no dialysis		
1 (15mg q2d)*	3 of 3	0
2 (25mg q2d)	3 of 3	0
3 (15mg qd)	Open	
4 (25mg qd)		
Group C: CrCl <30 mL/min on dialysis		
1 (5mg qd)*	3 of 3	0
2 (10mg qd)	3 of 3	0
3 (15mg qd)	Open	
4 (25mg qd)		

* Starting dose recommended in Revlimid® USPI
** 1 pt had suspected DLT but later deemed not DLT.
*** 6 pts required for MTD

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Clinical Features and Outcome of Very Elderly (>80 yrs) Patients with Multiple Myeloma

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Background: Although age is an important prognostic determinant in patients with multiple myeloma (MM), few data on clinical features and treatment outcome for elderly patients >80 years old are available. Patients and methods: We retrospectively analyzed the clinical features and outcomes of 139 consecutive patients between April 2005 and October 2012 admitted to our hospital. Results: We identified 29 (21%), 67 (49%), and 43 (31%) patients in cohorts >80, 66-79, and <65 years old, respectively. Patients >80 years had more impaired performance status (PS >3, P=0.003), lower serum albumin (<3.5 g/dL, P=0.019), and higher β2-microglobulin (>3.5 g/L, P=0.022) indicating more advanced disease. The 3-year Progression-free survival (PFS) of respective age groups were 24%, 33%, and 63%. By log-lank analysis, PFS of age>80 was significantly shorter than the other 2 groups (<65 vs. 66-79; p=0.057, 66-79 vs. >80; p=0.033, <65 vs. >80; p<0.001). These differences in PFS among the three age groups were translated to respective 3-year overall survival (OS) of 28%, 68%, and 71%, respectively. Patients with more than VGPR were pooled and survivals were compared among the three groups; 3-year PFS and OS were 80%, 49%, and 68%, and 28%, 68%, and 71%, respectively. There were no significant differences in PFS and OS between age groups. Conclusion: Although patients >80 years old showed poorer outcome compared to the other age groups, when those patients ob-

tained more than VGPR response, they showed similar outcome compared to the other age groups.

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LEOPARD: Phase II Study of Maintenance Lenalidomide and Prednisolone (RAP) Post-ASCT Incorporating MRD Assessments

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Aim To document change in disease response in post-ASCT MM patients who receive RAP. To quantify MRD by free light chain (FLC) and multiparameter flow cytometry (MFC) in patients who achieve CR. Methods Newly diagnosed MM patients 6-8 weeks after induction and single MEL200 ASCT commenced RAP until toxicity/relapse (lenalidomide 10mg/continuous daily increasing to 15mg after 8/52 and alternate day prednisolone 50mg). Serum for FLC was collected every 2/12. Patients in CR had serial BMATs for MFC. Interim analysis of first 30 of 60 subjects. Results After a median 388 days (107-587), 6/30 relapsed/progressed, 4 ceased due to AEs, 1 withdrew and 1 died (disease). Response (table): after commencing RAP, 16 patients improved response, including 9 sCR and 4 CR. 1 patient in sCR pre-RAP relapsed.18 patients who achieved CR/sCR had MFC studies performed. 10/18 had normal FLC ratios (FLC-). 10/18 patients were MFC- in all samples; 5 of these were FLC-, 1 was initially FLC+ and converted to FLC-, 2 were FLC- and then converted to FLC+ at relapse. 5/18 were MFC+ in most/all samples; 4/5 were FLC- and have not relapsed. In those who relapsed, 2/3 were MFC+ & 2/3 converted from FLC- to FLC+. Conclusion RAP improved depth of response post-ASCT, with very high CR rates (sCR 37%, CR 23%). Some achieving CR (pre RAP or on RAP) demonstrated further improvement to sCR. Most MFC- were or became FLC-; however, some were MFC+/FLC-, suggesting that MFC is more sensitive for detecting MRD than FLC. Additional MRD detection methods will be assessed: HevyLite and ASO-PCR (PB, aspirate and trephine).

	Response pre RAP	Best Response Achieved on RAP
Stringent CR (sCR)	3	11
CR	3	6
Unconfirmed CR	1	1
VGPR	18	10
PR	4	1
SD	1	0
PD	0	1

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CyBor-D Induction Therapy for Multiple Myeloma in Clinical Practice

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CyBorD is a highly active induction regimen for newly diagnosed multiple myeloma (MM) patients (pts) preparing for ASCT. From phase 2 trial data, CyBorD (bortezomib 1.3mg/m^2 IV on days 1,4,8,11, weekly cyclophosphamide 300mg/m^2 orally, and dexamethasone (DEX) 40mg days 1-4, 9-12, 17-20, given for four 28-day cycles) achieved an overall response rate (ORR) of 88% (>/=VGPR 61%). In an expanded cohort using weekly bortezomib 1.5mg/m^2 IV and DEX 40mg dropped to once weekly for cycles 3-4, similar responses were attained (ORR 93%, >/=VGPR 60%). Given that clinical trial efficacy can significantly overestimate real-life effectiveness, we reviewed our institutional experience with CyBorD in a non-clinical trial setting. Eighty-three ASCT-eligible MM pts who received CyBorD induction during September 2007-April 2012 were reviewed. Median age was 59 years (range 37-71). MM subtypes included: IgG 55%, IgA 20%, light chains only 22%, other 3%. After a median of 4 cycles, responses were high (ORR 93%; >/=VGPR 70%). Grade 3-4 neutropenia (3.6%) and thrombocytopenia (<1%) were uncommon, with no grade 3-4 neuropathy. Dose delays/reductions of any agents were required in 18%. Stem cell mobilization was not compromised. All patients, except 3, proceeded to ASCT. ORR at day +100 post-ASCT was 97% (>/=VGPR 79%). Weekly CyBorD induction is highly effective in clinical practice, with comparable response and toxicity profiles to phase 2 trial data. CyBorD has been widely adopted in Canada and can be considered as a standard comparator for future novel induction regimens.

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Heterogeneity of IMWG Defined Response Assessed by FLC Assay, Multicolor Flow Cytometry, and Heavy/Light Chain Analysis

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Purpose: Complete response (CR) or very good partial response (VGPR) is the major goal in treatment of multiple myeloma (MM), but the depth of response in CR or VGPR varies considerably. We examined the performance of immunofixation electrophoresis (IFx), free light chain (FLC) assay, multiparameter flow cytometry (MFC), and heavy/light chain (HLC) analysis for evaluation of response and prediction of prognosis. Method: Simultaneous serum and bone marrow samples from 136 MM patients at their best response were examined. Results: Among 136 patients, 33% achieved IFx-negative CR, 28% achieved stringent CR (sCR), and 22% achieved MFC-negative CR (IR) (< ×10*-4). VGPR was obtained in 25% of patients, and the remaining 42% showed PR or less. Normalization of FLC ratio among patients with CR, VGPR, and PR or less was 86%, 60%, and 9%, respectively. MFC negativity was achieved in 67% of CR patients, but only 3% of VGPR patients. In patients with IFx-negative CR, IR was obtained in 26/36 (62%) and 2/6 (33%) of patients with normal and abnormal FLC ratio, respectively. HLC analysis was performed in CR patients with IgA (n=14) and IgG (n=12) myeloma. Abnormal HLC k/L ratio was observed in one IgA patient and no IgG patients. Among patients with CR and VGPR, those who achieved IR or normal FLC ratio showed significantly better survival compared to those who did not. Conclusion: Although MFC, sFLC and HLC analysis frequently gave discrepant results, they appeared to give important complementary information for assessing the depth of CR and VGPR category.

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Final Results of MCRN-01: Multicenter Canadian Trial of Bortezomib-based Therapy without ASCT in t(4;14) Myeloma

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Given the efficacy of bortezomib (B) in t(4;14) myeloma, we designed a non-ASCT phase II study based on this agent in newly diagnosed pts which included: 1) 4 cycles of Doxil + B + dexamethasone (dex) (DBd) induction; 2) 8 28-day cycles of weekly oral cyclophosphamide + B 1.5 mg/m2 days 1,8,15 + prednisone 100 mg q 2 days post-induction therapy (CyBor-P); and 3) maintenance with dex 40 mg/wk. Between 02/2008-02/2012, 50 (10.2%) of 487 pts screened in 8 Canadian centers were + for t(4;14);13 were asymptomatic/ineligible/refused; the target of 38 pts has now been accrued (data complete in 36). Median age was 56 yrs (42-75); % marrow nuclei + for t(4;14) was 28% (2-80%) by unselected FISH; serum β2-M was 240 nmol/L (43-1695); albumin was 36 g/L (22-48). ISS stage was I in 10, 2 in 17 and 3 in 9. Best response includes: sCR in 8 (22%), CR in 9 (25%), VGPR in 12 (33%), PR in 4 (11%) and SD in 3 (9%). Ten pts have progressed; 6 have died (due to progression in 3 and other causes/consent withdrawal in 3). SAEs were reported in 19%; only 5 developed gr 2 neuropathy. Median PFS is 23.8 mos; actuarial 2-yr PFS is 47.3% (95%CI 30.4-73.7%). Median OS is not yet reached and 2-yr OS is 81.9% (95%CI 68.4-98.2%). We conclude: 1) this is the first reported prospective trial designed specifically for newly diagnosed high-risk myeloma pts; 2) the overall response rate (sCR + CR + VGPR + PR) with this program is 92% (81% >/= VGPR and 47%>/= CR; 4) the PFS and OS with this approach compare favorably with those seen both in older and newer studies of single/double ASCT (Table).

Author/year	Induction	# ASCT	Consolidation	Maintenance	Median PFS (mos)	Median OS (mos)
Chang/2004	VAD or dexamethasone	1	--	+/- thalidomide	9.9	18.8
Moreau/2007	VAD	2	--	+/- thalidomide	21	41.4
Avet-Loiseau/2010	VAD or BD	1 or 2	Lenalidomide	Lenalidomide	27	NA
Cavo/2010	VTD	2	VTD	Dexamethasone	69% (3yr)	NA
Neben/2011	PAD	2	--	Bortezomib	25	66% (3yr)
Reece/2013 (current study)	DBd	0	CyBor-P	Dexamethasone	23.8	81.9% (2yr)

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Phase I Study of the PARP Inhibitor Veliparib in Combination with Bortezomib in Relapsed or Refractory Multiple Myeloma

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Bortezomib induces a BRCAness state in MM cells and sensitizes them to the PARP inhibitor Veliparib by blocking homology-mediated repair of DNA breaks. We now report results from an ongoing phase I clinical trial (NCT01495351) combining bortezomib with Veliparib in relapsed / refractory MM. Patients received oral Veliparib on days 1 to 14, bortezomib (1.3 mg/m2) and dexamethasone (20 mg) on days 1, 4, 8 and 11 for 8 cycles followed by 6 maintenance cycles. Veliparib dose escalation (20 to 100 mg) followed a modified Fibonacci scheme. To date, 16 MM patients were enrolled, median age of 61 (47-80), median number of prior therapy: 3 (1-9) with 87.5% refractory to lenalidomide, 50% refractory to bortezomib and 82.1% previously exposed to it; del17p was detected in 66.7%. One DLT was encountered at the 100 mg level however the MTD is not yet reached. Grade 3-4 AEs include thrombocytopenia 37.5%; anemia in 12.5%, diarrhea in 12.5%; sensory neuropathy grade 1 in 37.5%. Response to therapy include CR in 3/16, VGPR+PR in 3/16, MR+SD in 7/16, PD in 3/16, for an overall response rate of 37.5% and SD or better in 81.2%. Significant (68 - 96%) reduction of PARP activity (poly-ADP-ribose levels) was achieved in vivo in PBMCs and BM sorted CD138+ cells between pre-treatment day 1 and post-treatment day 11 samples. In conclusion Veliparib in combination with bortezomib and dexamethasone appears to be well tolerated with evidence of significant anti-tumor activity in this heavily pre-treated population. Further dose escalation of Veliparib continues to determine the MTD of this combination

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A Phase I/II Multicenter Open Label Study of Vorinostat, Melphalan and Prednisone in Advanced Multiple Myeloma Patients

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Vorinostat is an oral histone deacetylase inhibitor promoting MM cell death through multiple pathways. The primary objective of this phase I trial was to determine the maximum tolerated dose of Vorinostat associated to Melphalan and Prednisone. Patients were sequentially planned to be enrolled into 1 of 4 escalating doses of Vorinostat using a standard "3+3" design for 6 cycles. Toxicity was scored according to the NCI Common Terminology Criteria (version 3.0). Phase I was completed after the inclusion of 15 patients. Three additional patients were enrolled to a further phase II (one patient not evaluable). The median age was 67 y (range 57-79 y). Median number of previous therapies was 3 (1 to 4). 83% of patients received iMIDs containing regimens and 77% bortezomib containing regimens. ABMT was previously performed in 77% of cases. A total of 63 cycles were completed. The 6 planned cycles were completed in 6/17 patients (35%). Grade 3-4 anemia, neutropenia and thrombocytopenia were detected in 18%, 53% and 53% of patients, respectively. Common non hematological toxicities (mostly grade 1/2) included fatigue (44%), gastrointestinal symptoms (44%) and neurotoxicity (33%). Four DLT were registered (mostly related to hematological toxicities). No SAE were recorded. At least Minimal Response was obtained in 64% of patients (18% PR and 46% SD). These data suggest that the association of MP and Vorinostat is feasible but has significant hematological toxicity in the setting of heavily pretreated myeloma patients.

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Bendamustine-based Salvage Therapy in Heavily Pretreated Refractory Myeloma Patients: KMM125 Study

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Bendamustine has structural similarities to both alkylating agents and purine analogues. As incomplete cross-resistance between bendamustine and other alkylating agents, it has been used as a salvage therapy. Since its anti-myeloma effect was reported, bendamustine has been emerged as another treatment option for relapsed or refractory myeloma. However, there is few data regarding the use of bendamustine in the salvage setting, especially in Asian patients. Thus, we performed a multicenter retrospective study. 22 patients from four hospitals in Korea received bendamustine 100mg^2 IV on day 1 and 2 in combination with prednisone in 28-day cycles. All patients were heavily pretreated including bortezomib, lenalidomide, cyclophosphamide, autologous and/or allogeneic stem cell transplantation (median number of previous treatments: 6). The median time of diagnosis to bendamustine treatment was 3.7 years, and the median age of patients

was 64 years. Despite all patients received bendamustine in the state of refractory disease, six patients showed response (1 near CR, 3 PR, 2 MR) and stable disease was in ten patients. However, the response was not durable, and grade III/IV neutropenia (n = 15) and thrombocytopenia (n = 11) were common toxicities. As a result, infectious complications including pneumonia were also commonly encountered. In conclusion, considering its efficacy in this clinical setting, bendamustine might be more effective if it is used earlier. However, close monitoring for infectious complications should be warranted.

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Survival of Unselected Patients with Symptomatic Multiple Myeloma

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The use of thalidomide, bortezomib and lenalidomide has changed the management of myeloma patients. We inspected whether the survival of unselected myeloma patients was improved. Patients and methods: We retrospectively analyzed 256 consecutive, unselected patients with newly diagnosed symptomatic myeloma (SMM: female 113 pts; Age 36-89 yr) who started treatment between Jan 1, 1996 and Dec 31, 2010 in our hospital. Results: The median survival time (MST) of all patients is 3.9 years. The patient was classified into the patient aged 65 and below and the patient aged 66 and over, and MST is 5.1 years and 2.3 years, respectively. Moreover the patient was divided by the times of onset of SMM and the survival was compared but a significant difference was not obtained between before 2007 vs. after 2007, before 2008 vs. after 2008, and before 2009 vs. after 2009. The patient was classified by ISS stage, and MST is 6.3 years, 3.6 years and 1.7 years for ISS stage 1, 2 and 3, respectively. Similarly the patient was divided by the times of onset of SMM and the survival was compared but a significant difference was not obtained between the same pairs. In myeloma patients of ISS stage 1, a prognostic improvement trend was seen in the latter by a comparison of before 2009 vs. after 2009. Conclusions: Treatment with novel agent choices increase and it is used for RRMM mainly, but has not yet led to improvement of survival of many myeloma patients. Treatment with novel agent such as initial therapy or the maintenance therapy may be necessary for extension for survival duration.

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Efficacy and Safety of Lenalidomide in Relapsed and Refractory Multiple Myeloma: Impact of Previous Therapies

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Lenalidomide and dexamethasone (Len/Dex) are a standard of care in the treatment (Tx) of patients with relapsed/refractory multiple myeloma (RRMM), after one prior therapy. The greatest benefits were observed with Len/Dex at first relapse. 51 RRMM pts treated with Len/Dex until PD, from 2007 to 2012 and complete follow-up records were included in this single-centre retrospective analysis. All patients had previously received thalidomide (T) and/or bortezomib (B). The median age was 69 years (40-83) and median number of pretreatments was 2 (1-6). Overall, 11 pts. (21,6%) had Len/Dex at first relapse, 19 pts (37,3%) at second relapse and 21 (41,1%) pts in subsequent relapses. 37 pts (73,0%) had cytogenetic analysis: 17 pts had high-risk disease. Overall response rate was 39,2% comprising 14 pts (27,4%) with PR, 5 pts (9,8%) with VGPR and 1 pt. (1,9%) with CR. Median treatment duration was 6 months (mo) (2-54). Median follow-up is 10 mo. None of the pts. suspended treatment due of toxicity. 25 pts (49,0%) received Len/Dex > 6 mo. Median overall survival (OS) was 11,0 mo and median progression free survival (PFS) was 6 mo, but both weren't reached in pts. in CR or VGPR. No significant differences in OS and PFS were observed according the number or agents in previous therapies. The outcome of these heavy treated patients with RRMM was inferior to published data but with shorter follow up and satisfactory toxicity profile. There were no differences in the outcome according the number of previous lines and the last drug administrated.

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Pomalidomide with or without Low-dose Dexamethasone in Relapsed and Refractory Multiple Myeloma: Updated Analysis

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Background: MM-002 is a multicenter, randomized, open-label phase 2 study evaluating the safety and efficacy of oral pomalidomide (POM) alone, or in combination with low-dose dexamethasone (POM + LoDEX), in patients (pts) with relapsed and refractory multiple myeloma (RRMM) who have received multiple prior therapies, including lenalidomide (LEN) and bortezomib (BORT). Methods: Pts with >=2 prior therapies and refractory to their last treatment were randomized to POM + LoDEX (POM 4 mg/day, days 1-21 of a 28-day cycle; LoDEX 40 mg/week) or POM alone. A sub-analysis based on age (<=65 vs >65 yrs) was performed. Endpoints included progression-free survival, response rate (based on European Bone Marrow Transplantation criteria), duration of response, overall survival, and safety. Results: The intent-to-treat efficacy analysis included 113 pts in the POM + LoDEX group and 108 pts in the POM group. The mean age of pts treated was 64 yrs (range 34-88). The efficacy outcomes for the overall population and the age sub-groups are presented in the Table. The most common grade 3/4 adverse events were neutropenia (41%), anemia (22%), thrombocytopenia (19%), and pneumonia (22%). Tolerability was similar across different age groups. Conclusions: In pts with RRMM who have received multiple prior treatments including LEN and BORT, POM with or without LoDEX was clinically effective and generally well tolerated. Response rates were consistent and durable regardless of age.

Table. Efficacy outcomes.

	≤ 65 years		> 65 years		Overall	
	POM + LoDex (n = 62)	POM (n = 69)	POM + LoDex (n = 51)	POM (n = 39)	POM + LoDex (n = 113)	POM (n = 108)
≥ PR, %	31	13	37	18	34	15
≥ MR, %	47	23	43	44	45	31
Median duration of response, mos[a]	10.1	8.3	7.7	10.6	8.3	8.8
Median PFS, mos	4.7	1.9	3.7	3.3	4.6	2.6

[a]For patients who achieved ≥ PR.
LoDEX, low-dose dexamethasone; MR, minimal response; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PR, partial response.

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Significant Improvement in Survival after ASCT after Year 2006. A Single Institution Study.

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Here we evaluate the outcome of 153 patients treated with ASCT sequentially in a single institution since 1994. Patients and methods: 153 patients, median age 56.5 [27.5-71.9] years, 43% females, ISS stages I/II/III: 48%/24%/28% has been enrolled. Induction therapy consisted of 4 cycles of VAD until 2008; thereafter, VTD, VTDC and VCD were used. Conditioning therapy: melphalan 200 mg/m^2, or for patients randomized into a group with triple ASCT: 100mg/m^2. Results were analyzed by 3 treatment periods: 1) before year 2000, 2) between 2000 and 2006, and 3) after 2006. Results: In the entire cohort PFS from ASCT and OS from diagnosis were 26.1 and 76.9 months, respectively (median follow up: 54.6 months). Prognostic parameters such as age, B2M, LDH and Hb, did not change significantly or showed a slight worsening (BMPC infiltration & ISS stage) over time. PFS after ASCT was 10.2, 23.9, and 33.4 months in cohorts 1, 2 and 3, respectively, p=n.s. OS after ASCT was significantly longer in patients transplanted after 2006 (median not reached, OS at 4 years: 90.3%) compared to patients transplanted earlier (OS in cohorts 1 and 2: 60.9 and 71.4 months, respectively), p<0.03. (Figure 1) Conclusion: OS improved significantly in patients transplanted after 2006. This OS increase seems to be partly due to improvements in induction therapy but mainly due to advances in post relapse therapy. The availability of thalidomide (2000) was not associated with better outcome but OS increased with the EU approval of bortezomib (2004) and of lenalidomide (2007).

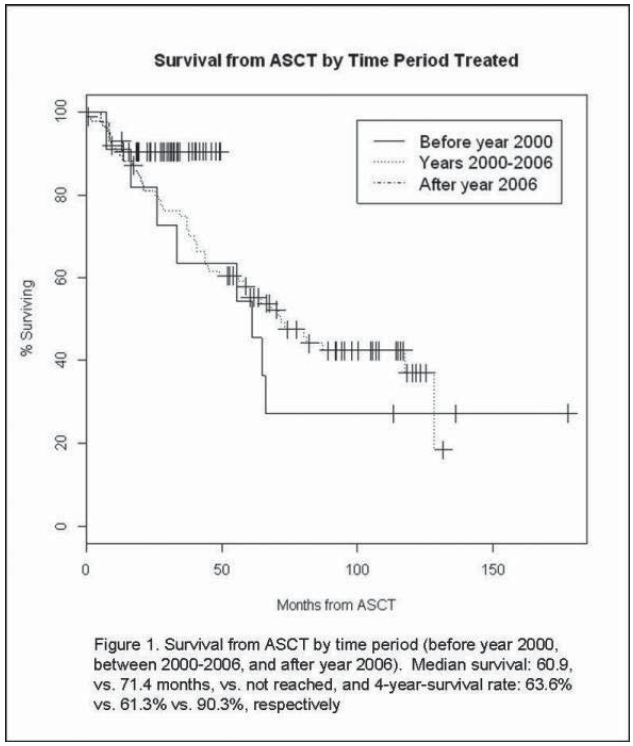

Figure 1. Survival from ASCT by time period (before year 2000, between 2000-2006, and after year 2006). Median survival: 60.9, vs. 71.4 months, vs. not reached, and 4-year-survival rate: 63.6% vs. 61.3% vs. 90.3%, respectively

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Efficacy & Safety of Lenalidomide 25 mg + Low-Dose Dexamethasone in Chinese Patients with Relapsed/Refractory Myeloma

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Background: Lenalidomide (LEN) + low-dose dexamethasone (DEX) was associated with a response rate of 53% in heavily pretreated relapsed/refractory multiple myeloma (RRMM) patients (pts) in the Chinese registration trial MM-021. Methods: In this phase 2, multicenter, open-label study, 199 pts received LEN (25 mg/d on days 1-21) and DEX (40 mg on days 1, 8, 15 and 22) (20 mg in pts aged >75) in 28-d cycles until progression. LEN starting dose was adjusted per protocol according to creatinine clearance (CrCl) at 25 mg/d for pts with none-to-mild renal insufficiency (RI) (CrCl >=60 mL/min); 10 mg/d for moderate RI (CrCl 30 to <60 mL/min) and 15 mg/every other day (eod) for pts with severe RI (CrCl <30 mL/min). This post-hoc analysis investigated LEN starting dose, dose modifications, and duration of treatment. Results: Pts had a median age of 59 yr, 66% (n=131) had none-to-mild RI and 57% had received >=4 prior therapies. The majority of pts (n = 144; 72%) initiated LEN treatment according to the recommended starting dose of 25 mg/d; 45 (23%) pts started at 10 mg/d, and 10 (5%) pts at 15 mg/eod per protocol. The median number of LEN cycles administered was 9 (range 1-25). Dose reductions were required in 38 (19%) pts across all starting doses, with a median time to first dose reduction of 3.1 mos. The median dose intensity was 25 mg, indicating compliance with the planned treatment schedule. Overall clinical outcomes are shown in the table. Conclusions: LEN 25 mg was well tolerated in Chinese RRMM pts and provided clinical efficacy despite renal condition.

Table. Clinical Outcomes

Outcome	
ORR (≥PR), n (%) 187 evaluable pts	89 (48)
Median PFS, months (95%CI) 187 evaluable pts	7.4 (6.4–9.3)
OS rate at 1 year, % 199 intent-to-treat pts	72
Lenalidomide dose reductions, (%)	19
Median time to first dose reduction, months (range)	3.1 (0.9–12.9)
Median dose (range)	25 (6.3–25)
Discontinuations due to AE, n (%)	10 (5)
Grade 3–4 AEs, n (%); N=199[a]	
Neutropenia	50 (25.1)
Anemia	52 (26.1)
Thrombocytopenia	29 (14.6)
Febrile neutropenia	1 (0.5)
DVT	1 (0.5)
Peripheral neuropathy	2 (1.0)

[a]not all adverse events are reported in this table.

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Phase 2 Study of Elotuzumab plus Lenalidomide/Dexamethasone (Len/Dex) in Relapsed/Refractory Multiple Myeloma (RR MM)

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Background: Elotuzumab (Elo) is a humanized anti-CS-

1monoclonal antibody that enhances natural killer cell mediated antibody dependent cellular cytotoxicity of CS1 expressing myeloma cells. In the Phase 1 portion, Elo (5-20 mg/kg) + Len/dex resulted in an 82% objective response rate (ORR) in patients (pts) with RR MM (Lonial JCO 2012). In the phase 2 portion reported here, the primary objective was ORR (per International Myeloma Working Group criteria) in RR MM pts previously treated with 1-3 prior therapies. Methods: Pts received Elo 10 or 20 mg/kg IV (d1, 8, 15, 22 every 28 days in cycles 1-2 and d1, 15 in cycles >=3) + Len 25 mg PO (d1-21) + dex 40 mg PO weekly or 28 mg PO + 8 mg IV on Elo dosing days until disease progression, unacceptable toxicity or death. Results: Among 73 pts (median age 63 yr), ORR was 84% overall; 92% with 10 mg/kg and 76% with 20 mg/kg. With a median follow-up of 20.8 mos, median progression free survival (PFS) was not reached in the 10 mg/kg cohort and 18.6 mos in the 20 mg/kg cohort. Most common treatment emergent grade >=3 events (>=10%) included lymphopenia (19%), neutropenia (18%), thrombocytopenia (16%), anemia (14%), leukopenia (10%) and hyperglycemia (10%). Investigator-designated (any grade) infusion reactions were reported in 14%; 1 pt had a grade 3 event (rash). Four cases of second primary malignancies were reported (5%); all were deemed unrelated to Elo. Conclusions: Elo 10 mg/kg + Len/dex was generally well tolerated and resulted in a high ORR and PFS not reached after 20.8 mos of median follow-up in pts with RR MM.

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Interim Analysis of Clinical Trial of MPB Followed by Bortezomib Maintenance Therapy for Elderly Patients with ND-MM

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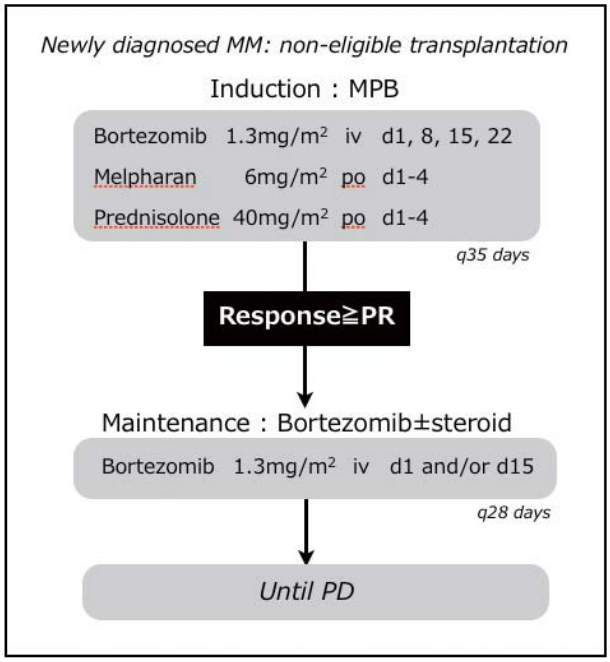
BACKGROUND: Although novel agents such as bortezomib(Bor) has conducted remarkable improvement for multiple myeloma(MM), intensive chemotherapy has induced severe adverse events(AEs), resulting in highly discontinued rate, especially often seen in Japanese clinical studies. Therefore, we conducted p2 study, BROAD-J study, based on a weekly MPB as induction therapy followed by Bor-maintenance therapy (MT) with every two weeks or a month administration. METHODS: The authors evaluated the persistant rate and the safety/efficacy of MPB induction therapy [Melpharan (6mg/mq) and Prednisolone(40mg/mq) on days 1 to 4, Bor: 1.3mg/mq, d1,8,15,22, every 35-day cycle until achieving PR and more] followed by Bor-MT (1.3mg/mq, once or twice a month until progressive disease) for elderly frail patients(pts) with newly diagnosed(ND) MM. Eighty-three ND-MM pts were enrolled from December 2011, and we demonstrated interim analysis of 78 pts who are able to be estimated. RESULTS: Mean age was 73.5 years(60-89), and sex ratio was 40:38(M:F). The subtypes of MM were IgG 48, IgA 11, IgD 1 and BJP 18, and ISS was I 16, II 31, and III 31. Sixty-one pts(78%) are still on the study(29 pts on MPB phase and 32 pts on MT phase), while 17 pts discontinued mainly because of progressive disease(10pts) and AEs(4pts). The mean MPB cycles among all pts was 3(1-9), and 33% of pts achieved VGPR and more. In MPB phase, 32% of pts showed ≧grade 3 AEs, whereas only 5pts had ≧grade 3 AEs in MT phase. CONCLUSIONS: The strategy of BROAD-J was effective and well tolerated. It was attractive for elderly ND-MM pts.



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Single versus Double Autologous Stem Cell Transplantation (ASCT) for Newly Diagnosed Multiple Myeloma: GMMG-HD2 Trial

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We have performed a prospective, multicenter, randomized trial of a single (arm A) vs. double (arm B) high-dose therapy (HDT) followed by ASCT in multiple myeloma. A total of 385 pts up to 65 yrs was recruited between 1998 and 2002. 358 patients were evaluable for the intention-to-treat (ITT) analysis (177 in arm A; 181 in arm B). Pts in both treatment arms were comparable in age, SD stage, beta2-MG, albumin, and CRP. All pts were treated with 3-6 cycles of a VAD-like regimen as induction. HDT consisted of Melphalan 200 mg/m2. The 1st HDT was administered in 91% (arm A) and 93% (arm B), respectively. 47 pts withdrew prior to the 2nd HDT in arm B, a 2nd ASCT was not performed in additional 29 pts for other reasons. 93 pts in arm B received two ASCT. A total of 273 pts was evaluable for per protocol (PP) analysis. According to protocol non-inferiority of the single ASCT arm with respect to progression-free survival (PFS) could be shown. The estimated hazard ratio (arm B vs arm A) was HR=0.90 with a (one-sided) lower 95% limit of 0.74 for the ITT analysis and HR=0.89 with a (one-sided) lower 95% limit of 0.71 for the PP analysis. Neither ITT nor PP analysis revealed a significant difference for PFS between the two treatment arms (P_{ITT}=0.36, P_{PP}=0.36). This result is based on a long term follow up analysis in August 2012. These data do not support a double HDT as standard frontline treatment in general. However, it' s noticeable that only about 51% of pts received the intended treatment in the double ASCT arm. The role of double HDT in the era of new drugs is under investigation.

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MM-021: A phase 2 Study of Lenalidomide plus Low-dose Dexamethasone in Chinese Relapsed/Refractory Myeloma Patients

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Background: There is an unmet clinical need in Chinese patients (pts) with relapsed/refractory multiple myeloma (RRMM). The MM021 trial assessed the efficacy, safety and pharmacokinetics (PK) of lenalidomide (LEN) + low-dose dexamethasone (DEX; Rd) in Chinese RRMM pts. Methods: In this phase 2, multicenter, single arm, open-label study 199 pts received LEN (25mg/day on days 1-21) and DEX (40mg on days 1, 8, 15 and 22) or (20mg in pts aged >75) in 28-day cycles until progression. Primary endpoint: overall response rate (ORR, >=partial response). Secondary endpoints: duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety and PK. Results: Efficacy was evaluated in 187 pts. Median age was 59 yrs, 86% had advanced MM (Durie-Salmon stage 3) and 57% had >=4 prior therapies. After a median treatment of 8 mos (range 1-23), ORR was 48% (N=187) with complete response in 4%, which was consistent regardless of renal function. Median time to first response was 2 mos (range 1-10), DoR was 9 mos (range 0-19) and PFS was 7.4 mos (95% CI: 6.4-9.3), and 1-yr OS rate was 72%. Most common grade 3/4 adverse events (N=199) were anemia (26%), neutropenia (25%),

thrombocytopenia (15%) and pneumonia (13%). Febrile neutropenia and DVT were experienced by 1 pt (0.5%) each. LEN was rapidly absorbed and eliminated, with no evidence of accumulation. Coadministration with DEX did not affect LEN multiple-dose PK. Conclusion: Rd was associated with a relatively high response rate and is generally well tolerated in this heavily pretreated population of Chinese RRMM pts.

Table. Response rate in patients receiving LEN + low DEX.

Patient populations	n (%)
Overall efficacy population 187 evaluable patients	89 (48)
Prior therapies (199 evaluable patients)	
1–4	86 (43)
> 4	113 (57)
Renal impairment (199 evaluable patients)	
None-to-mild (CrCl ≥ 60 mL/min)	131(66)
Moderate (CrCl ≥ 30 to < 60 mL/min)	54 (27)
Severe (CrCl < 30 mL/min)	14 (7)
Patients with IgD (199 evaluable patients)	7 (4)

CrCl, creatinine clearance, IgD, immunoglobulin.

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Phase II Trial of Bortezomib Based Regimen for Transplant-ineligible Multiple Myeloma-TOMATO Study-

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[Introduction] Bortezomib is a primary drug for multiple myeloma (MM). Recently various bortezomib based regimens have been tried and showed high response rate. However, suitable dose and schedule for elderly patients in routine clinical setting are still under debate. In this study, we conducted a multicenter randomized phase II study in Tohoku area. (UMIN register No-3472). [Patients and Methods] Untreated transplant-ineligible MM received three cycles of MP (melphalan 9mg/m2X4d+60mg/m2x4d). Patients not reached to PR were randomly assigned to receive seven cycles of BD (bortezomib-dexamethasone) or VMP (bortezomib-MP), consisting of two cycles of 1.3mg/m2 bortezomib twice per week followed by five cycles of 1.3mg/m2 bortezomib once per week for 6 weeks. [Results] From June 2009 to Dec 2011, 42 patients were enrolled. Eighteen patients who did not obtain PR proceeded bortezomib phase. As of October 2012, ORR of BD and VMP was 100% (n=9) and 83.3% (n=5), respectively. Severe adverse events (AEs) were peripheral neuropathy grade 3 (n=2[22%]) in BD and ileus grade 3 (n=1[11%]) in VMP. The number of withdrawal due to AE was 2 in the both group. The mean cumulative dose of bortezomib of BD and VMP was 34.5 mg/m2 and 26.5 mg/m2, respectively. The long-term disease control tended to correlate with the cumulative dose of bortezomib. [Conclusion] These results showed bortezomib-based regimen is effective for transplant-ineligible MP failure patients. It may be important for obtaining high response to give enough amount of bortezomib by avoiding AE.

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Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Patients with Smoldering Multiple Myeloma: A Pilot Study

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Background Patients (Pts) with MM are at increased risk of invasive pneumococcal infections but the 23-valent pneumoccocal vaccine is poorly immunogenic in immunocompromised pts. The PCV13 is now available for > 50 years but data on its immunogenicity in pts with MM are needed. Method 20 pts (5 men, mean age 63 years) with smoldering MM (IgG n=14, IgA n=5, BJ n=1), received 1 dose of PCV13. Quantitative antibody titers were measured by ELISA for 7 vaccine serotypes at baseline, 1 and 6 months after vaccination. Serotype response was defined as > 2-fold increase in antibody concentration from baseline and value > 1 μg/ml (ELISA). Pts

were defined as responders if they were responding to at least 4 serotypes. Functional antibody titers were measured by Opsonophagocytic Assay (OPA) only for responders in ELISA (serotype response: > 4-fold increase from baseline and titers > 8). Primary endpoint was the proportion of responders in ELISA at 1 month. Results 12 pts (60%) were responders in ELISA, among whom 10 were also responders in OPA. 17 pts (85%) were at least responding to one serotype, but only 2 (10%) were responding to the 7 serotypes in ELISA. At 6 months, only 6 of the 10 tested responders had persistent immunity. Conclusion One dose of PCV13 is immunogenic in pts with SMM but only 60% are responding to at least 4 serotypes. A more immunogenic schedule is needed.

	% of Responders	
Serotype	(ELISA) (n=20)	OPA* (n=12)
4	40	75
6B	50	67
9V	45	67
14	55	75
18C	70	75
19F	70	83
23F	55	75

*only for pts responders in ELISA

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sPAD is Effective and Safety Induction Therapy for Untreated Multiple Myeloma Patients

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Bortezomib is first generation proteasome inhibitor which is used as induction therapy for multiple myeloma (MM) patients. Recently, bortezomib-including triplet therapies are recommended by several committees. Among of triplet therapies, PAD (bortezomib, doxorubicin, and dexamethasone), which was reported in the analysis of randomized phase III trial is effective therapy. Complete response (CR), including near CR, was superior after PAD induction than VAD induction. However, peripheral neuropathy (PN) was observed in 37% of PAD induction arm (grade 3 or 4 PN was 24%). Recently, some investigators reported that subcutaneous bortezomib offers non-inferior efficacy to standard intravenous administration, with an improved safety profile. Therefore, we performed a phase 2 PAD study using subcutaneous bortezomib (sPAD) in Japanese MM patients. Between July 2011 and November 2012, 20 patients with symptomatic MM were enrolled in this trial. They received bortezomib (1.3 mg/m^2 X 4) by subcutaneous injection, dexamethasone (20 mg X 8) , and doxorubicin (20 mg/m^2 X 2) , as their induction regimen. We compared this sPAD with bortezomib dexamethasone (BD) therapy (N=40), as historical control. Response rate (VGPR or CR) of sPAD was superior to BD (80% vs. 30%).Grade 3 or worse PN (5% vs. 28%; p=0.040) was significantly less common with sPAD than BD. Subcutaneous administration was locally well tolerated. These results suggest that sPAD is a safe and promising induction regimen for Japanese multiple myeloma patients.

P-221

Ten-year Long Term Survival after Up-front ASCT in Multiple Myeloma: Results from Two Prospective Clinical Trials

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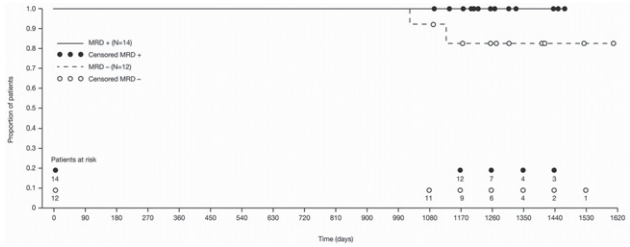
We performed a post-hoc analysis of two prospective clinical trials of ASCT in newly diagnosed MM patients, the first one comparing single versus double ASCT (321 patients) and the second incorporating thalidomide-dexamethasone into double ASCT (357 patients). Details of the studies were previously reported (Cavo M et al, JCO 2007 and JCO 2009). After a median follow-up of 61 months in the first study, CR was sustained for more than 5 and 10 years in 24% and 12% of the patients, respectively. On multivariate analysis, CR was the most important variable significantly extending PFS and OS; random assignment to double ASCT was an additional variable extending PFS After a median follow-up of 84 months in the second study, CR was sustained for more than 5 and 8 years in 42% and 9% of the patients, respectively. On multivariate analysis, achievement of CR, absence of t(4;14) ± del(17p) and baseline high levels of hemoglobin were independent variables predicting for longer PFS and OS. Overall, 23% and 20% of patients in the first and second study were alive over 10 or 8 years, respectively. Long-term survivors showed a significantly prolonged CR duration, PFS

and post-relapse OS, in both the studies, as respect to the remaining patients. Sustaining a durable response for more than 42 months was favourably affecting survival after relapse on multivariate analysis. In a logistic regression analysis, independent factors predicting for long-term survival in both the trials appeared to be attainment of CR, sustaining the response for more than 42 months and application of double ASCT.



P-222

Progression-free and Overall Survival with 3 and 4 Drug Combinations in Newly Diagnosed MM: Updated Data for ITT and MRD

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The Ph 2 EVOLUTION study (NCT00507442) prospectively evaluated efficacy and tolerability of 3- and 4-drug combinations of bortezomib (V), cyclophosphamide (C), lenalidomide (R) and dexamethasone (D) in 140 pts with treatment-naive MM (Kumar et al. Blood 2012). This trial incorporated central laboratory assessment of minimal residual disease (MRD) status using flow cytometry. Here we report updated PFS and OS, as well as MRD status of pts by CR and correlation with survival outcomes. Within 48 hrs of marrow collection at baseline and suspected CR, samples were analyzed on a FACSCanto flow cytometer using antibodies against CD138, CD38, CD45, CD19, CD56, kappa and lambda. An algorithmic approach was employed to determine presence of clonal plasma cells (PC); if PCs or CD56+ clonal PCs were <0.01% of total nucleated events, sample was considered MRD negative (MRD-). As of Dec12, median follow up was 43 mo (range 0.4-56). 2-year OS rates were 85%, 97%, 100% and 94% in the VDCR (n=48), VDR (n=42), VDC (n=33) and modified VDC (n=17) arms, respectively. 57 pts were MRD-evaluable, of whom 26 had CR/sCR. Median PFS in MRD+ pts (n=38) was 26 mo (range 3-49) and not reached (NR) in MRD- pts (n=19; 3-52 mos). 6-mo PFS was 100% in both MRD+ and MRD- pts; 1-yr PFS was 90.2% in MRD+ and 88.9% in MRD- pts. Median PFS in MRD-evaluable CR/sCR pts was NR; 6-mo and 1-yr PFS were each 100%. Figure shows OS by MRD status in CR/sCR pts. Long-term outcomes appear promising. Despite limited events, more events were evident in MRD+ pts, but a significant difference cannot yet be discerned.

P-223

Cardiac and Pulmonary Safety Analysis of Single-agent Carfilzomib Treated Relapsed and/or Refractory Multiple Myeloma

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Background: Patients (pts) with multiple myeloma (MM) often have cardiac and pulmonary comorbidities exacerbated by MM therapies and are predisposed to pulmonary infections. Cardiac and pulmonary safety data from 4 phase 2 studies of carfilzomib (CFZ), recently approved in the US for the treatment of relapsed and refractory MM, are presented herein. Methods: Pts from trials PX-171-003-A0, PX-171-03-A1 (both NCT00511238), PX-171-004 (NCT00530816), and PX-171-005 (NCT00721734) were included. CFZ was dosed at 20-27 mg/m^2 in a 28-day cycle for all studies except 005 (15-27 mg/m^2). Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query preferred terms were grouped for clinically related events. Results: Overall, 73.6% of pts had a past medical history of cardiovascular events. Most common cardiac or pulmonary AEs are shown in the table. For a cardiac AE, 4.4% of pts discontinued treatment and there were 5 deaths (a total of 8 [1.5%] cardiac-related deaths including 3 pts with a cardiac component to their death, all of which were possibly related to carfilzomib). Dyspnea events were mainly </=Grade (G) 2 with treatment discontinuations in 1.5% of pts. Pneumonia (most common respiratory AE [12.7%]) led to dose reduction in 0.4% of pts and discontinuation in 1.9% and resulted in the death of 2 pts. Conclusions: The rates of cardiac AEs and pulmonary infections reported here are similar to those reported for other MM therapies. Importantly, dose reductions and dose discontinuations due to these AEs were uncommon.

	AE, %	
	All G	≥G3
Cardiac arrhythmia	13.3	2.3
Cardiac failure	7.2	5.7
Ischemic heart disease	3.4	1.3
Dyspnea	42.2	4.9
Any pulmonary infection	18.8	13.3

P-224

Activity of ARRY-520 in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM): Results from Subgroup Analyses

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Background: ARRY-520 is a novel kinesin spindle protein (KSP) inhibitor with clinical activity in RRMM. Progression free survival (PFS) and overall survival (OS) data for RRMM patients treated with ARRY-520 are presented. Methods: Eligible patients (pts) had RRMM with >2 prior lines of therapy including both bortezomib (BTZ) and an immulomodulatory agent (IMiD). Pts were treated with ARRY-520 (1.5 mg/m2/day IV on D1,2 q 2 wks) with prophylactic granulocyte colony-stimulating factor support. Results: As of 12/14/2012, 32 pts were enrolled with a median of 6 prior regimens and a median follow-up for survival of 19 months. The most commonly reported adverse events included thrombocytopenia, anemia, neutropenia and fatigue. No treatment-related neuropathy was observed. The attached table reports median PFS and OS for all pts and subgroups. The serum protein α-1 acid glycoprotein (AAG) tightly binds ARRY-520, impacting pharmacokinetics. As we have reported previously, the ARRY-520 response rate is significantly higher in pts with low AAG (less than or equal to 1.1 g/L): 22% vs. 0% for patients with AAG >1.1 g/L. Pts with baseline low AAG also showed significantly longer PFS and OS than pts with AAG >1.1 g/L. There is no correlation between AAG levels and baseline ISS stage in this study. Summary: New drugs are needed for pts with RRMM. ARRY-520 is a 1st-in-class KSP inhibitor showing encouraging clinical activity in RRMM. AAG is a potential predictive marker for increased ARRY-520 activity.

Subgroup	N	PFS (Mos)	OS (Mos)
All Pts	32	4.4	19.0
AAG ≤1.1 g/L	23	6.8	20.2
AAG >1.1g/L	6	3.3	4.5
ISS Stage I at Baseline	10	20.2	20.2
ISS Stage II at Baseline	13	3.2	19.1
ISS Stage III at Baseline	9	3.3	6.2
BTZ Refractory	17	4.9	19.0
Len Refractory	24	3.7	19.1
Refractory to Len and BTZ	13	3.4	7.9
Refractory to Last Therapy	7	6.3	Not Reached

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Oprozomib (OPZ) Treatment in Patients (pts) with Hematologic Malignancies: Updated Results from a Phase 1b/2 Trial

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Background: OPZ, a structural carfilzomib analog, is an oral proteasome inhibitor. The present study assesses OPZ in pts with hematologic malignancies. Methods: The phase 1b/2 dose-escalation study (NCT01416428) sought to determine the MTD and safety profile of OPZ. Secondary endpoints included pharmacokinetics (PK)/dynamics and response (IMWG). OPZ capsules (split-dose) were administered on days 1-5 of a 14-day cycle (C). Split-dose escalation began at

120 mg (60 mg × 2, 4-6h interval) and increased in 30-mg increments (3+3 design). Results: As of November 2012, the study enrolled 13 pts (11 multiple myeloma [MM]; 2 chronic lymphocytic leukemia [CLL])-3 each at 120, 150, and 180 mg, and 4 at 210 mg. Pts received a median of 4.5 prior regimens (range 2-11). No DLTs were observed in C1 (MTD was not reached). After a median of 5 C (range 1-20), adverse events (AEs) were typically G1/2 gastrointestinal (GI). PK exposure was consistent with split-dosing with >80% proteasome inhibition (whole blood) 4h after 2nd dose of 180 and 210 mg/d. Response was assessed in 10 pts-3 partial, 2 minimal, 4 stable, and 1 progression. Attempting to improve GI tolerability, dose escalation with the OPZ capsule was capped at 210 mg/d and is continuing with a tablet formulation on 2 schedules (days 1-5 or days 1, 2, 8, and 9). The preliminary findings will be presented. Conclusions: The MTD was not reached with the OPZ split-dose capsule up to 210 mg/d. Split-dose OPZ demonstrated significant proteasome inhibition, encouraging safety, and efficacy. Investigation is ongoing with the OPZ tablet.

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PFS, Time to Next Therapy (TTT) and Time from Progression to Therapy (TPT) in MM Patients at First Relapse

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The introduction of novel agents and technologies turned MM behave as a chronic relapsing malignant disease and emphesise the goal of therapy : prolongation of te Time Without Symptoms, Therapy, and Therapy related Complication (TWiSTT). Yet the PFS parameter is still the most used . We evaluate the Time from Progression to next Therapy (TPT) in 34 consecutive pt's (14F, 20M,median age at progression 59y) with 1st relapse of MM, treated by a single team. Progression was defined according to IMWG criteria and initiation of therapy was based on CRAB + sFLC/albumin mass. The median PFS and TTT for the entire group were 16m and 29.5m respectively. The median TPT is 12m, 12m, and 8m for the entire group, pt's post ABMT for 1st line (n=19, median age 54y) and non transplant pt's (n=15, median age 64y), respectively. Conclusion. The Time from Progression to next Therapy (TPT) may significantly affect the TWiSTT and may differ according to parameters such as age, previous therapy and maintenance therapy. This should be considered when analyzing data, and may suggest an advantage to the use of the TTT parameter in MM studies

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Continuous Lenalidomide Therapy in Patients with Newly Diagnosed Multiple Myeloma Aged 65-75 Years: MM-015 Update

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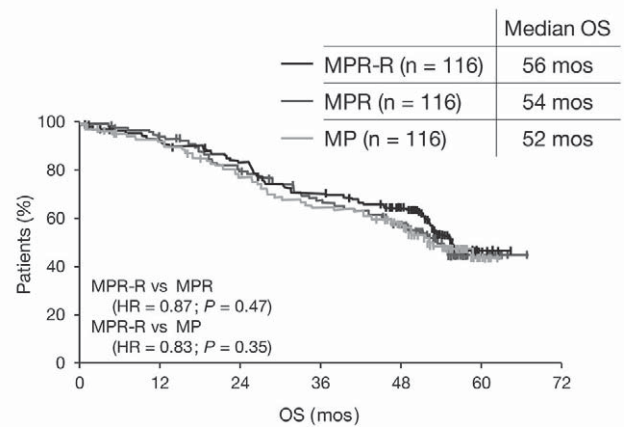
In a phase 3 randomized trial (MM-015), melphalan-prednisone-lenalidomide induction followed by lenalidomide maintenance (MPR-R) was compared with MPR or MP followed by placebo in 459 transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). Median progression-free survival (PFS) in the overall population was significantly higher with MPR-R (31 mos) than MPR (14 mos; P<0.001) or MP (13 mos; P<0.001). The benefit was observed mainly in patients aged 65-75 years. Here we provide updated efficacy and safety data from this young patient population. The proportion of patients aged 65-75 years was similar across treatment groups (76% MPR-R, 76% MPR, 75% MP). With a median follow-up of 30 mos at final adjudication prior to unblinding, MPR-R significantly prolonged median PFS vs MPR and MP (31 vs 15 and 13 mos, respectively; P<0.001). With an updated median follow-up of 53 mos, OS was 56 mos with MPR-R, 54 mos with MPR, and 52 mos with MP (Figure). During induction, grade 3/4 neutropenia occurred in 68% (MPR-R), 63% (MPR), and 31% (MP), thrombocytopenia was reported in 36% (MPR-R), 41% (MPR), and 12% (MP), and febrile neutropenia in 4% (MPR-R), 3% (MPR), and 0% MP. During lenalidomide maintenance, the most common grade 3/4 newly occurring or worsening AEs (>=5% of patients) were thrombocytopenia (8%), anemia (7%), neutropenia (5%), diarrhea (5%) and bone pain (5%). Continuous treatment with lenalidomide is highly effective in transplant-ineligible NDMM patients aged 65-75 years, and could be considered a standard of care in this patient population.

Figure. OS in patients aged 65-75 years by treatment regimen.



P-228

Meta-analysis of the Efficacy and Safety of Bortezomib (BTZ) Retreatment in Patients (pts) with Multiple Myeloma (MM)

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BTZ is administered for a finite course; thus MM pts may remain sensitive to BTZ-based therapy at relapse. We conducted a meta-analysis to assess efficacy and safety of BTZ-based retreatment in studies of pts with relapsed (rel) and/or refractory (ref) MM. The proportion of BTZ-ref pts was identified where available. Other prognostic factors were extracted and used in weighted stratified analyses of TTP, PFS and OS. Random-effect pooled estimates were calculated for ORR (>=PR) and rates of common AEs. 23 studies (N=1051 pts) were identified. BTZ was given IV in all studies. Retreatment comprised BTZ +/- dex in 4 studies and BTZ-based combination therapy in 19. BTZ-ref pts were included in 11 studies; 6 studies included only rel pts. Across studies with data available, pooled weighted average ORR was 39% (95%CI :31-47) and median TTP, PFS and OS were 7.5, 5.8 and 16.6 months. Stratified univariate analyses showed outcomes were generally consistent across groups while pts with <=4 prior therapies and rel (but not ref) pts had higher ORRs of 43% and 57% respectively. By random-effects meta-regression analysis, compared to ref pts, rel pts were associated with a higher ORR by 28-41 percentage points. The most common grade 3/4 AEs were thrombocytopenia (35%), neutropenia (15%), anemia (14%), pneumonia (10%) and peripheral neuropathy (3%). Based on these findings, BTZ retreatment is efficacious and well tolerated in rel pts. In an era of new and emerging treatment options, these data indicate BTZ retreatment continues to be a highly effective option in previously treated pts.

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MLN9708, an Investigational Oral Proteasome Inhibitor (PI), in Relapsed or Refractory Light-chain (AL) Amyloidosis

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In this phase 1 study (NCT01318902), patients (pts) with relapsed or refractory AL (RRAL) received the oral PI MLN9708 at 4.0 or 5.5 mg (d 1, 8, 15; for up to 12 28-d cycles). Pts with less than a hematologic PR after 3 cycles added dexamethasone (dex) 40 mg. At data cut-off (Oct 8, 2012) 22 pts had been enrolled, including 17 at the MTD of 4.0 mg. In these 17 pts, median age was 66 years (range 54-78); median number of prior therapies was 2 (1-8). A median of 2 (1-4) organ systems were involved (heart, kidney, or both in 8, 4, and 4 pts, respectively). Cardiac biomarker stage was I/II/III in 7/9/1 pts. Pts received a median of 3 cycles (1-12), 5 pts had added dex. Of the 17 pts treated at 4.0 mg, 5 were bortezomib (btz)-naive and 12 were btz-exposed. All-cause AEs included diarrhea (47%), nausea, fatigue (each 35%), peripheral edema (29%), and pain in extremity (muscular, 24%). Drug-related Gr 3 AEs included thrombocytopenia and rash (each 12%). 1 pt died due to disease-related heart failure. Of 15 pts evaluable for hematologic response treated at 4.0 mg, 2 had CR (1 added dex), 5 VGPR (1 added dex), and 1 PR; response duration of up to 14.7 mos has been seen to date. Of 9 pts evaluable for organ response, 3 had cardiac responses. MLN9708 PK properties in this study appear similar to studies in multiple myeloma pts. These data suggest weekly oral MLN9708 4.0

mg appears active and tolerable in pts with RRAL supporting the ongoing phase 3 trial of MLN9708+dex or physician's choice (NCT01659658). Updated data from the full MTD cohort (n=21) will be presented.

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Safety and Pharmacokinetics of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, Alone and in Combination

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Weekly MLN9708 (d 1, 8, 15; 28-d cycles) has been evaluated as a single agent (SA) in relapsed/refractory (RR) MM (NCT00963820; N=60) and in combination with lenalidomide (len) and dex in newly diagnosed MM (NCT01217957; N=65). In the ongoing Ph 1 SA study, MTD was 2.97mg/m^2; DLTs included Gr 3 rash and GI events. Pts received a median of 2 (1-11) cycles; 30% received >=4 cycles. Common drug-related AEs included thrombocytopenia (45%), diarrhea (37%) and nausea (35%); Gr >=3 AEs included thrombocytopenia (33%), diarrhea and neutropenia (each 17%). All-grade peripheral neuropathy (PN) was seen in 10%, with no Gr >=3 events. PK data showed rapid absorption, a terminal half-life of 4-12 days, and a proportional increase in plasma AUC with dose (0.8-3.95mg/m^2). Thus, SA MLN9708 appeared generally well tolerated; the long terminal half-life supports weekly dosing. This schedule was then used in the ongoing Ph 1/2 len-dex combination study; the MLN9708 MTD was again 2.97mg/m^2 with similar DLTs. Based on toxicity/efficacy balance across multiple cycles, the recommended Ph 2 dose was 2.23mg/m^2, converted to a 4.0mg fixed dose based on population PK analysis. Pts received a median of 6 (1-19) cycles of MLN9708. Common AEs included rash (68%), fatigue (48%), nausea (42%), and PN (32%, 3% Gr 3). MLN9708 PK data showed no apparent differences between SA and combination dosing, suggesting no PK interaction with len or dex. Data from these studies provide the rationale for weekly dosing of MLN9708 4.0mg (vs placebo) plus len-dex in an ongoing Ph 3 trial in RRMM (NCT01564537).

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Deregulation of Cell Cycle Control and DNA Damage Repair Genes in TP53 Deleted and/or MDM4 Amplified Poor Outcome MM Pts

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TP53 del on chr 17p13 is one of the genomic aberration most significantly associated with poor outcome in MM. The deregulated expression of TP53 inhibitors and/or activators might account for p53 pathway silencing. MDM4, one of the most potent inhibitor of p53, is located on chr1q32.1, a region frequently amplified in MM. Unpaired analysis of CNAs (6.0 SNP array) and GEP (U133 Plus2.0 array) were used to investigate the frequency and the prognostic role of TP53 del and/or MDM4 amp in 89 newly diagnosed MM pts, assuming that both of these chromosomal aberrations might contribute to impaired p53 function. All pts have been treated with VTD as induction therapy prior to, and as consolidation after, ASCT. By CNA analysis, 9/89 pts carried a 482 Kb minimal deleted region including TP53 on chr17p13.1, and that 27/89 pts carried a 1.1 Mb minimal amplified region including MDM4 on chr1q32.1. The GEP of pts stratified into two subgroups according to the presence or the absence of amp MDM4 and/or del TP53 (group A = 34 pts; group B = 55 pts) highlighted an overall deregulation of pathways related to the cell cycle, the DNA damage repair and the cell adhesion and cytoskeleton remodeling. The rate of near CR after VTD induction was 38% in group A and 20% in group B; the presence of TP53 del and/or MDM4 amp correlated with shorter median TTP (40.13 m. vs not reached, p=0.005) and OS (57.6 m.vs not reached, p=0.02). The results overall suggest that the involvement of the p53 pathway alteration in MM might be wider than expected, possibly due to the activation negative regulators of p53.

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Oligoclonal Bands Prevalence in MM Patients Who Achieved ≥ VGPR after Standard or High-dose Chemotherapy Treatment

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Introduction-Oligoclonal bands (OB) are monoclonal proteins distinct from those originally identified during the multiple myeloma (MM) diagnosis. Some authors consider that appearance of these bands confers a better prognosis and may be linked to immune reconstitution. There is no data on the exact prevalence of OB emergence in patients who achieved response better than very good partial response (VGPR) after different treatment schedules. Objectives-To determine the prevalence of OB in MM patients treated with and without high-dose chemotherapy who obtained response ≥ VGPR, and to determine if the emergence of such bands influences the PFS. Methods-This is a retrospective cohort study. Data were collected from records of patients who identified distinct OB emergence from the diagnosis. Subsequently, new sample collections from the positive patients were taken in order to monitor the progress and duration of the maintenance of these bands. Results-Data from 73 patients were included from July 1996 to December 2011. Fifty-two (71%) patients were submitted to high-dose chemotherapy and 21 (28%) were submitted to conventional treatment. Median age was 55y (30-88) and 52% were male. IgG was the most frequent component (60%). The ISS was 34% in stage I, 34% in II, and 26% in III. Median follow-up was 46m (12-200). The new OB prevalence identified by SPE and IF was 35 cases (46%), 30 patients after ASCT and five after conventional chemo. PFS was better in the OB group (p = 0.034). Conclusion-The OB prevalence in this patient group was 46% and PFS was superior in the OB group.

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Adoptive Immunotherapy with Engineered T Cells Expressing a TCR Targeting NY-ESO-1 and LAGE-1 Antigens after ASCT for MM

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This clinical trial investigates T cells engineered with an HLA-A0201 restricted, affinity-enhanced TCR that recognizes an epitope expressed by the NY-ESO-1 and LAGE-1 cancer testis antigens; cells are infused two days following high-dose chemotherapy given prior to autologous stem cell transplant (ASCT) in patients with high risk or relapsed multiple myeloma (MM). Inclusion criteria are 1) eligibility for auto-SCT, 2) PS of 0-2, 3) high risk MM or relapse after prior therapy, 4) HLA-A0201 positivity, and 5) NY-ESO-1 and/or LAGE-1 positive tumor by RT-PCR. T cells are activated and expanded using anti-CD3/28 antibody conjugated microbeads, and gene modified with a lentiviral vector. Disease response is evaluated in accordance with the IMWG criteria at 6 weeks, and 3 and 6 months post infusion. Patients are monitored for persistence of gene modified cells and marrow is monitored for NY-ESO-1 and LAGE-1 antigen. 21 pts have enrolled, 17 patients have been infused (50% HR cytogenetics, 20% prior ASCT) with an average of 2.7 x 109 gene modified cells. 3 mos post ASCT, 77% experienced a VGPR or better. Infusions were well tolerated. GI toxicity resulting from autologous GVHD occurred in a subset of patients, possibly at a higher frequency than previously reported with non-gene modified T cell infusion after ASCT. Gene modified cells persisted at 6-12 months at approximately 10-100 gene modified cells per uL of blood. Disease progression has occurred in 4 pts and has been accompanied by very low levels or loss of engineered T cells or absence of target antigen on tumor.

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Outcome of Autologous Stem Cell Transplantation for Multiple Myeloma in the Era of Novel Agents

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Background: Autologous stem cell transplantation (ASCT) has been a part of the standard therapy for newly diagnosed multiple myeloma. Recently, the introduction of novel agents improved the response rate of the treatment for the multiple myeloma and the role of ASCT in the era of novel agents is unclear. Methods: We reviewed ASCT for multiple myeloma between 2001 and 2012 in our institution. Results: Since

2001, we performed ASCT for 155 patients. Ninety patients were treated with tandem ASCT. In 126 patients were treated with VAD as an induction therapy, and 29 patients were treated with BD, very-good-partial-remission (VGPR) or complete remission (CR) was obtained in 25.5% of the patients treated with VAD, and in 37.9% with BD regimen before the transplantation. Overall survival (OS) did not differ significantly between VAD and BD induction, estimated 2 year-OS was 87.2% vs. 81.8% respectively. In both VAD and BD induction, OS was superior with tandem transplantation (p=0.003 and 0.039, respectively). OS was not significantly differ between the patients who achieved VGPR or better, and partial remission (PR) or worse in both induction regimen. However, OS was superior with the patients who achieved VGPR or better after the first ASCT in VAD induction (p=0.036). In BD induction, the patients who achieved VGPR or better after the first ASCT, the estimated 2 year-OS was 100%. Conclusion: In the era of novel agents, the role of ASCT is still critical. VGPR or better response after the first ASCT contributes to the improvement of the survival.

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Polyclonal and Monoclonal Antibody Based FLC Assays Provide Discrepant Clinical Information in Multiple Myeloma Patients

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Background: Guidelines for the assessment of serum FLC in MM patients are based upon the Freelite assays, which utilise polyclonal antisera. New assays utilising monoclonal antisera have become available. Here we assess the new assay to monitor MM patients. Patients and Methods: Sera from 61 MM patients (25IgG κ, 13IgG λ, 5IgA κ, 3IgA λ, 13 negative IFE, 2 biclonal; 35 males; median sample number 6(1-17); follow-up 206(7-819) days) treated with bortezomib combinations were analysed retrospectively with Freelite and N Latex FLC (NL) assays. Results were compared to historic data. Results: At presentation the FLC concentrations reported showed poor correlation (Median κ(mg/L): Freelite 41.1(0.3-8701), NL 16.7(0.2-4493), R2=0.742; Median λ(mg/L): Freelite 8.3(1-5280), NL 9.8(1.6-299), R2=0.395). 57/61 patients had an abnormal FLC ratio with Freelite and 54/61 with NL; 4 patients were detected by Freelite alone and 1 patient had borderline results by both assays. During follow up Freelite identified clonal disease (confirmed by IFE) in 4/61 patients when the NL assay ratio had normalised. Furthermore 1 patient with progressive disease was identified by the Freelite assay after 586 days, but not by the NL assay until 670 days. Finally 1/1 NSMM patient was only able to be monitored by the Freelite assay. Conclusion: MM patient assessment using the Freelite assay has formed the basis of international guidelines. Here the NL assay failed to provide similar clinical information and further studies are required to establish its utility.

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Use of Heavy/Light Chain (HLC) and Free Light Chain (FLC) Ratios for Monitoring Oligosecretory Multiple Myeloma Patients

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Background: Using standard techniques (SPEP / total Ig') accurate assessment of oligosecretory MM (o-MM) patients' responses to therapy present a significant challenge. When involved FLC (iFLC) levels are >100mg/L, guidelines recommend their use as a tool to monitor patients. Here we analyse the utility of heavy/light chain Ig' k / Ig' l ratios (HLCr) for monitoring o-MM patients with iFLC <100mg/L. Methods: IgG and IgA HLC analysis was performed on stored serial samples from 8 (3 IgAk, 2 IgAl, 1 IgGk and 2 IgGl) o-MM patients with FLC<100mg/L (median sample n= 9 (range 3-17), follow up months 32 (9-72), M:F 1:1, ISS 6 x s1, 1 x s2, 1x s3) Results: HLCr was abnormal in 8/8 patients at presentation. In both IgG and IgA patients there was overall concordance with changes in HLCr and clinical assessment. 2 IgG patients showed no response to therapy and 1 patient had a CR; HLCr remained abnormal and became normal, respectively. In 2 IgA patients achieving CR HLCr normalised at the time of maximum response, in 1 patient the ratio subsequently became abnormal before significant increases in tIgA. In 3 IgA patients achieving <PR, HLCr remained abnormal at maximum response. 2/5 IgA patients relapsed from maximum response, in 1 IgAl patient HLCr showed a greater degree of change at relapse than tIgA, in 1 IgAk patient an increasingly abnormal HLCr preceded relapse by ~12 months. Discussion: SPEP and tIgA are inaccurate in o-MM patients and more sensitive tests are required to assess patient responses; HLCr may provide an increased ability to monitor patients.

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Reduced Intensity Conditioned Allo-SCT for Multiple Myeloma Relapsing after Auto-SCT; a Study by the EBMT CMWP

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Reduced-intensity conditioned allogeneic stem cell transplantation (RIC allo-SCT) for multiple myeloma (MM) is a controversial up-front treatment. Its role as salvage therapy in patients who have relapsed after prior auto-SCT is not well defined. We performed an analysis of 413 MM patients reported to the EBMT between 1999 and 2008 who received a related or unrelated RIC allo-SCT for the treatment of relapse or progression after prior auto-SCT. Median age at RIC allo-SCT was 54.1 years, and 44.6% of patients had undergone 2 or more prior auto-SCTs. Median OS from RIC allo-SCT for all patients was 24.7 months (95%CI, 19-31). In multivariate analysis, CMV seronegativity of both recipient and donor ("CMV double seronegativity"), and <2 prior auto-SCT were associated with better OS, with age almost reaching significance. The 5-year survival from RIC allo-SCT for CMV negative recipients with a CMV negative donor was 41.1% (95% CI, 30-54). Median PFS from RIC allo-SCT for all patients was 9.6 months (95%CI, 7-12). CMV double seronegativity and patient/donor gender mismatch were associated with better PFS in multivariate analysis. Cumulative NRM was 21.5% at 1 year. CMV double seronegativity and time from the first auto-SCT to RIC allo-SCT <2.6 years were associated with lower NRM in multivariate analysis. The results of this study demonstrate that RIC allo-SCT can be an effective salvage treatment in a subgroup of MM patients relapsing after auto-SCT, and identify patient and donor CMV seronegativity as the key prognostic factor for transplant outcomes.

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Changes in HLC IgA Kappa / IgA Lambda Ratios can be Used to Monitor IgA Multiple Myeloma (MM) Patients

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IMWG guidelines recommend the use of SPEP/total IgA (tIgA) and IFE to monitor IgA multiple myeloma (MM) patients. Recently, immunoassays that quantify IgA κ/IgA λ (heavy/light chain; HLC) have been developed. Here, we compared changes in HLC IgA κ/gA λ ratios (HLCr) with SPEP/tIgA measurements during IgA MM patient monitoring. HLCr were measured in 45 IgA MM patient (Wilhelminenspital 19 IgA κ, 11 IgA λ ; MRCVII trial 12 IgA κ, 3 IgA λ ; median follow-up n=496 days (range 32-2722 days); patient samples n=7 (1-32); age n=60yrs (32-81yrs); M/F ratio 22/19 (4 not reported)) sera and results compared a normal IgA κ/IgA λ HLCr (0.80-2.04) and to historic data. Oligosecretory MM patients were removed. HLCr were abnormal in 45/45 patients at presentation (IgA κ HLCr=211, range 10-6226; IgA λ=0.027, 0.002-0.118), including 19/45 patients with co-migrating IgA (by SPEP). 18/45 patients achieved <VGPR, all of whom had concordant changes in HLCr. 27/45 patients achieved equal or >VGPR, all of whom were identified by improving HLCr (median HLCr decrease 95%, range 77-98%), including 10 patients' whose HLCr normalized (9/10 were IFE negative). Finally, 24/45 patients progressed, all were identified by abnormal HLCr ratio. In 10/24 an increasingly abnormal HLCr predicated progression before any other measurement (median 78 days, range 24-294 days). HLCr changes can be used to monitor IgA MM patients, irrespective of co-migration with other proteins by SPEP. In addition, HLCr may offer early indication of disease progression.

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HLC Pair Suppression Correlates with Short Survival

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The HLC assay allows measurement of the non-involved pair of the involved M-component, i.e. in IgA kappa myeloma the precise quantification of IgA lambda. Here, we studied retrospectively HLC pair suppression in patients with IgA and IgG myeloma and its correlation with clinical parameters and survival. Methods: The Hevylite assay was used for measurement of HLC pair suppression (defined as a reduction of the lower level of normal (LLN) by <33% and severe HLC pair suppression as <50% of LLN) at start of therapy in 94 newly diagnosed MM patients. Median age is 69 (41-87) years. Patients were enrolled between 1994 and 2010 and received different treatment regimens. Median follow up is 48 months. Hb, creatinine, calcium and β-crosslaps, a marker of bone degradation and substitute for bone disease (modified CRAB criteria) were studied as clinical parameters. Results: Severe HLC pair suppression by >50% correlated with OS (46.6 vs. 84.4 months, p <0.044) (figure 1) while no significant correlation was noted at a lower cut-off (>33%) (56.9 months vs. not reached, p=0.303). The magnitude of HLC pair suppression correlated weakly with β-crosslaps (r^2=0.038) and with creatinine levels (r^2=0.04). Patients with equal or >2 of the clinical parameters abnormal had higher HLC pair suppression compared to those with equal or <1 (median 79,54% vs. 88,48%) Severe HLC pair suppression is associated with shorter survival. The observed trend for correlations between HLC pair suppression and abnormal modified CRAB criteria will be analyzed in a large patient group.

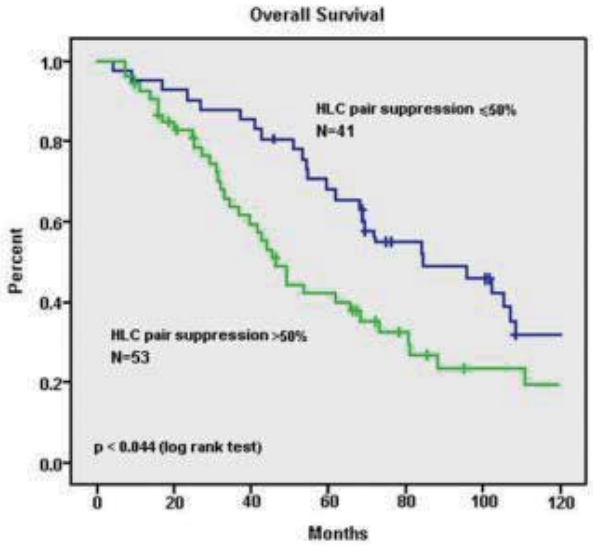

Figure 1. Severe HLC pair suppression is associated with short survival

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Neurological Monitoring During Bortezomib and/or IMIDs Treatment in Multiple Myeloma Patients

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We performed a prospective study to investigate the benefit of early diagnosis in reducing the development of severe treatment-related peripheral neuropathy (PN) in multiple myeloma (MM) patients (pts). Ninety-three pts were evaluated: median age 59 years, 44 men, 53 pts were undergoing 1st, 29 2nd and 11 >3rd line of therapy. Sixty-two pts developed PN: 20 were receiving Bortezomib-Thalidomide (VT), 27 Bortezomib, 9 Thalidomide, 4 Lenalidomide and 2 Lenalidomide-Thalidomide. Patients with PN were older, median age 59 vs 43 years (p<0.01), had a longer duration of disease, 45 vs 22 months (p<0.01), and were more frequently treated with VT and V or T alone (p<0.05). No significant correlation was found between the occurrence of PN and the cumulative doses of V and T. According to the sural nerve action potential study (SAP), in the VT group the neuropathy appeared after a median of 1.6 months of treatment and worsened after 3 months. After the diagnosis of PN, 18 pts required V/T dose reduction, 4 temporary drug discontinuation and 4 treatment interruption, while 36 pts continued therapy under a close neurological monitoring; 28/62 pts had a PN resolution. Our study shows that an early diagnosis of PN and MM treatment adjustment can avoid the development of grade 3-4 PN, and that through careful neurologic monitoring only 7% of pts had to stop treatment. Age, duration of disease and treatment were predictive factors of PN development. A reduction of SAP occurred early in pts who developed PN, suggesting that biological factors may predispose to the development of PN

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Impact of Bortezomib Incorporated into Autotransplantation on Outcomes of Myeloma Patients with High-risk Cytogenetics

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We performed an analysis of 1610 newly diagnosed multiple myeloma (MM) patients enrolled in four phase 3 studies comparing up-front bortezomib-based (B-) vs non bortezomib-based (NB-) single or double autotransplantation [ASCT(s)]. All patients had available data on the presence or absence of del(13q), t(4;14) and/or del(17p). In comparison with NB-ASCT(s), B-ASCT(s) significantly improved PFS in the overall population (HR: 0.76), a benefit retained across low risk (HR: 0.79) and high risk (HR: 0.58) subgroups. A trend for improved OS (HR: 0.85) was also seen with B-ASCT(s). In a stratified multivariate analysis, independent variables associated with extended PFS and OS in the overall population included B-ASCT(s) (HR: 0.74 and 0.79), achievement of CR (HR: 0.46 and 0.44) and double ASCT (HR: 0.44 and 0.31). These variables were independent predictors for prolonged PFS and OS also in patients with t(4;14) and/or del(17p). Patients who carried both these abnormalities had the poorest prognosis and in a multivariate analysis were likely to benefit only from double ASCT (HR: 0.13 for PFS and 0.28 for OS). In conclusion, B-ASCT(s) significantly improved PFS in comparison with NB-ASCT(s), but did not overcome the adverse prognosis related to the presence of t(4;14) and/or del(17p). More mature data are needed before definite conclusions on the impact of B-ASCT(s) on OS can be drawn. Apparent PFS and OS benefits observed with incorporation of novel agents into double ASCT in the subgroup of patients with t(4;14) and/or del(17p) need to be confirmed in prospective randomized studies.

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MM-003 Trial: POM + Low-dose DEX Extends OS and PFS vs. High-dose DEX in Patients Double-refractory to LEN and BORT

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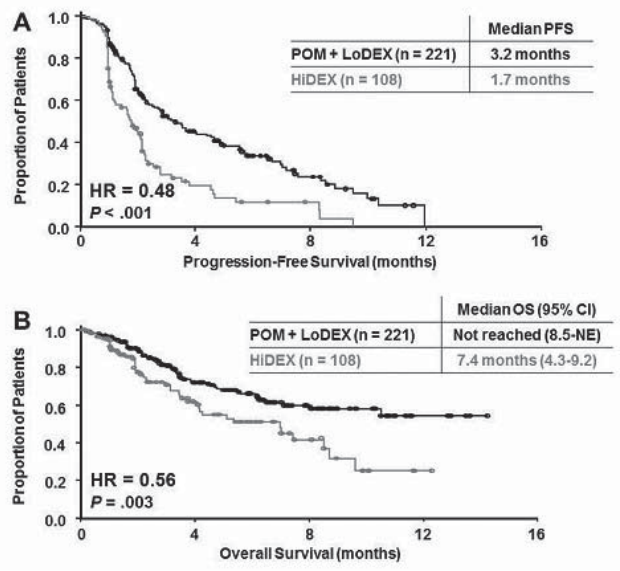
Background: Multiple myeloma (MM) patients (pts) refractory to both lenalidomide (LEN) and bortezomib (BORT) have a poor prognosis with short overall survival (OS). High-dose dexamethasone (HiDEX) is a common salvage treatment (Tx). Pomalidomide (POM) has activity in relapsed/refractory MM pts with prior LEN and BORT. MM-003 compared POM + low-dose dexamethasone (LoDEX) vs HiDEX in pts who failed LEN and BORT including those refractory to both.

Methods: Pts must have been refractory (progressive disease [PD] during or within 60 days) to their last prior Tx and failed LEN and BORT (alone or in combination) following ≥2 consecutive cycles of each. Tx was described (Dimopoulos. ASH 2012). Progression-free survival (PFS) was the primary endpoint. This subanalysis examined results of LEN and BORT double-refractory pts (PD during or within 60 days of last LEN Tx and last BORT Tx).

Results: LEN and BORT double-refractory pts comprised 73% (221/302) of the POM+LoDEX and 71% (108/153) of the HiDEX arm. With 4 mo median follow-up, PFS and OS were significantly longer with POM+LoDEX vs HiDEX in pts refractory to both LEN and BORT (PFS 3.2 vs 1.7 mo, $P<.001$; OS not reached [NR] vs 7.4 mo, $P=.003$; Figure). There was an OS benefit despite 29% of HiDEX pts receiving POM after PD. Results were comparable to the overall

population (PFS 3.6 vs 1.8 mo, *P*<.001; OS NR vs 7.8 mo, *P*<.001).

Conclusions: Similar to the overall MM-003 population, POM+LoDEX significantly extended PFS and OS vs HiDEX in LEN and BORT double-refractory pts. POM+LoDEX should be considered a new option for these pts.



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Outcomes of Young Patients (50 Years or below) with Multiple Myeloma (MM)

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Background: MM is infrequent in the young population. The median overall survival (OS) of patients 40 years of age or under, diagnosed prior to 1993 was reportedly 54 months at our institution. Both conventional therapy and stem cell transplantation (SCT) favorably impact survival of young MM patients. However, the impact of novel agents in this population is unclear. We studied outcomes of young patients presenting in the period coinciding with increased availability of novel agents. Methods: Records of 1538 MM patients diagnosed between 01/99 and 12/08 were reviewed. The demographics, characteristics and therapies in patients 50 years or below at diagnosis were analyzed. OS was determined using the Kaplan-Meier method. Results: Of 1538 newly diagnosed MM patients, 183 (12%) were 50 years or below. Median follow-up of these 183 patients was 102 months. Table 1 outlines the disease and patient characteristics. Between 1-16 (median 3) regimens were used. 89% underwent SCT with 22 patients undergoing allo-SCT. Bortezomib (52%),lenalidomide (62%), thalidomide (58%) & pomalidomide (13%) were used in front-line and/or relapsed setting. Median OS was 95 months (95% CI; 81,117). The estimated median OS of patients in Mayo standard-risk category was 147 months vs. 57 months for intermediate plus high-risk categories (p=0.03) (Figure). Conclusion: Young MM patients diagnosed in the novel-agent era have a significantly improved OS compared to the historical control of similar age group. Young patients with high-risk features have worse outcomes compared to the standard risk patients.

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Melphalan and Prednisolone Therapy Compared with Melphalan and Prednisolone plus Thalidomide in Real Life Patients.

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Combination of melphalan and prednisolone (MP) was standard treatment of multiple myeloma (MM) for decades. Since the introduction of novel agents the clinical outcome in MM has improved. Several prospective studies with thalidomide, the first novel agent, combined with MP, (MPT) compared to MP have been performed, most of them showing MPT gives a better response rate and median overall survival (OS) than MP. Aims: To look upon a real life population and see if addition of thalidomide gained real life patients. In a material of 1642 patients with symptomatic MM collected from 14 Swedish sites from earliest January 2000, until latest June 2012 we collected all patients treated in first and second line of therapy with MP (n=600 and 213) and MPT (n=170 and 66). Patients were evaluated for OS. Multivariate Cox model analysis was made to adjust for Ig-class, age, hypercalcemia haemoglobin and albumin levels at time for MM-diagnose. OS in the MP group after 1st line of therapy was 27 months and in the MPT group 50 months (95% confidence interval 24-30 and 44-84 months respectively). The relative risk for death in the MPT group vs the MP group was 0.61 (95% confidence interval 0.45-0.84) after adjusting for other prognostic markers. After 2nd line of therapy OS in the MP group was 22 months and in the MPT group 35 months

(95% confidence interval 18-25 and 29-not reached). Relative risk for death after MPT vs MP was 0.55 (0.38-0.83), p<0.01). Treating with MPT gave a significantly better overall survival after both 1st and 2nd line of therapy compared to treatment with MP only.

Fig 1a OS 1st line of treatment

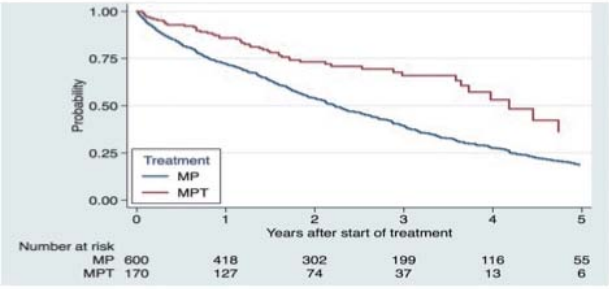
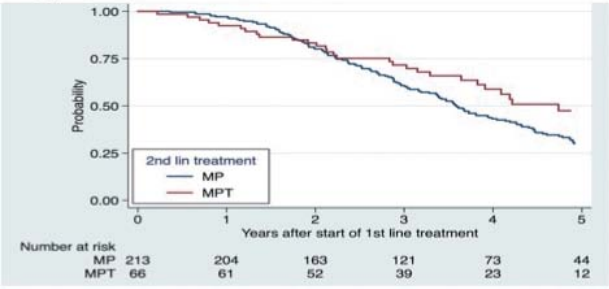


Fig 1b OS 2nd line of treatment



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Discordance between M-protein and Serum Free Light Chain Ratio in Patients with Multiple Myeloma

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Introduction: Serum free light chain (sFLC) assay has been widely applied for response evaluation in patients with multiple myeloma (MM). However, the incidence and clinical significance of discordance between quantitative M-protein level and sFLC ratio remains unclear. Methods: From January 2009 to December 2011, we enrolled consecutive patients diagnosed with IgG or IgA MM at Taipei Veterans General Hospital. All paired data of M-protein and sFLC ratios were collected. Bone marrow examinations and serum immunofixation electrophoresis were used as benchmarks to determine the disease status and the false negativity of these two assays. Follow-up was continued until December 31, 2012. Results: 267 serial samples from 45 IgG or IgA MM patients were studied to explore the discordance between M-protein and sFLC ratio. Discordance was noted in 57 (21.3%) samples from 20 (44.4%) patients. Among them, sFLC assays were falsely negative in 10 patients and falsely positive in 1 patient. The discordance is not related to immunoglobulin subtypes. After a median follow-up of 23.0 months (range 0.6-45.7 months), the survival outcomes were not different in patients with concordant or discordant assay results (P = .271). Conclusion: Discordance between M-protein and sFLC ratio is common in MM patients. The significance of discordant assays is individualized and should be carefully interpreted with serial follow-ups. Prospective studies are required to determine the temporal relationship between sFLC ratio normalization and paraprotein clearance.

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Asymptomatic Relapse

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Asymptomatic Relapse After Stem Cell Transplantation Is there a way to manage rationally? Sergio Giralt, MD The patterns of myeloma relapse have changed significantly over the last 20 years. Prior to the advent of bortezomib and thalidomide Alegra et al. patients relapsing after an autologous stem cell transplant (SCT) fell into one of four categories: a) Insidious (18%) characterized by asymptomatic elevations of the paraprotein peak. b) Classic (66%) monoclonal component along with clinical symptoms. c) Plasmacytomas (14%). d) Plasmacytic leukemia (2%). Similar results were seen by Lenhoff et al., except the insidious form accounted for 31% of relapses, the classical form accounted for 51% of relapses. As with the Alegre study patients relapsing with an insidious or classical form of disease were likely to respond well to conventional salvage therapy. In contrast, relapse with multiple symptoms, transformed disease or a short duration of first response implied bad prognosis. In both of these series most patients were not receiving maintenance therapy. In contrast, Zamarin et al reported that in the context of maintenance therapy 85% of patients presented without symptoms, although occult skeletal lesions were found in 40% of asymptomatic patients tested following serological progression. Thus in the context of maintenance therapy associated with more frequent disease assessment the incidence of asymptomatic relapse is increasing, the natural history of these patients as well as the optimal evaluation needs to be determined to guide therapy rationally.

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Factors Influencing the Outcome of ASCT in 17-year Cohort of 338 Patients in a Single Centre

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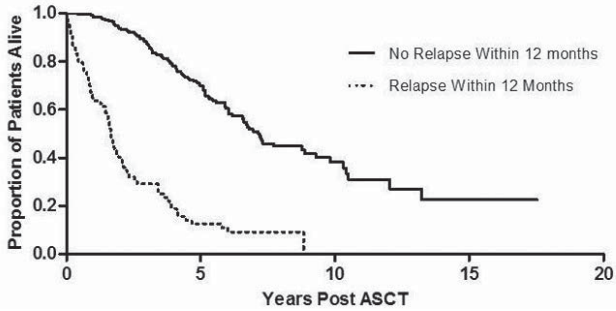
The role and timing of ASCT are being examined as new regimens induce deep responses in most patients. Patients received upfront ASCT (1993-2010), details in Table 1. 26.5% received novel agents (the rest had VAD-based regimens). 26.9% were in >=VGPR pre-ASCT. TRM at 100 days was 3.3%, and 49.1% attained >=VGPR at 3 months. Median follow up was 6.1yrs, PFS 2.0yrs and OS 5.8yrs; 266 patients have relapsed, 169 have died. ISS stage 1, female gender, use of maintenance/consolidation and disease response (>=VGPR pre- and 3 months post-ASCT) predicted longer PFS (p's<0.05). Timing of relapse was the most important predictor of survival (median OS 1.6yrs if relapse within 12 months vs 7.2 if not, p<0.001, Fig 1). Reduced OS was also associated with male gender, advanced ISS, non-IgG isotype, CD56-negativity, and age at ASCT (p's<0.05). Adverse cytogenetics was associated with both reduced PFS and OS (p's=0.01). Median post-relapse survival (PRS) was 2.6yrs; IgG isotype, CD56-positivity, later year of, and younger age at ASCT, and longer TTP from ASCT predicted longer PRS. Maintenance/consolidation did not reduce PRS. Use of novel agents pre-ASCT did not influence PFS or OS, but treatment with bortezomib (n = 99) at 1st relapse predicted longer PRS (p<0.001) and OS (p=0.02). Optimisation of post-ASCT strategies and choice of agent at relapse may be as important determinants of outcome as disease response pre-ASCT. The striking influence of early (within 12 months) relapse identifies a group of patients for whom new strategies are urgently required.

Table 1: Patient characteristics

Parameter	Percentage
Age (years)	Mean = 56.4, SD = 7.5
Male	63.0%
Time from diagnosis (years)	Mean = 1.2, SD = 1.1
Chain isotype: IgG / IgA / Light Chain / Other	55.8 / 20.5 / 16.6 / 7.1%
ISS stage (available in 71%) ISS 1 / 2 / 3	 48.8 / 25.4 / 25.8%
Cytogenetics (available in 38%) High risk* / Neutral or Normal FISH / Other	 23.8 / 73.1 / 3.1%
CD56 positive (available in 33%)	68.1%
Lines of therapy (available in 99%) 1 / 2 / 3 or more	 64.0 / 25.9 / 10.1%
Received maintenance/consolidation (available in 99%)	39.7%

* defined as t(4;14), t(14;16), 1q gain, and/or 17p loss

Figure 1: Overall Survival by Timing of Relapse



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Results from Real Life: Lenalidomide & Dexamethasone in Relapsed or Refractory Multiple Myeloma Outside Clinical Trials

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Introduction: Clinical trials evaluating the combination of lenalidomide with dexamethasone (LenDex) in relapsed or refractory multiple myeloma (rMM) included patients (pts) with up to 3 previous lines of treatment. Data on its efficacy in pts with a greater number of lines is scant. Aims and Methods: To evaluate the efficacy and safety of LenDex in highly treated rMM, we studied all pts treated in our Center (Len: 5-25 mg id, D1-21 of 28; Dex: 40 mg qw; until progression or autologous stem cell transplant, ASCT), over a 4.5 year period. IMWG response criteria and CTCAE 4.0 toxicity criteria were used. Results: 31 pts(17 male), median age of 62 y(41-78); 22 IgG, 6 IgA, 3 light-chain (2 kappa); 10 with ISS-3 at diagnosis and 13 ISS-2. Median time from diagnosis to LenDex of 45(3-144) months(m); median of 4(1-10) previous lines: 74% with bortezomib, 65% thalidomide, 54% ASCT, 35% radiotherapy. FISH cytogenetics at diagnosis were available in 6 pts: 3 normal, one del(17p), one del(13q) and one t(4;14). Efficacy and safety: 353 cycles of LenDex were evalu-

ated. The overall response rate was 65% (48% VGPR or better; 19% progressed under LenDex); median progression-free survival (PFS) was 24.8 m. Toxicity was mainly hematologic, with grade 3/4 neutropenia in 35% and grade 3/4 infections in 25% of pts; grade 1/2 peripheral neuropathy in 9%, 2 cases of thromboembolism and a case of prostate cancer. Discussion: In an unselected cohort of highly treated rMM pts, LenDex induced responses in 65%, with a PFS of 25 months, and acceptable toxicity, on par with MM009/010 trial results.

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Hevylite Assay - Sensitive Measurement in MGUS, Multiple Myeloma (MM) and Waldenstroms Macroglobulinemia Patients (pts)

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Indroduction: A novel polyclonal immunoassay specific for the different light chain types of intact immunoglobulins (Ig; HLC) and the serum free light chain (FLC) test enable measurement of changes in the production of clone specific Ig and of the non-involved polyclonal Ig of the same isotype. Methods: We investigated the new HLC compared to the capillary zone electrophoresis (CZE), total Ig and FLC. Serum FLC and HLC (IgG κ /IgG λ , IgA κ /IgA λ) measurements were performed using polyclonal antisera assays (Freelite™ and Hevylite™, Binding Site, Birmingham, UK). Sera samples were measured for total IgG, A, M and total protein (TP) by cobas 8000 Roche, for γ -Globulin (EGG) and M-spike with SEBIA capillaries. In addition, sFLC- and HLC-ratios were calculated. Results: We assessed 146 consecutive MM pts with abnormal M-spike via CZE: 57 IgG κ -MM, 24 IgG λ -MM, 8 IgA κ -MM, 7 IgA λ -MM, 5 SMM, 5 LC-MM, 28 MGUS and 12 IgM Waldenstroms macroglobulinemia (WM). The comparison of involved HLC and isotype matched FLC revealed a high correlation (Table 1A). When IgG- and IgA-MM patients were analyzed separately a high degree of correlation existed between involved HLC and total involved Ig, TP, M-spike and EGG (Table 1B). Conclusions: Very sensitive detection of IgG-,A-,M- κ and λ bands with Hevylite antibodies is feasible and correlation with various MM parameters apparent. The Hevylite-test is of clinical value and should be used as additional indispensable technique to the M-spike, particularly in MM pts in remission and WM in which the M-spike is low and more challenging to quantify.

Table 1A: Spearman correlation coefficients between involved HLC and isotype matched FLC

HLC	FLCκ	FLCλ
IgGκ (n=109)	0.55, p<0.0001	
IgGλ		0.79, p<0.0001
IgAκ (n=17)	0.82, p<0.0001	
IgAλ		0.83, p<0.0001
IgMκ (n=20)	0.46, p=0.041	
IgMλ		0.58, p=0.010

Table 1B: Spearman correlation coefficients between HLC and standard methods

	EGG	TP	M-spike	Total Ig
IgGκ-MM (n=57)				
IgGκ	0.73, p<0.0001	0.90, p<0.0001	0.82, p<0.0001	0.91, p<0.0001
IgGκ/λ ratio	0.57, p<0.0001	0.61, p<0.0001	0.67, p<0.0001	0.73, p<0.0001
IgGλ-MM (n=24)				
IgGλ	0.79, p<0.0001	0.81, p<0.0001	0.89, p<0.0001	0.89, p<0.0001
IgGκ/λ ratio	-0.62, p=0.002	-0,75, p<0.0001	-0.79, p<0.0001	-0,81, p<0.0001
IgAκ-MM (n=8)				
IgAκ	0.62, p=0.102	0.98, p<0.0001	0.78, p=0.041	1.0
IgAκ/λ ratio	0.29, p=0.493	0.71, p=0.047	0.45, p=0.310	0.64, p=0.119
IgAλ-MM (n=7)				
IgAλ	-0,36, p=0.432	0.93, p=0.003	0.90, p=0.015	0.96, p<0.0001
IgAκ/λ ratio	0.63, p=0.129	-0,74, p=0.058	-0,79, p=0.059	-0,96, p=0.001

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Carfilzomib, Pomalidomide and Dexamethasone (CPomd) for Relapsed/Refractory Multiple Myeloma (RRMM): A Phase I/II Trial

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Background: We report the results of the first phase I/II trial of CPomd in pts with RRMM. Methods: The primary objective was to determine maximum tolerated dose (MTD) of CPomd. Secondary objectives included overall response rate and progression free survival (PFS). All patients were refractory to prior lenalidomide and RR to most recent therapy. Results: MTD was established as C 20/27mg/m2, Pom 4mg, d 40mg. At this dose, 1 of 6 pts experienced a DLT of febrile neutropenia (FN). At dose level 2 (C 20/36mg/m2, Pom 4mg, d 40mg), 2 of 6 patients experienced DLTs (grade 4 thrombocytopenia(plt) and grade 3 rash). Median number of prior regimens was 6. Drug related AE's occurring in >20% of pts included fatigue, anemia, plt, neutropenia, diarrhea,

dyspnea, skin rash/pruritis, elevated creatinine, and hypocalcemia. There was a low incidence of FN (2) and no grade 3/4 peripheral neuropathy. Notable SAEs were Grade 3 pneumonia (3), pulmonary embolism (1), and congestive heart failure (1). Response is listed in Table 1. The 6 month PFS was 71% (95% Cl: 56.8-88.9%); overall survival at 12 months is 90% (95% Cl: 80.2-100%). Conclusions: CPomd is well tolerated and achieves a high response rate in a heavily pre-treated population with limited grade 3/4 toxicities. The combination has encouraging preserved response rate and survival independent of FISH/cytogenetics. Enrollment is ongoing in an 82 patient phase II trial. Acknowledgements: Onyx Pharmaceuticals, Inc. and Celgene Corporation.

P-251

Time to Engraftment Following High-dose Mel and ASCT in Pts Receiving IMID and/or Bortezomib during Induction Therapy

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A stem cell (SC) dose of 4-6 million cells/kg or greater is recommended following high-dose melphalan (mel). This study assessed factors that influence SC engraftment in patients (pts) receiving IMIDS and/or proteasome inhibitor in induction. All pts (n=454) who underwent ASCT at our center between 2007 and 2011 were included in the analysis. The impact of age at diagnosis, gender, number of SCs collected and infused, and use of induction lenalidomide (len) on time to engraftment (TTE) of neutrophils (>=500 for 3 consecutive days) and platelets (plts) (>=20k and 50k for 3 consecutive days) was evaluated. The KM method and univariate and multivariable Cox models were used. Among 454 pts, 56% were male, median age at diagnosis was 57 (range 40-73), and 98% received an IMID and/or bortezomib during induction. Median TTE for neutrophil, plt>=20, and plt>=50 was 12 (IQ range 11-12), 19 (IQ range 14-23), and 21(IQ range 16-26) days, respectively. TTE for neutrophils and plts>50k was significantly faster for pts with >=4 million SCs/kg infused (hazard ratio [HR]= 1.5,95% CI [1.1-2.0], HR=1.6, 95% CI[1.2,2.2], respectively) after adjusting for other variables. TTE for neutrophils and plts>20k was significantly faster for females (HR= 1.3,95% CI [1.1-1.6], HR=1.2, 95% CI[1.0,1.5], respectively) after adjusting for other variables. No differences were detected by len treatment (p>0.05). Thus, number of SCs infused and gender were predictive of TTE in pts treated with IMIDs and bortezomib in induction. These data support infusion of at least 4-6 million SCs/kg following high-dose mel.

P-252

Hevylite Assay Resolves Discordant Results between Serum Protein Electrophoresis and Serum Free Light Chain Assay

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Introduction: Serum free light chain (sFLC) assay is a useful tool to diagnose a clonal plasma cell proliferation that only produces an oligoclonal band. However, in some patients with symptomatic multiple myeloma, the sFLC assay shows a normal kappa/lambda ratio in spite of apparent M-spike in the serum protein electrophoresis (SPE). To explain such a discordancy, the existence of a malignant clone that produces light chain in exactly 1:1 ratio to the heavy chain has been presumed.

Recently, Hevylite assay was introduced to diagnose clonality of heavy as well as light chain of serum immunoglobulins. We have applied the Hevylite assay to a patient who has normal kappa/lambda ratio by sFLC assay in spite of the presence of M-spike in the SPE.

Patient and Methods: The patient is an 86 year-old female with D/S stage IIIA IgG kappa myeloma diagnosed in November 1999. Until now, the patient was treated with MP, thalidomide, and bortezomib. During the last 1 year period the patient kept having a measurable disease with an M-spike in the SPE under the treatment with daily thalidomide plus biweekly bortezomib. However, her kappa/lambda ratio by sFLC assay remained normal.

Results: We applied a recently introduced Hevylite assay to the sera of this patient and found her IgG kappa/IgG lambda ratio kept abnormal in spite of normal kappa/lambda ratio by sFLC assay while SPE kept showing an M-spike. In addition, the Hevylite assay can differentiate a polyclonal increase in serum IgG levels.

P-253

Randomized Phase II Trial Comparing Continuous Lenalidomide and Dexamethasone (cLd) to ASCT in First Line MM Therapy

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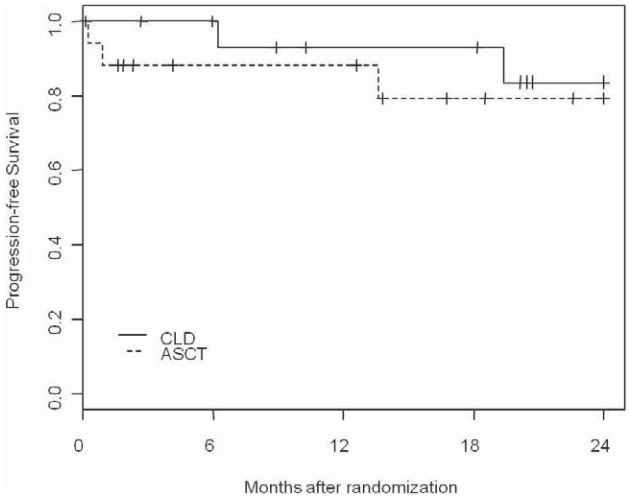
Background: The importance of ASCT in first line treatment of MM is currently being questionedin the era of novel agents. The controversy led us to design a phase II trial comparing cLdto ASCT in patients(pts) responding toinduction Ld. Methods: symptomatic MM pts without need of aggressive therapy (e. g. acute renal failure or symptomatic bone disease) received induction withL 25 mg PO days 1-21 and d 40 mg PO weekly (28d cycle) x4 cycles. Pts with POD during induction, or SD after 4 cycles came off study. All others were randomized to cLd(d stopped at 1 year) v/s ASCT followed by L maintenance. Results: 43 pts initiated Ld. ORR to induction was 78% [6 CR (14%), 1 uCR (2%), 1 nCR (2%), 5VGPR (12%), 21PR (48%), 3 SD (7%), 2POD (5%), 4 not evaluabledue to toxicity or other (9%)]. 9pts were removed prior to randomization, all achieving>PR (1 CR, 5VGPR, 2 PR, 1 in treatment)with alternative induction and proceeding to ASCT. 34ptswere randomized, 18 to cLd and 16 to ASCT.Stratification was based on prognostic risk taking into account ISS and cytogenetics. At 1 year from start of treatment, improved response by at least 1 level occurred in 19% and 23%, on cLd and ASCT arms, respectively (n=26). POD occurred in 2 and 3 ptson cLd and ASCT arms, respectively. Median PFS has not been reached in either arm (median follow up 20.2 mo for patients without POD).Conclusions: This interim analysis suggests thatin transplantation-eligible patients responsive to Ld, cLdand ASCT result in similar PFS. This response adapted approach appears safe and the trial is ongoing.



P-254

Clinical Features and Outcomes of Patients without Monoclonal Plasmacytosis of Bone Marrow Who were Classified to Symptomatic Myeloma by WHO Criteria

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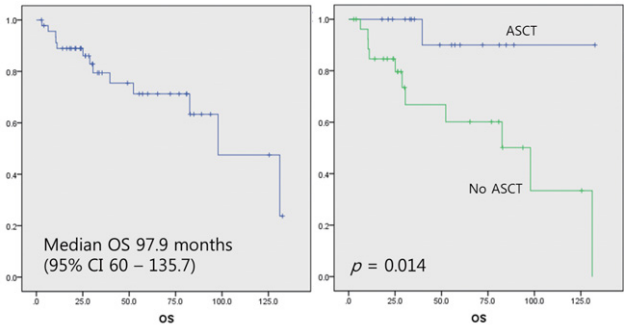
By IMWG criteria, symptomatic patientswith monoclonal gammopathy, plasmacytoma, and no clonal bone marrow plasmacytosis could not be to any category of monoclonal gammopathy because IWMG criteria require at least 10% of clonal BMplasmacytosis for diagnosis of symptomatic myeloma. To identify clinical features and outcome in these patients, the Korea Multiple Myeloma Working Party performed multicenter retrospective analysis.From Jan 1998 to Dec 2012, 47 Patients who met all following criteria were enrolled from KMWG web-based registry: presence of 1) monoclonal protein,2)plasmacytoma,3) end-organ damage,

and 4) no clonal BM plasmacytosis.The median age was 56. Nine(19%) patients showed history of previous solitary plasmacytoma. Thirty five (74%) patients complained bone pain andthirty nine (78%) patients showed osteolytic bone lesion at diagnosis.Among 45 treated patients, 17(36%) patients received autologous stem cell transplantation (ASCT).The median overall survival (OS) was 97.9 months (95% confidence interval: 60.0-135.7 months). Serum LDH level, cytogenetics, International Staging System, and ASCT were significantly associated with OS in univariate analysis (p=0.021, p=0.072, p=0.016, and, p=0.014, respectively). However, multivariate analysis demonstratedno significant factor in this cohort. In conclusion, symptomatic patients with monoclonal gammopathy, plasmacytoma, and no clonal BM plasmacytosis showed fairly long survival by anti-myeloma treatment andare considered to show distinctive clinical features among monoclonal gammopathies.



P-255

Heavy/Light Chain (HLC) Analysis Provides a Sensitive Method of Quantifying Monoclonal IgA Proteins That are Difficult to Measure by Electrophoresis

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Introduction

Accurate quantification of IgA monoclonal immunoglobulins (M-Ig) due to co-migration with other serum proteins is difficult andcan impact the assessment of patient responses. Total IgA (tIgA)may be usedhowever it does not distinguish between monoclonal and polyclonal IgA.Here we assessnewly developed immunoassays measuring IgA κ /IgA λ (HLC, and their ratios (HLCr))to identify and quantify M-Ig in IgA MM and MGUS patients.

Methods

IgA HLCr was measured retrospectively in 220 patients (210 MM, 10 MGUS) at presentation.HLCr was considered abnormal if they were outside the published normal range (NR 0.8-2.04). Results were compared to historic SPEP and tIgA.

Results

220/220 patients had an abnormal HLCr at presentation (IgA κ median 409.26 (2.33-7353), IgA λ median 0.01 (0.0025-0.795).209/220 patients were positive by SPEP, however in 87/209 patients the M-Ig migrated in the β-region making quantification of M-Ig problematic. Finally 11/220 patients (7 MM, 4 MGUS) SPEP was negative (n=5) or not quantifiable (n=6). In 23/220 patients,tIgA concentrations were within the normal range, including 4 patients where SPE was negative.

Discussion

Co-migration of M-IgA with other serum proteins makes accurate quantification difficult, which during the course of a patient's disease can make response assessments inaccurate. Furthermore, in patients with <10g/L M-Ig the errors of quantitation are significant (>30%). IgA HLC analysis provides an alternative, sensitive method of identifying and quantifying M-Ig in patients irrespective of co-migration.

P-256

Comparison of the Polyclonal Antibody Based Freelite and Monoclonal Antibody Based N Latex Assays in Screening for Patients with Monoclonal Gammopathies

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Introduction: IMWG guidelines recommend SPEP and free light chain (FLC) measurements using polyclonal antibody based assays (Freelite) for screening for monoclonal gammopathies (MG). Recently a monoclonal antibody based assay (nlatex) has been developed. Here we compare the sensitivityof both assays for screening MG patients.

Methods: Serum from 390 patients (M/F:168/222, median age 65(19-100) sent for standard hematological investigation (SPEP+Freelite; Binding Site, UK). Samples were also analysed with the nlatex assay.

Results:279/390 patients were normal by all assays and in 102 patients MG was identified using standard methods. 36/102 patients (11 MM, 19 MGUS, 2 CLL, 2 lymphoma, 1 cryoglobulinemia, 1 plasmacytoma) were positive by both assays, in addition an abnormal Freelite ratio identified 3 MM patients (2 IgG κ, 1 IgA κ), 4 patients with hematological malignancies (2 WM, 1 CLL, 1 lymphoma) and 12 MGUS patients (8 IgG, 1 IgA, 2 IgM, 1 FLC). By contrastnlatex assay

did not identify any additional symptomatic patients and was abnormal in 4 MGUS (2 IgG, 1IgA, 1 IgM) patients missed by Freelite. FurthermoreiFLCmeasured by Freelite was greater than nlatex in 11 MM patients and enabled monitoring of 2/11 MM patients that nlatex was not able to monitor.

Conclusion:Studies have shown that SPEP and Freeliteis a sensitive algorithm for identifying MG. In this study a novel assay for the identification of FLC' s has poorer sensitivity than Freelite for both symptomatic and MGUS patients and further work is required to establish its utility in clinical practice.

Section D: Preclinical Strudies and New Drugs

P-257

NS-018 Suppresses Myeloma Cell Proliferation and Osteolysis by Inhibiting JAK2 and Src Signaling.

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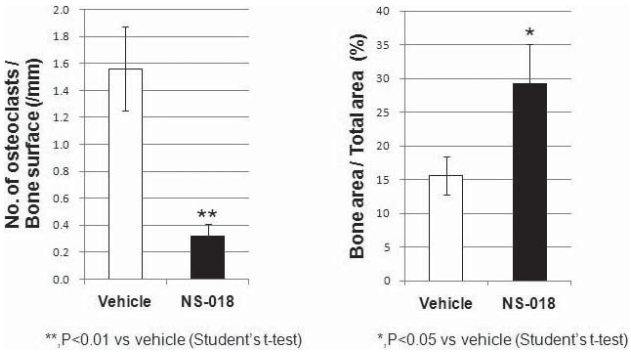
Autocrine and paracrine secretion of cytokines such as IL-6 and RANK ligand (RANKL) by myeloma cells and bone marrow stromal cells is believed to be involved in the pathology of multiple myeloma (MM). IL-6 is a major cytokine which supports the proliferation and survival of MM cells. JAK and STAT are important downstream molecules in the IL-6 signaling pathway, whereas RANKL promotes the differentiation of precursor cells into osteoclasts and thus induces osteolysis, which may lead to bone lesions, a major complication of MM. Src mediates signaling by the RANKL receptor and plays an important role in osteoclast formation. NS-018 is a potent dual JAK2 and Src kinase inhibitor under clinical development for myelofibrosis. NS-018 inhibits JAK2 and Src with IC50 <10 nM in in vitro kinase assays. A docking study of NS-018 into an X-ray crystallographic structure of Src kinase revealed that its mode of binding to JAK2 and Src kinases is very similar. In the present study, NS-018 inhibited IL-6-induced phosphorylation of STAT3 and IL-6-induced proliferation of myeloma cell lines in a dose-dependent manner. NS-018 suppressed RANKL-induced osteoclast formation in vitro through Src inhibition. Correspondingly, in a mouse model of intratibial transplantation of MM cells, NS-018 significantly decreased the number of osteoclasts, resulting in an increase in bone area (Figure). In conclusion, NS-018 inhibited IL-6-induced myeloma cell proliferation by blocking the JAK signaling pathway and suppressed osteoclast formation both in vitro and in vivo by blocking the Src signaling pathway.



**,P<0.01 vs vehicle (Student's t-test)

*,P<0.05 vs vehicle (Student's t-test)

P-258

Eradication of Clonogenic Myeloma Cells through ADCC by Defucosylated Anti-HM1.24 Monoclonal Antibody with Lenalidomide

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Multiple myeloma (MM) still remains incurable even in the era of novel agents. MM cancer stem cells have been postulated to be responsible for disease relapse; and a new treatment modality targeting clonogenic MM cells is urgently needed. Side population (SP) is considered to contain MM cancer stem cell-like cells. We demonstrated that a defucosylated humanized monoclonal anti-HM1.24 (YB-AHM) induced marked antibody-dependent cellular cytotoxicity (ADCC) against MM cells. Lenalidomide (Len) has drawn considerable attention to its augmentation of ADCC. In the present study, we therefore aimed to clarify the cytotoxic effects of YB-AHM with Len on clonogenic MM cells. HM1.24 was highly expressed on both SP and non-SP fractions in RPMI 8226 cells. YB-AHM and Len in combination significantly reduced the SP fraction of RPMI 8226 cells from 0.015% to 0.00182%. This combination treatment also inhibited the colony formation of RPMI 8226 cells [4 ± 5 vs 62 ± 2 (mean ± SD) colonies/well, p<0.01]. Notably, although SP fraction of MM cell lines and primary MM cells expressed pluripotency-associated transcription factors such as Sox2 and Nanog mRNA, these mRNA expression levels were decreased when treated with YB-AHM plus Len for 24 hours. These results demonstrate that defucosylated anti-HM1.24 has a potential to eradicate clonogenic myeloma cells in combination with Len, and suggest that this combination therapy might provide a novel therapeutic strategy targeting clonogenic drug-resistant MM cells.

P-259

Multiple Myeloma Precursor Disease and Curcumin.

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Introduction: Serum free light chain (sFLC) analysis is a valuable tool when monitoring response to chemotherapy in patients with light chain-secreting monoclonal gammopathies. Aim: We performed a randomised, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study to assess the effect of curcumin on FLC response and bone turnover in MGUS and SMM patients. Methods: 36 patients were randomised into two groups ie 4g curcumin or 4g placebo and then crossed over. At completion, all patients were given the option of entering the open-label, 8g extension study. Blood and urine were collected at specified intervals for specific marker analysis. FLC analysis was performed by immunonephelometry. Group values are expressed as the mean + 1 SEM. Data from different time intervals within groups was compared using paired student t-test. Results: 25 patients completed the 4g arm and 18 the 8g arm of the study. Curcumin therapy decreased the free light chain ratio , the difference between clonal and nonclonal light chain (which is recommended for serial evaluation of treatment) and the involved free light chain .uDPYD as a marker of bone resorption, decreased in the curcumin arm (5-22%) and then increased on placebo arm, however these responses did not reach significance. Serum creatinine levels decreased on curcumin therapy (P<0.05). Conclusion: The data suggest that curcumin may stabilize disease activity or potentially slow the disease process in MGUS and SMM patients. "No conflict of interest to disclose".

P-260

Curcumin Enhances the Cytotoxic and Chemo-sensitising Effects of Lenalidomide in Human Multiple Myeloma Cells.

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Background: About one third of patients with relapsed or refractory myeloma respond to thalidomide-containing treatment, and this response rate improves to 60% with a lenalidomide -containing regimen. Lenalidomide-containing therapy also has the added advantage of overcoming resistance to both conventional chemotherapy and to thalidomide. Studies have shown that curcumin can circumvent chemoresistance in vitro and potentiate the effect of thalidomide and bortezomib against human multiple myeloma in a nude mice model and in the U266 human multiple myeloma cell line. Methods: we designed an in-vitro study to investigate the cytotoxic and chemo-sensitising effects of curcumin alone and in combination with lenalidomide on the human myeloma H929 cell line. Results: Incubation of H929 cells with curcumin (30uM) or lenalidomide (2.5mM) for 3 days resulted in 26.35% (±1.06) and 30.81%(±2.98) apoptotic cells respectively. When 30uM curcumin was combined with 2.5mM lenalidomide, 50.4% (±3.37) apoptotic cells were detected by flow cytometry and the increase was significant compared to either curcumin alone or lenalidomide alone (anova p=0.0026). Furthermore, gene analysis studies show that curcumin enhances the cytotoxic effect of lenalidomide via suppression of the cereblon and multi-drug resistant genes. Conclusion: Curcumin can potentiate not only the cytotoxic effect of lenalidomide or thalidomide, but also enhance the chemo-sensitising effects of these agents resulting in clinical implications for the combined use of these agents.

P-261

Computer-aided Screening Identified a Novel STAT3 Inhibitor that Displays Potent Anti-myeloma Activity

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The STAT3 signaling pathway is frequently dysregulated in multiple myeloma (MM), and suppression of STAT3 activity could lead to MM cell apoptosis. To find novel agents that inhibit STAT3 activity and induce myeloma cell death, we performed a computer-aided screening out of 100,000 compounds. One compound called kifocitanib (KIF) was identified. Computer modeling analysis revealed that KIF was well docked into the STAT3 activity pocket and inhibited STAT3 activity. Subsequent studies revealed that KIF inhibited JAK2 and STAT3 activation in a time- and concentration-dependent manner. More importantly, KIF inhibited STAT3 activity in the presence of IL-6, a critical stimulator of the STAT3 signaling pathway. KIF also suppressed expression of STAT3 regulated genes, including Bcl-2, Mcl-1, VEGF, and D-cyclins. By interfering with the STAT3 signal transduction, KIF inhibited proliferation and induced apoptosis of MM cells at a low concentration which was minimally required to inhibit STAT3 activity. In a myeloma xenograft model, orally administrated KIF delayed MM tumor grow within 7 days at a dose of 30 mg/kg, significant decrease was observed within 2 weeks, but KIF presented minimal toxicity. In the analysis of the MM tumor species from mice models, KIF suppressed the expression of STAT3 and phospho-STAT3, accompanied by the decrease of cyclin D3, one of the targets of STAT3 signaling pathway. Therefore, via virtual screening, cell-based and animal studies, we identified a novel inhibitor of STAT3 signaling which displayed great potential for myeloma therapy.

P-262

Cathepsin K Inhibition Robustly Induces Bone Formation in Bone Lesions in Myeloma.

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Multiple myeloma (MM) enhances osteoclastogenesis while suppressing osteoblastogensis to develop devastating bone destruction. Although the recent improvement of anti-tumor efficacy by novel agents, bone regeneration in MM bone lesions still remains an unmet clinical issue. Unlike other anti-resorptive agents, cathepsin K inhibitors potently suppress bone resorption while sparing cytotoxic damage in osteoclasts (OCs). In the present study, we explored the effects of cathepsin K inhibition on bone destruction in MM. The ca-

thepsin K inhibitor KK1-300-01 (KK1) potently suppressed pit formation enhanced in the cocultures of rabbit bone cells with MM cells. However, KK1 did not affect osteoclastogenesis, and allowed OCs to facilitate in vitro mineralized nodule formation by MC3T3-E1 cells, suggesting the preservation of OC-driven osteoblastogenesis by KK1. We next examined the in vivo effects of KK1 using human INA6 MM-bearing SCID-rab models, which exhibit tumor progression with osteolytic lesions in implanted rabbit bones. Oral dosing of KK1 prevented bone destruction with marked increase in bone trabecular size and BMD in the rabbit bones and tumor reduction within their bone marrow cavity. Histological analyses showed increased bone volume/total volume with a marginal change in OC numbers in the treated mice. Besides inhibiting bone resorption with resultant reduction of the release from bone of anti-anabolic factors such as TGF-beta, cathepsin K inhibition is suggested to enhance bone formation by retaining OC-derived "coupling" for bone formation.

P-263

Anti-myeloma Activity of Bendamustine is Augmented in Acidic Conditions, but Considerably Varies among Myeloma Cells

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Myeloma (MM) cells and osteoclasts create a highly acidic milieu in MM bone lesions by proton produced by osteoclasts and lactate by MM cells. The acidic condition up-regulates the anti-apoptotic mediator Pim-2 in MM cells, which has been demonstrated to significantly contribute drug resistance in MM cells. Bendamustine, a purine analogue/alkylator hybrid agent, has shown clinical activity against various human cancers, including MM. However, the potential mechanisms of action of bendamustine remain largely unknown. In the present study, we therefore explored anti-MM activity by bendamustine in acidic conditions. Bendamustine dose-dependently induced cell death in INA6 and TSPC-1 cell lines from 12.5 microM, but not in RPMI8226, U266 and OPC cells even at 100 microM. Interestingly, bendamustine at 50 microM showed more potent cytotoxic effects on INA6 and TSPC-1 cells at pH6.0 than pH7.4; the acidic conditions was able to trigger bendamustine's cytotoxic effects on RPMI8226, U266 and OPC cells which are resistant to bendamustine at pH7.4. Similarly, the Pim inhibitor SMI-16a preferentially exerted anti-MM activity in acidic conditions; bendamustine and SMI-16a cooperatively enhanced anti-MM effects in RPMI8226 and U266 as well as INA-6 cells at pH6.0. Intriguingly, bendamustine reduced Pim-2 protein levels in MM cells at pH6.0. These results demonstrate that anti-MM effects of bendamustine are augmented in acidic conditions, but considerably vary among myeloma cells, and that Pim inhibition further enhances the bendamustine's anti-MM activity in acidic conditions.

P-264

The Anti-myeloma Activity of the rmhTRAIL and Its Synergism in Combination with 17-AAG

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Aims: To investigate the anti-myeloma activity of rmhTRAIL and its synergism in combination with 17-AAG. Methods: The proliferation inhibition of rmhTRAIL and 17-AAG to RPMI8266 and U266 cell lines was evaluated by MTT assay. The apoptosis, TRAIL receptors and mitochondrial membrane potential (MMP) were detected by flow cytometry. Immunochemistry was used to evaluate the expression of FLIP and XIAP in tumor cells of mouse xenograft model. Results: The proliferation of RPMI8226 could be inhibited by rmhTRAIL and 17-AAG, the half inhibition concentration (IC50) were 34.6 ± 1.1ng/ml and 1304.5 ± 53.4ng/ml respectively at 72 hour. U266 was sensitive to 17-AAG whose IC50 was 631.2 ± 14.9ng/ml at 72 hour, but resistant to rmhTRAIL. rmhTRAIL and 17-AAG had synargistic inhibiting effect on RPMI8226 cells, but not on U266 cells. RPMI8226 cells could be induced apoptosis by rmhTRAIL and 17-AAG, and combined rmhTRAIL and 17-AAG had synargistic effect. U266 cells could also be induced apoptosis by 17-AAG, but not rmhTRAIL, and they had also synargistic effect. MMP of RPMI8226 and U226 cells could be depressed by rmhTRAIL or 17-AAG ($P<0.05$). Combined rmhTRAIL and 17-AAG could not change expression levels of TRAIL receptors. rmhTRAIL (5mg/kg, d1-10) or 17-AAG (80mg/kg, d1-4) could inhibit proliferation of plasmacytoma and expression of FLIP and XIAP in plasmacytoma. Conclusion: rmhTRAIL provided potent anti-myeloma activity in vivo and in vitro, whereas U266 cells were resisitant to rmhTRAIL, and the two drugs had synargistic anti-myeloma activity.

P-265

Bortezomib Overcomes the Cell Adhesion-mediated Drug Resistance by Down-regulating HDAC Expression in Multiple Myeloma

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Multiple myeloma is notorious for the resistance to conventional chemotherapy, which can reduce tumor burden but fails to impact on the clinical course and overall survival of myeloma patients. High-dose chemotherapy with autologous stem cell transplantation considerably improves the treatment outcome; however, cure is still rare in patients with myeloma. To improve the prognosis of myeloma patients, it is essential to develop the modalities overcoming drug resistance by clarifying its underlying mechanisms. We have been studying the mechanisms of drug resistance in multiple myeloma, and found that VLA-4 (a heterodimer of CD49d and CD29) is implicated in cell adhesion-mediated drug resistance in myeloma cells and histone deacetylases (HDACs), which are overexpressed in putative myeloma stem cell fractions, induce innate resistance to DNA-damaging agents via chromatin compaction. Our investigations have also revealed that novel agents are able to overcome drug resistance in multiple myeloma. For instance, bortezomib can overcome cell adhesion-mediated drug resistance by suppressing the expression of the CD49d subunit of VLA-4. Furthermore, HDAC inhibitors could sensitize myeloma cells to bortezomib and conventional anti-cancer drugs not only in the in vitro culture system but also in murine xenograft models. These results strongly suggest that the introduction of novel agents with unique mechanisms of action, such as bortezomib and HDAC inhibitors, may change the paradigm of myeloma treatment.

P-266

A Novel Screening Tool Identified CD317/HM1.24 as a Potent Target for Immunotoxin-based Treatment of Multiple Myeloma

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Targeted immunotherapy, based on antibodies against tumor-associated antigens, is a promising approach for the treatment of multiple myeloma (MM). To enable the identification of antibody candidates suitable for the development of Pseudomonas exotoxin A (ETA)-based immunotoxins, we established a novel screening tool. Two fusion proteins that consist of a truncated ETA version (ETA') and either a human kappa light chain (α -kappa-ETA')- or a multi species Fc-specific (α -Fc-ETA') domain antibody allow the selective and efficient screening of multiple antibodies. The α -kappa-ETA' binds to human/chimeric antibodies or Fab fragments, while the α -Fc-ETA' recognizes murine antibodies. Due to the formation of non-covalently linked antibody-immunotoxin complexes, no individual recombinant immunotoxins need to be produced. We evaluated a panel of antibodies against MM-associated antigens for their ability to mediate antigen-dependent, ETA' -induced cytotoxicity against human myeloma cell lines. The CD38, CS1, IL-6R and CD138 antibodies tested turned out to be ineligible, whereas only a CD317/HM1.24 antibody specifically inhibited the proliferation of all antigen-positive MM cell lines used at low nanomolar ETA' and antibody concentrations. The subsequently designed HM1.24-ETA' immunotoxin proved to be highly toxic against freshly isolated primary patient cells and prevented plasmacytoma formation in the INA-6 xenograft model. Thus, with the novel screening tool, we identified CD317/HM1.24 as a promising target for efficient ETA'-based immunotherapy for the treatment of MM.

P-267

Survivin Selective Inhibitor YM155 Induces Apoptosis and Suppresses Proliferation in Multiple Myeloma Cells

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Survivin is a member of the inhibitor of apoptosis protein (IAP) family with its dual roles in mitosis and apoptosis, and emerges as an attractive target for cancer therapy. YM155, a novel molecular targeted agent, suppresses survivin, which is overexpressed in many tumor types. However, the effect of this agent on multiple myeloma (MM) cells remains unclear. In this study, we investigated the effects of YM155 on proliferation and survival of MM cell lines, U266 and RPMI8226. YM155 inhibited cell proliferation of these cells in a dose-dependent manner. Annexin V assay demonstrated that YM155 induced apoptosis in these cells. Immunoblot analysis showed that YM155 reduced Akt protein level in these cells. We also observed the activation of caspase-3 in YM155-treated cells, indicating that YM155 induces caspase-dependent apoptosis. Furthermore, YM155 inhibited the expression of X-linked inhibitor of apoptosis (XIAP) and Mcl-1. Interestingly, YM155 suppressed a mitotic arrest deficiency-2 (Mad2), which is one

of the spindle assembly checkpoint proteins, suggesting the possibility that YM155 induces a mitotic failure. And YM155 treatment resulted in inhibition of interferon regulatory factor-4 (IRF4) expression, which is known as Achilles heel of MM cells. Taken together, YM155 induces apoptosis and inhibits proliferation in MM cells via not only inhibiting survivin but also the other molecular mechanisms. Further study is needed to clarify the molecular mechanism of apoptosis induced by YM155 in MM cells. Our results may provide a platform for clinical trials of YM155 in MM.

P-268

Targeting CRM1 by SINEs Block Multiple Myeloma Cell Growth, Osteoclastogenesis, and Myeloma-induced Osteolysis

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The key nuclear export protein CRM1 may directly contribute to the pathophysiology of human multiple myeloma (MM). Here, we characterized the biological role of CRM1 in MM and defined molecular mechanisms whereby novel oral, irreversible, selective inhibitors of nuclear export (SINEs) targeting CRM1 mediate anti-MM activity in the bone marrow microenvironment. CRM1 is highly expressed in MM cells and plasma cell leukemia. CRM1 shRNA knockdown decreases viability of MM cells. Specifically, SINEs blocked proliferation and survival of multiple MM cell lines and patient MM cells (LD50 < 200 nM), cultured alone or with bone marrow stromal cells (BMSCs) or osteoclasts. SINEs triggered nuclear accumulation of CRM1 cargo tumor suppressor proteins (p53, IκB, FOXO1A, FOXO3A, p27, PP2A) and induce growth arrest and apoptosis, as well as inhibit c-myc and NFκB activity. KPT-185 also induces proteasome-dependent downregulation of CRM1 protein; concurrently, they upregulate transcripts of CRM1, p53-targeted, apoptosis-related, anti-inflammatory, and stress-related genes. In SCID mice with diffuse human MM bone lesions, SINEs (KPT-251, KPT-276) suppress growth and induce apoptosis of MM cells, inhibit MM cell-induced osteolysis, and prolong survival. Moreover, KPT-185 and KPT-330directly impair osteoclastogenesis and bone resorption via blockade of RANKL-induced NFκB and NFATc1, without impacting osteoblasts and BMSCs. Together, these results confirm CRM1 as a promising novel target in MM, and strongly support the ongoing clinical development of KPT-330 to improve patient outcome.

P-269

Nelfinavir Triggers Proteotoxic Stress and is Active in Bortezomib-refractory Myeloma Patients: SAKK 65/08 Phase I Trial

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The HIV protease inhibitor nelfinavir has anti-myeloma activity in mice via proteotoxic stress through HSP90- and proteasome inhibition. We have performed a phase I trial of oral nelfinavir in combination with bortezomib in patients with hematologic malignancies (SAKK 65/08, ASH 2012). We here report the effects of nelfinavir single agent on biomarkers of proteotoxic stress, and its preliminary activity in combination with bortezomib in bortezomib-refractory multiple myeloma (MM) patients. We investigated the effect of nelfinavir single agent (3 dose levels: 1250, 1875, 2500 mg bid) on protein expression of the chaperones PDI (Protein disulfide isomerase), BIP (Binding immunoglobulin protein), CHOP (C/EBP homologous protein) and PARP (Poly -ADP-ribose polymerase) in peripheral blood mononuclear cells (PBMC) as indicators of proteotoxic stress-induced apoptosis in 12 patients with hematologic malignancies (including 8 MM). PDI and BIP increased by 87% and 74% (p=0.02 and 0.008), CHOP and PARP by 56% and 57 % (p=0.008 and 0.04). Nelfinavir therapy inhibited proteasome activity (mean inhibition 14.9% of total activity, p=0.005, all compared to baseline). Seven MM patients with bortezomib-refractory myeloma after lenalidomide failure were treated with nelfinavir (2500 mg bid) in combination with standard dose bortezomib. Four patients achieved a PR (IMWG criteria), including 2 patients progressing under bortezomib immediately before bortezomib/nelfinavir. Nelfinavir induces proteotoxic stress in vivo and is active in combination with bortezomib in bortezomib-refractory MM.

P-270

A Multiepitope Cocktail of XBP1, CD138 and CS1 Induces Myeloma-specific CTL in T Cells from Smoldering Myeloma Patients

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The purpose of these studies was to evaluate a cocktail of HLA-A2 peptides, heteroclitic XBP1 $US_{184-192}$, heteroclitic XBP1 $SP_{367-375}$, native $CD138_{260-268}$ and native $CS1_{239-247}$, in vitro for their ability to elicit multipeptide-specific cytotoxic T lymphocytes (MP-CTL) from smoldering multiple myeloma (SMM) patients' T cells. Our results demonstrate that MP-CTL induce effective anti-MM responses including CD137 (4-1BB) upregulation, T cell proliferation, IFN-γ production and degranulation in a peptide-specific and HLA-A2-restricted manner. Phenotypically, we observed an increase in the total $CD3^+CD8^+$ T cell population (>90%) and a high level of cellular activation ($CD69^+$) within the memory CTL ($CD45RO^+/CD3^+CD8^+$) subset in response to $HLA\text{-}A2^+$ MM cells. Interestingly, SMM patients could be categorized into 2 distinct groups, high and low responders, by their level of MP-CTL expansion. In high responders, the effector memory ($CCR7^-$ $CD45RO^+$) CTL subset was enriched while low responders contained a higher frequency of the terminal effector ($CCR7^-$ $CD45RO^-$) CTL subset. In addition, higher levels of anti-MM activity were detected from high responders' MP-CTL as compared to low responders' MP-CTL upon recognition of $HLA\text{-}A2^+$ MM cells. In conclusion, these results suggest that a multipeptide vaccine has the potential to induce effective and durable memory CTL in SMM patients and provides the framework for targeting the XBP1, CD138 and CS1 antigens in clinical vaccine trials for SMM patients to delay or prevent progression to active MM.

P-271

Identification of HLA-A24-specific Immunogenic XBP1, CD138 and CS1 Epitopes against Multiple Myeloma

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The purpose of these studies was to identify immunogenic epitopes specific to HLA-A24, the most prevalent MHC class I allele in Asian countries and the second most in North America, as an immunotherapeutic strategy to target antigens associated with multiple myeloma (MM) pathogenesis. The full length amino acid sequences from XBP1 unspliced (US), XBP1 spliced (SP), CD138 or CS1 protein were analyzed by multiple search software programs to predict HLA-A24 epitopes with high binding stability, extended half-time disassociation rates, proteasomal C terminal cleavage and TAP transport. A total of 25 peptides were synthesized and screened at various concentrations (12.5 μ/ml - 1 mg/ml) and the peptides having the highest HLA-A24 affinities were selected for generation of specific cytotoxic T lymphocytes (CTL). The respective peptide-specific CTL demonstrated HLA-A24 restricted anti-MM responses including $CD8^+$ T cell proliferation, cytokine (IL-2 and IFN-γ) production and degranulation (CD107a upregulation) against $HLA\text{-}A24^+$ KMS11 but not $HLA\text{-}A24^-$ OPM1 or U266 MM cell lines. The anti-MM responses by the respective CTL were detected exclusively in $CD3^+CD8^+$ T cells which was the predominant (>90%) cell population following CTL generation with each of the peptides. In conclusion, we report novel immunogenic HLA-A24-specific XBP1 unspliced, XBP1 spliced, CD138 and CS1 peptides that elicit anti-MM responses and have the potential to broaden immunotherapeutic approaches beyond HLA-A2-specific peptides to treat the patients with MM or its pre-malignant diseases.

P-272

Restoration of Drug Sensitivity by Pim Inhibition in BCRP-expressing Drug-resistant Myeloma Cells

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Bone marrow microenvironment in acidic bone lesions in myeloma (MM) confers drug resistance in MM cells. We have demonstrated that Pim-2 kinase is up-regulated in myeloma (MM) cells in bone lesions as a critical anti-apoptotic mediator. Here, we explored the role of Pim-2 in drug resistance in MM cells and the therapeutic impact of Pim inhibition on ABC transporter-expressing MM cells. Pim-2 expression in MM cells was up-regulated in cocultures with bone marrow stromal cells (BMSCs) or in media acidified by lactic acid or HCl. The retention of auto-fluorescence emitting mitoxantrone and doxorubicin, substrates of the ABC transporter

BCRP, in BCRP-expressing RPMI8226 and U266 cells was reduced further in cocultures with BMSCs and/or in acidic media as determined in flow cytometry. However, the Pim inhibitor SMI-16a at 50 microM substantially restored the intracellular levels of these drugs; the intracellular retention of these drugs by the Pim inhibition was more prominent in cocultures with BMSCs in acidic conditions. "Side population (SP)" is regarded as a highly drug-resistant fraction with enhanced BCRP activity. Interestingly, the Pim inhibitor SMI-16a minimized SP fractions in RPMI8226 and KMS11 cells; the reduction of SP fractions by the Pim inhibition was also more marked in acidic conditions. Importantly, the Pim inhibition restored drug sensitivity in MM cells to doxorubicin in acidic conditions. These results suggest that Pim-2 may become an important therapeutic target of MM cells which preferentially gain drug resistance in acidic bone lesions.

P-273

Zoledronate-activated γδ T Cell-based Immunotherapy for Patients with Multiple Myeloma and MGUS.

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Introduction and Aims: To evaluate the potential antitumor activity of zoledronate-activated γδ T cells in vivo, we reported a study involving administration of zoledronate-activated γδ T LAK cells to patients with multiple myeloma (MM) (Exp Hematol. 2009;37:956), and initiated a new study with monoclonal gammopathy of undetermined significance (MGUS). Methods: Six patients with MM and four with MGUS received four intravenous infusions, at two week intervals, of γδ T LAK cells generated from culture of peripheral blood mononuclear cells (PBMCs) in the presence of zoledronate and IL-2. If serum M protein in a patient with MM or free light chain (FLC) with MGUS remained or decreased from base line levels following four intravenous infusions, the patient had further four treatments at two or four week intervals. Results: No serious treatment related adverse events were observed during the study period. The percentage of V γ9 γδ T cells in PBMCs and absolute numbers of V γ9 γδ T cell in PB, in particular those of CD45RA-CD27- effector memory (TEM) V γ9 γδ T cell subsets increased in all of the patients with MM. Serum M protein remained base line levels in four of six patients and increase in two of six patients with MM. Serum FLC had a tendency to decrease slightly in two patients with MGUS, and this study is underway in other two patients. Conclusion: Administration of zoledronate-activated γδ T LAK cells could be a promising immunotherapy approach in the treatment of patients with MM and MGUS.

P-274

Anti-myeloma Activities of TAS-117, a Novel Selective Akt Inhibitor, in Combination with Bortezomib or Carfilzomib

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The PI3K/Akt pathway plays a crucial role in growth of multiple myeloma (MM) cells in the bone marrow (BM) milieu. We have previously shown that bortezomib activates Akt, and that inhibition by perifosine enhances bortezomib-induced cytotoxicity, which has already translated to phase III clinical trials. In this study, we examined anti-MM activities of a novel potent and selective Akt inhibitor TAS-117 in combination with proteasome inhibitors (bortezomib and carfilzomib). TAS-117 blocked phopho-Akt induced by bortezomib or carfilzomib in MM.1S cells, associated with enhanced cytotoxicity via apoptosis, even in the presence of BM stromal cells. Interestingly, TAS-117 alone induces endoplasmic reticulum (ER) stress, evidenced by induction of phospho-eIF2 α, phospho-IRE1 α and BiP/GRP78. Moreover, TAS-117 in combination with bortezomib or carfilzomib significantly enhanced CHOP expression, a marker of fatal ER stress, followed by PARP cleavage. These results suggest that TAS-117 enhances cytotoxicity of these agents, at least in part, via enhanced ER stress-induced apoptosis. Finally, we examined anti-MM activities of TAS-117 with bortezomib in a human MM cell murine xenograft model. Specifically, oral administration of TAS-117 in combination with subcutaneous bortezomib administration significantly inhibited MM.1S plasmacytoma growth. Taken together, TAS-117 in combination with bortezomib or carfilzomib blocks MM cell growth in vitro and in vivo, providing the preclinical framework for clinical evaluation of combination treatment to improve patient outcome in MM.

P-275

PAT-SM6, a GRP78 Binding Monoclonal IgM Antibody with Anti-myeloma Activity - a Translational Approach

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Monoclonal antibodies have entered the therapy of multiple myeloma (MM) and are currently being evaluated in phase I-III trials. The heat shock protein family member GRP 78/BIP of the Hsp70 complex is highly expressed in MM and can be targeted by the human monoclonal IgM PAT-SM6. The antibody' s pentameric structure allows the interaction with multiple GRP78 molecules clustered on the cell surface of transformed cells resulting in an antibody-target-cell-complex with high avidity. PAT-SM6 reacts with a broad spectrum of MM cell lines as well as with patient derived primary myeloma cells. In an immunohistochemistry-based survey with bone marrow biopsies of 20 MM patients PAT-SM6 displayed a homogenous binding profile with 80-100% (mean 92%) positive myeloma cells. Binding was demonstrated in de novo MM as well as in multiple relapses, indicating that the target structure is stably expressed in myeloma throughout disease progression and lacks binding on other tissues including healthy plasma cells. Moreover, antibody treatment of both MM cell lines and primary MM cells caused significant cell death (range 74.3 - 33%) and further analysis revealed the induction of apoptosis as main mode of action. Based on these results a phase I dose escalating study in patients with relapsed multiple myeloma (NCT01727778) is initiated. Preliminary results from the first dose cohort (0.3mg/KG, n=3) show an excellent tolerability and changes within the immune compartment of the patients. In summary, PAT-SM6 provides a promising approach for immune therapy of multiple myeloma.

P-276

Targeting Metabolic Plasticity of Myeloma with FDA Approved Ritonavir and Metformin.

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Multiple Myeloma (MM) exhibits aerobic glycolysis and the Warburg effect. We previously demonstrated that inhibition of GLUT4-mediated glucose transport in MM elicits either apoptosis (sensitive) or growth arrest (resistant) phenotypes. We also demonstrated the pre-clinical utility of targeting GLUT4 for MM using a HIV protease inhibitor ritonavir that has an off-target inhibitory effect on GLUT4. We hypothesize that cells resistant to GLUT4 inhibition/glucose deprivation revert to mitochondrial metabolism and/or autophagy to prevent cell death. Treatments with autophagy inhibitor chloroquine or fatty acid oxidation inhibitor etomoxir ruled out autophagy and fatty acid oxidation as sources of compensatory metabolites. We discovered that mitochondrial substrates 2-methyl pyruvate or galactose rescue sensitive cells from glucose-deprivation elicited toxicity suggesting that cells "resistant" to glucose-deprivation engage in compensatory mitochondrial metabolism to maintain viability. In support of this hypothesis glucose-deprived or ritonavir treated "resistant" cells are "sensitized" to exhibit apoptosis upon co-treatment with metformin that targets mitochondrial complex 1 activity. The synergistic elicitation of toxicity with ritonavir and metformin was also observed in additional MM cell lines and was effective in the context of resistance promoting stromal micro-environments, with no effect on normal PBMC. Ritonavir/metformin combination is well tolerated in diabetic HIV patients suggesting that this regimen could be repurposed for treatment of MM.

P-277

Expression of a CD138-specific Chimeric Antigen Receptor Enhances Cytotoxic Activity of NK Cells in Multiple Myeloma

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The adoptive immunotherapy targeting CD138 could potentially represent a new strategy for multiple myeloma (MM). In this study, we generated genetically modified NK -92MI carrying a chimeric antigen receptor that consists of a CD138-specific scFv antibody fragment (NK-92MI-SCFV), via a flexible hinge region connected to the CD3 ζ chain as a signaling moiety. While activity of the retargeted NK-92MI-SCFV against CD138-negative targets(K562, ARH-77) remained unchanged, the gene modified NK-92MI-SCFV displayed markedly enhanced cytotoxicity toward CD138 highly expressing MM cell lines and primary MM cells even

at low effector-to-target(E:T) ratios, as determined by LDH-release and flow cytometric apoptotic detection. In CD138 highly expressing human MM cell lines (U266, RPMI8226, NCI-H929, LP-1) and 5 primary MM cells, the cytotoxicity of NK-92MI-SCFV were increased by 27-273%, 53-212% and 33-222% at E:T ratio of 1:1, 5:1 and 10:1 respectively, compared with parental NK-92MI($P<0.01$). Correspondingly, the significantly increased secretion of granuzyme and γ -interferon by NK-92MI-SCFV in response to CD138 expressing MM cells were also demonstrated by ELISA, which increased to 1.7-2.3 times and 2.5 -34 times of those produced by parental NK-92MI at E:T ratio of 10:1, respectively ($P<0.001$). Importantly, NK-92MI-SCFV much more potently inhibited MM tumor growth in vivo and prolonged host survival in the xenograft NOD-SCID mouse models of human MM, than parental NK-92MI. This study provides the rationale for adoptive immunotherapy of CD138-SCFV-modified NK cell line in myeloma.

P-278

A Homopiperazine Derivative K-7174 is an Orally Active Proteasome Inhibitor with a Novel Mode of Proteasome Binding

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[Introduction] The proteasome inhibitor (PI) bortezomib is now widely used for the treatment of multiple myeloma (MM), and its clinical efficacy has been proven. This suggests that bortezomib is indispensable for the treatment of MM. However, the prolonged treatment is associated with toxicities, drug resistance, and patient inconvenience due to intravenous administration. Therefore, a novel orally active PI distinct from bortezomib is demanded. [Results] In this study, we found that K-7174, a homopiperazine-derived small molecular compound, (1) induced marked accumulation of ubiquitinated proteins in MM cell lines, (2) inhibited the activity of three proteasome subunits in purified 20S proteasome and MM cell lines, and (3) induces cytotoxicity in both MM cell lines and primary MM cells. (4) Intraperitoneal and oral administration of K-7174 significantly inhibited tumor growth in NOD/SCID mice transplanted with MM cells. (5) K-7174 kills bortezomib-resistant MM cells carrying a β5 mutation and primary cells from a patient resistant to bortezomib. (6) X-ray crystallographic studies revealed that K-7174 directly binds to 20S proteasome with a distinct binding mode from bortezomib. [Conclusion] These results provide evidence for the utility of this compound as a novel orally active PI, which is distinct from not only bortezomib but also other PIs in its chemical structure and effects on proteasome activities.

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Inhibitory Kir and NKG2A Modulate NK Cell Anti- myeloma Responses at Atmospheric and Hypoxic Oxygen Levels

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Multiple Myeloma (MM) is an incurable disease, caused by malignant plasma cells residing in the frequently hypoxic bone marrow. Immunotherapy with allogeneic NK cells offers new therapeutic perspectives but clinical efficiency should be improved. Based on inhibitory receptor expression various human NK cell subsets can be distinguished. Here, we addressed which subset mediates the most effective anti-MM response. We simultaneously analyzed inhibitory receptors (KIR2DL1, -2DL2/3, -3DL1 and NKG2A) and NK cell degranulation (CD107a) upon co-culture with a panel of MM cell lines characterized for HLA-ABC/E. This revealed that KIR-HLA interaction inhibits NK cell degranulation. The most potent anti-MM response was mediated by NK cell subsets exclusively expressing KIRs specific for the HLA molecules not expressed by the MM cells. This phenomenon was even more clear under clinically relevant conditions, where we targeted hypoxic (0.6% oxygen) MM cells with IL-2 activated NK cells. NKG2A+ NK cells vigorously degranulated in response to HLA-E negative MM cells but this was completely inhibited when HLA-E was expressed by the MM cells. The latter observation is of high clinical importance as we also show that primary MM cells (n=6) express high levels of HLA-E. Together, this demonstrates that NKG2A negative, KIR-HLA mismatched NK cells represent the most potent effector subset for clinical application in MM patients. We developed a method to expand this subset from peripheral blood and we envision that infusion of high numbers of these NK cells will enhance clinical efficiency.

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Hypoxia Induced Impairment of NK Cell Killing against MM can be Overcome by IL-2 Activation of NK Cells

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We aim to develop allogeneic Natural Killer (NK) cell immunotherapy for Myeloma. As myeloma cells are present in hypoxic regions and the tumor environment can be immunosuppressive, we hypothesized that hypoxia inhibits NK cell anti-MM responses. NK cells were isolated from healthy donors by negative selection and NK cell function and phenotype were examined at oxygen levels representative of the BM using flowcytometry. Additionally, NK cells were activated with IL-2 to enhance NK cell cytotoxicity under hypoxia. Hypoxia reduced NK cell killing of MM cell lines in an oxygen dependent manner. NK cell degranulation was not influenced by hypoxia indicating that NK cells had been activated. Adaptation of NK- or MM cells to hypoxia was not required, hence, the oxygen level during the killing process was critical. Hypoxia did not alter surface expression of NK cell ligands (HLA-ABC, -E, MICA/B and ULBP1-2) and receptors (KIR, NKG2A/C, DNAM-1, NCRs and 2B4). It did, however, decrease expression of the activating NKG2D receptor. Pre-activation of NK cells by IL-2 abrogated the detrimental effects of hypoxia and increased NKG2D expression. This emphasized that activated NK cells can mediate anti-MM effects, even under hypoxic conditions. Hypoxia abolishes killing potential of natural killer cell against multiple myeloma, which can be restored by IL-2 activation. Our study shows that for the design of NK cell-based immunotherapy it is necessary to study biological interactions between NK- and tumor cells also under hypoxic conditions.

P-281

HDACi and IMiDs Enhance Anti-myeloma Activity of the Anti-KMA Monoclonal Antibody MDX-1097

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MDX-1097 is a monoclonal antibody being assessed as a single agent in a Phase II clinical trial for the treatment of κ-type multiple myeloma (κ MM). MDX-1097 binds kappa myeloma antigen (KMA), a tumor specific antigen, and exerts its anti-tumour effects through multiple mechanisms including antibody-dependent cell cytotoxicity (ADCC). We investigated whether MDX-1097 could be combined with established or novel anti-MM therapeutic agents to improve the treatment of κ MM. Treatment of human κ MM cell lines (κ HMCLs) with immunomodulatory drugs (IMiDs) or histone deacetylase inhibitors (HDACi) significantly increased cell surface expression of KMA. These IMiD or HDACi-treated κ HMCLs, when spiked with MDX-1097, were more susceptible to ADCC-mediated cell death in the presence of peripheral blood mononuclear cells (PBMCs) compared to untreated κ HMCLs. The increase in KMA expression presumably allows more binding of MDX-1097, which in turn recruits more PB immune effector cells to κ HMCLs and thereby increases ADCC. PBMCs treated in vitro with IMiDs were more potent at inducing ADCC against MDX-1097 spiked κ HMCLs. Similarly, in vivo lenalidomide exposed PBMCs isolated from MM patients were more effective in killing MDX-1097 spiked κ HMCLs compared to PBMCs obtained from the same patients prior to treatment. Finally, combining IMiD-treated PBMCs with IMiD-treated, MDX-1097 spiked κ HMCLs resulted in a further increment in ADCC. This data provides a rationale for the clinical evaluation of a combination therapy involving IMiDs or HDACi and MDX-1097 for the treatment of κ MM.

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Targeting JAK1/2 with Ruxolitinib Blocks IL-6 Induced Plasma Cell Growth and Overcomes Resistance to Dexamethasone

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Malignant plasma cell growth and survival is regulated by cytokines in the tumor environment. Interleukin(IL)-6 plays a key role by activating important signalling pathways through its gp130 receptor associated Janus kinases (JAK). Ruxolitinib (INC424/INCB018424; Novartis/Incyte) is the first JAK inhibitor approved for patients with myelofibrosis and is selective for JAK1 and JAK2. Among human plasma cell lines, ruxolitinib showed a strong cytotoxic activity on the IL-6 dependent INA-6 line (IC50 0.23 μM), even in the presence of stromal cells. Stromal cell viability and IL-6 production were not affected. Consistent with the inhibition of IL-6 induced STAT3 phosphorylation, apoptosis was in-

duced, resulting in 39% and 63% annexin V-positive cells in the presence of 1 μM ruxolitinib after 48 or 72 hours, respectively. Significant growth inhibition was achieved in tumor cells from a patient with plasma cell leukemia that were stimulated with IL-6 (IC50 0.16 μM). Combining ruxolitinib with PI3K and mToR inhibitors resulted in enhanced activity. In dexamethasone-sensitive cells, IL-6 mediated drug resistance was reversed by ruxolitinib. In conclusion, ruxolitinib has strong direct cytotoxic activity against malignant plasma cells that are dependent on JAK/STAT pathway activation. For a disease with such a heterogeneous molecular pathology, it may be rationale to combine a JAK/STAT inhibitor with inhibitors of complementary pathways. Thus, ruxolitinib, as a generally well tolerated drug, may offer a potential new therapeutic option for patients with multiple myeloma.

P-283

Combination Treatment with ICAM-1 Antibody BI-505 and Lenalidomide or Bortezomib has Potent Antimyeloma Activity in Vivo

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The n-CoDeR derived fully human high affinity IgG1 antibody BI-505, specific for ICAM-1 has demonstrated single agent in vivo anti-myeloma activity in numerous well-established myeloma disease models. The BI-505 epitope is highly expressed on myeloma cells in patients and BI-505 is presently being evaluated in a phase I study in patients with relapsed or refractory multiple myeloma. We here demonstrate significantly enhanced in vivo anti-myeloma efficacy when bortezomib (Velcade) or lenalidomide (Revlimid) is combined with BI-505 compared to single agent treatment. Combined treatment was evaluated in a clinically relevant disseminated multiple myeloma model comprising U266 myeloma cells grafted to nod/scid IL-2R γ-/- mice. Treatment was initiated when disease was established and the treatment protocol was designed to reflect clinical aspects with respect to drug doses, dosing frequency and administration route. Mouse survival was significantly enhanced when treatment with bortezomib or lenalidomide was combined with BI-505. We additionally demonstrate enhanced anti-myeloma activity in a well-established subcutaneous RPMI-8226 xenograft model, where combined treatment with bortezomib and BI-505 or lenalidomide and BI-505 resulted in complete remission of established tumors in the majority of mice. Collectively, our data demonstrate in vivo proof-of-concept for enhanced anti-myeloma activity when BI-505 is added on to bortezomib or lenalidomide treatment, providing a rationale for future clinical assessment of combination therapies with BI-505.

P-284

Targeting Heat Shock Proteins for Immunotherapy of Multiple Myeloma Induces Potent Antitumor Immunity

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Background: Heat shock proteins (Hsps), which is overexpressed in almost all patients with multiple myeloma (MM), is of great importance to the survival of MM cells since it plays an important role in preventing MM cells from apoptosis, inducing resistance to chemotherapy, and might be an ideal target for the MM immunotherapy. Methods: We identified and synthesized Hsps peptides for human leukocyte antigen (HLA)A*0201positive (HLA-A*0201+) and confirmed their immunogenicity by transgenic HLA-A*0201+ mice and further examine the function of T cells induced by selected peptides in vitro and in vivo. Results: We detected, using peptide specific tetramers, low frequencies ranging from 0.8% to 1.2% of Hsps peptide-specific CD8-positive (CD8+) T cells in patients with myeloma, and generated peptide-specific T-cell lines from HLA-A*0201-positive blood donors and patients with myeloma. These T cells efficiently lysed peptide pulsed but not unpulsed T2 or autologous dendritic cells, HSP-positive /HLA-A*0201+ myeloma cell lines U266, ARH-77, and HLA-A*0201+primary myeloma cells from patients. No obvious killing was observed on HSP -positive /HLA-A*0201-negative (HLA-A*0201-) myeloma cell lines and primary myeloma cells or HLA-A*0201- normal lymphocytes, including PBMC cells. More importantly, these T cells could eradicated the myeloma in vivo effectively. Conclusions: T cells induced by HSP peptide are potent cytotoxic T cells against myeloma cells in the context of HLA-A*0201 molecules. Hence, HSP might be a potentially important antigen for immunotherapy in MM.

P-285

Development of an Automated Microfluidic FISH Platform for Point-of-care Risk Stratification of Multiple Myeloma

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Chromosomal analysis is a critically important diagnostic tool for disease stratification and treatment decisions, but fluorescence in situ hybridization (FISH) is not available in many centers due to cost and complexity. With these limitations in mind, we have developed a novel robotic FISH platform that incorporates lab-on-a-chip technology and machine intelligence to "call" the results for FISH staining of bone marrow cells localized in a microfluidic channel. The use of a multi-channel microfluidic chip allows simultaneous independent testing with 10 different probe sets or samples at a cost lower than that for a single conventional FISH test. Machine learning and pattern analysis software enhance the automation of this FISH-on-a-Chip platform by making it possible to intelligently set thresholds and evaluate each test in the context of the probe approach being used, the presence of controls, regional population differences, and end-user preferences. Our approach also enables the calling of FISH results even with low-resolution images, minimizing computational requirements and greatly reducing the overall cost and size of the imaging system. Collectively, these physical and computational improvements will increase the level of automation during screening while reducing the cost-per-test. The result is a viable approach for near point-of-care diagnostics. This platform will make FISH more widely accessible as a standardized screening strategy for multiple myeloma, performed at near point of care, with results in less than 24 hours.

P-286

Detection and Quantification of Cereblon Protein and mRNA in Primary CD138+ Multiple Myeloma Cells and Cell Lines

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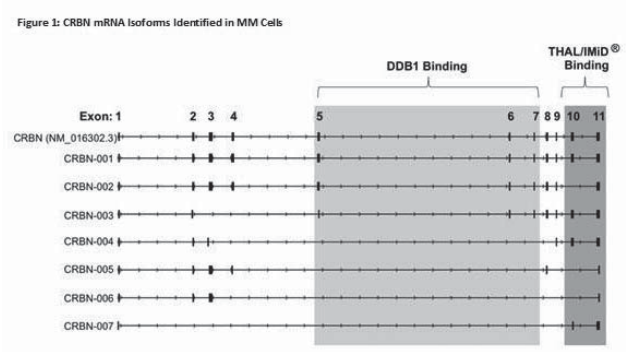
Background: Cereblon (CRBN), a component of the E3 Ubiquitin Cullin 4 Ring Ligase (CRL4) complex, has been identified as a target of the immunomodulatory agents thalidomide, lenalidomide, and pomalidomide. CRBN binding by these agents mediates their anti-proliferative effects in multiple myeloma (MM) cells. However, the role of CRBN quantification as a marker for disease responsiveness or resistance to these drugs remains to be fully defined.

Methods: CRBN isoform mapping was undertaken using a nested PCR approach and Sanger sequencing. Cereblon immunohistochemistry (IHC) was performed on the Leica Bond-Max system.

Results: Our data show that we developed and characterized a monoclonal antibody CRBN65 that is highly specific and sensitive by both western analysis and IHC as shown by the use of blocking peptide. CRBN65 is compared to 7 commonly used commercial CRBN antibodies and has superior specificity. Therefore CRBN65 antibody should be used as a gold standard in detecting CRBN protein. CRBN mRNA is measured using standard Taqman probes and there is no correlation between CRBN mRNA and protein levels in MM cell lines. Furthermore, identification of novel multiple CRBN splice variants indicate canonical and non-canonical alternative splicing events which add further complexity to measurement and detection of CRBN gene expression.

Conclusion: Taken together, our data emphasize the importance for developing standardized reagents and assays for both mRNA and protein level measurement of CRBN before using them as markers for clinical response or resistance.



P-287

CC-122: A Pleiotropic Pathway Modifier with Immunomodulatory, Antiangiogenic & Anticancer Activity in Multiple Myeloma

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Background: Thalidomide (THAL) and its analog immunomodulatory agents lenalidomide (LEN) and pomalidomide (POM) are active in many hematologic cancers. Modulation of cereblon (CRBN)-bound E3 ubiquitin ligase complexes is implicated in the MOA of these compounds. CC-122 is a non-phthalimide analog of the immunomodulatory drugs and first-in-class pleiotropic pathway modulator (PPM™) that binds the CRBN-E3 ubiquitin ligase complex. CC-122 activity in multiple myeloma (MM) was investigated in pre-

clinical studies.

Results: CC-122 inhibited MM cell proliferation in a CRBN- and dose-dependent manner. CC-122 induced cell cycle arrest at G_0/G_1, reduced phosphorylated pRb levels and increased CDK inhibitor p27 expression. CC-122 has greater activity in LEN-resistant MM cells vs LEN and pomalidomide (POM) and had anticancer activity in a xenograft MM model. CC-122 demonstrated immunomodulatory activity 10-fold more potent vs LEN, including enhanced T-cell production of cytokines and chemokines (eg, IL-13, TNF-α, GM-CSF, RANTES), as well as IFN-γ production from NK cells. CC-122 has greater antiangiogenic activity vs LEN and POM and inhibited new vessel growth, endothelial cell sprout formation, migration, and invasion. CC-122 had less of an antiplatelet effect and less potency with regard to CRBN binding vs LEN or POM.

Conclusion: CC-122 has antiproliferative, immunomodulatory, and antiangiogenic properties and may have clinical significance in the treatment of lymphoproliferative disorders. Ph I studies for MM, NHL, and solid tumors are ongoing.

Table: Activities of LEN, POM, and CC-122

Activity	Assay/Cell Line	LEN (μM)	POM (μM)	CC-122 (μM)
Immune modulation (EC_{50})	T-cell IL-2	0.17	0.010	0.012
	NK-cell IFN-γ	0.052	0.0011	0.0015
Anti-proliferative (IC_{50})	H929 (MM)	1	0.09	0.09
	LEN-resistant H929 (MM)	> 30	6.0 to > 30	0.8 to 2
Anti-angiogenesis (IC_{50})	Human Umbilical Artery	1.7	0.33	0.0094
Anti-platelet (IC_{50})	Immature MK colonies	0.41 to 1.3	0.35 to > 10	> 10
	Intermediate MK colonies	1.3 to > 10	1.4 to > 10	> 10
CRBN binding (IC_{50})	CRBN competition binding to THAL-beads	3	2	30

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Preclinical Characterization of SAR650984, a Humanized Anti-CD38 Antibody for the Treatment of Multiple Myeloma

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CD38 is a type II transmembrane glycoprotein with both ADP-ribosyl cyclase ectozyme activity and potential receptor functions. CD38 is highly expressed at the surface of malignant plasma cells of multiple myeloma. SAR650984 is a humanized IgG1 antibody targeting CD38 in early clinical development. Several potential mechanisms of action of SAR650984 have been identified including ADCC, CDC and pro-apoptotic activity (AACR2009 #859, #2048, #2797). Here we report further preclinical characterization of SAR650984 on epitope mapping, evaluation of CD38 enzymatic inhibition, exploration of pro-apoptotic activity in MM cellular models and patient samples, and in vivo activity in combination with bortezomib. Fab fragments derived from SAR650984 were co-crystallized with soluble human CD38 to a 1.5A resolution. Loop H3 of the paratope protrudes out of the SAR650984 Fab structure and is critical for the complex stabilization. The conformational changes observed upon CD38 binding allosterically inhibits of the catalytic activity of CD38. Binding of SAR650984 to CD38 impacts cell growth and survival as demonstrated by increased apoptosis signal in MM cells and primary patient samples. SAR650984 apoptosis induction was evidenced in vivo, in SCID mice bearing SUDHL8 lymphoma, by a robust and sustained induction of cleaved caspase 7. In combination with bortezomib, SAR650984 demonstrated synergy in NCI-H929 MM xenograft model. These results further confirm the multiple mechanisms of action of SAR650984 and strongly support continued clinical evaluation of SAR650984 in the treatment of MM.

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Targeting the BRAF V600E Mutation in Multiple Myeloma

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Background: In multiple myeloma (MM), there has been little progress in the specific therapeutic targeting of oncogenic mutations. Whole-genome sequencing data has recently revealed that a subset of patients carry an activating mutation (V600E) of the BRAF kinase. However, the clinical relevance of this mutation in MM has yet to be defined. Methods: We screened 421 bone marrow and soft tissue biopsies from 379 patients with a monoclonal gammopathy, including 251 cases with symptomatic MM, for the presence of the BRAF V600E mutation by mutation-specific immunohistochemistry followed by confirmatory Sanger sequencing. The mutations status was correlated with patient outcome and treatment of a relapsed and refractory patient with confirmed BRAF V600E mutation with the mutation-specific inhibitor vermurafenib was initiated. Results: The mutation was found in 2.8% of

symptomatic cases (7/251), including first occurrence at relapse or detection only in a subclone. There was a significantly higher incidence of extramedullary disease (57% vs. 18% (p=0.02)) in patients in whom the mutation was detected when compared to controls. Most importantly, we report on a patient with relapsed MM and extensive extramedullary disease, refractory to all approved therapeutic options, who has rapidly and durably responded to low doses of the specific BRAF inhibitor, vermurafenib. Conclusion: This is the first evidence of the clinical and therapeutic relevance of BRAF V600E mutations in this disease, proving the principle of specific inhibition of driver mutations in MM.

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The New Drug Partner for Combination Therapy in Myeloma: Development of ACY-1215 a Selective HDAC6 Inhibitor

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HDACs are a family of enzymes that regulate critical cellular functions. First generation, non-selective, HDAC inhibitors are active in multiple myeloma (MM) in combination with standard therapies, but are associated with severe fatigue, gastrointestinal effects and myelosuppression. ACY-1215 is the first selective HDAC6 inhibitor to reach clinical trials and data support the well-tolerated safety profile observed in preclinical studies. HDAC6 acts in the cytoplasm of MM cells regulating aggresome formation, an alternative route for degradation of excessive and misfolded proteins. Knockdown of HDAC6 significantly increased the activity of the proteasome inhibitors (PIs) bortezomib and carfilzomib in MM cells. ACY-1215 recapitulates these results and shows synergistic cell killing with PIs providing the rationale for inhibiting the two major pathways of protein degradation in the clinic to treat multiple myeloma. The inhibition of HDAC6 correlates with preferential increase in acetylated tubulin. Further, ACY-1215 synergizes with immunomodulatory agents in the presence or absence of dexamethasone to induce apoptosis in MM cells. The monotherapy experience with ACY-1215 demonstrates few treatment related adverse events and is associated with stable disease up to 10 cycles of treatment (Blood, V20(21):4061). Based on the preclinical and early clinical data ACY-1215 has entered phase 1b combination trials with bortezomib (ACY-100) and with lenalidomide (ACE-MM-101) in patients with relapsed and refractory MM. Recent preclinical and clinical data will be presented.

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Development of Novel Non-Bisphosphonate Inhibititors of hFPPS for the Treatment of Multiple Myeloma.

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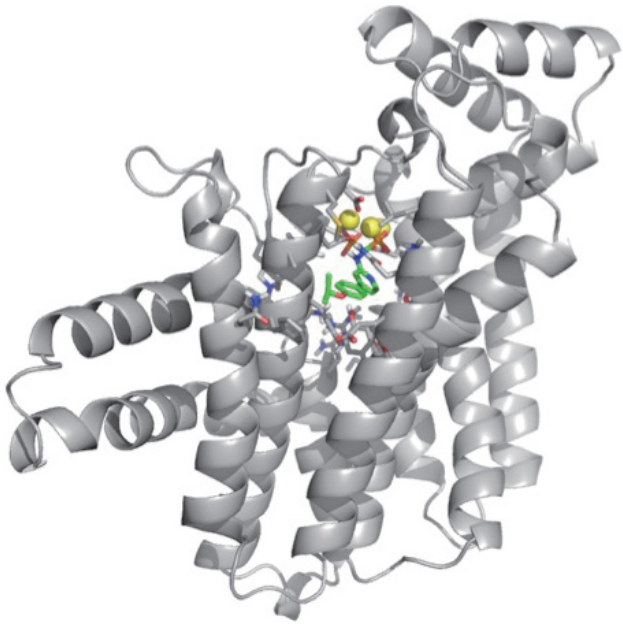
Recent clinical trials have demonstrated that nitrogen-containing bisphosphonates (N-BPs), inhibitors of the human farnesyl pyrophosphate synthetase (hFPPS) are disease modifying agents in Multiple Myeloma (MM), likely improving overall survival. Bisphosphonates are the only class of approved drugs that specifically target hFPPS and they do so by binding to a DMAP/GPP substrate sub-pocket of the active site through metal-mediated interactions. Owing to their charged nature, avidity for bone and overall poor cellular bioavailability, nitrogen-containing bisphosphonates (N-BPs) can be considered poor clinical drugs. hFPPS, however, remains a tantalizing drug target as it is ultimately responsible for the farnesylation of GTPases including H-Ras and K-Ras, which have been found to be widely mutated in MM. In addition, hFPPS is widely expressed in MM cell lines and patient samples. We synthesised a library of structurally diverse inhibitors and used structural techniques (NMR, ITC, DSF and X-ray crystallography) to probe their interactions with hFPPS. We have identified a number of non-N-BPs that bind to an allosteric pocket of hFPPS and demonstrate superior bio-physical properties than N-BPs. In addition, we demonstrate that some of our inhibitors block intracellular ERK phosphorylation and induce apoptosis in human MM cells. These compounds are expected to have greater oral bioavailablility than the current N-BPs drugs and may lead to a novel class of anti-MM therapeutics.



P-292

A Protein Knock-down & Knock-in Approach to Study the Function of CRBN in the IMiD Response in Multiple Myeloma Cells

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Immunomodulatory drugs (IMiDs®) have shown anti-cancer effects in different indications by direct inhibition of cancer cell proliferation as well as modulation of its microenvironment. Cereblon (CRBN), a component of a Cullin-ring ligase (CRL) E3 ubiquitin ligase complex, is the target of the IMiDs, and binding of CRBN by these agents mediates their effects in multiple myeloma (MM) cells.

To understand the significance of CRBN to IMiD activity, we designed a protein knock-down/knock-in strategy in a panel of MM cell lines. Inducible small hairpin RNA (shRNA) constructs targeting un-translated and coding regions of human CRBN were infected in a panel of IMiD-sensitive MM cell lines and compared to a non-targeting negative control. Reduction of CRBN protein had no effect on growth rate or viability in any line tested but led to an IMiD-resistant phenotype. Furthermore, IMiD effects on cell cycle regulator proteins and IRF4/c-Myc survival pathway were abrogated by the reduction of CRBN. In an IMiD-resistant line lacking detectable CRBN protein, overexpression of recombinant CRBN re-sensitized the cells to the effects of the IMiDs. Overexpression of recombinant wild-type CRBN in IMiD-sensitive lines enhanced the anti-proliferative activity of IMiDs. These effects were not observed when a thalidomide-binding defective mutant CRBN ($CRBN^{YW/AA}$) was expressed in IMiD-sensitive or resistant lines.

These results collectively suggest that CRBN is not critical for the proliferation or viability of MM cells but is critical for the anti-proliferative activity of IMiD compounds.

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Exon Mutations in Cereblon (CRBN) and DNA Damage Binding Protein 1 (DDB1) Genes are Rare in Myeloma Cells and Patients

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Background: CRBN, a target of thalidomide and immunomodulatory agents (IMiDs®) lenalidomide (LEN), and pomalidomide (POM), is a component of the E3 ubiquitin cullin 4 ring ligase (CRL4) complex and includes DDB1. Two CRBN mutations have been reported in multiple myeloma (MM) patients (pts): truncating mutation (Q99) and point mutation (R283K). CRBN has a bi-allelic focal deletion in the MM1.R cell line. No DDB1 mutations have been described previously. We investigated the incidence of CRBN and DDB1 mutations by next generation sequencing in MM cell lines and MM pts.

Results: Out of 20 cell lines, one heterozygous CRBN mutation (D249Y) was found in the LEN-resistant ANBL6R cells which is located in the putative DDB1 binding domain while 2 silent mutations were in the KMS-12-BM (rs17027638) and OPM-2 cells. One DDB1 heterozygous mutation (E303D) was identified in ANBL6 cells. No CRBN mutations were found in 62 MM pts; however 5 single nucleotide variations (SNV) were identified. 3 out of 5 had an SNV at position 735 (Y245Y), 1 each at position 219 (H73H) and 939 (C313C) respectively. The first 2 SNVs (rs17027638 and rs1045309) are described but not the last. We found a single SNV (P51P; rs2230356) in 6/62 patient samples for DDB1.

Conclusions: Mutations within the coding sequences of CRBN and DDB1 are rare in MM pts and cell lines. Most intrinsically LEN-resistant cells and cell lines made resistant to LEN or POM do not have CRBN or DDB1 mutations sug-

gesting other sources of IMiD drug resistance such as genetic or epigenetic mechanisms for regulating CRBN and DDB1.

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Pomalidomide and Dexamethasone are Synergistic in Preclinical Models of Lenalidomide-refractory Multiple Myeloma (MM)

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The combination of pomalidomide (POM), a second-generation immunomodulatory drug, with low-dose dexamethasone (DEX) has shown progression-free survival and overall survival improvements in relapsed/refractory MM patients. We investigated the MOA behind POM-DEX combination in lenalidomide (LEN)-resistant human MM cell lines, HMCLs.

A panel of LEN-resistant HMCLs were treated with POM or LEN (0-100 μM) for 5 days. Single-agent POM showed significant anti-proliferative activity in 6/7 LEN-resistant HMCLs tested and significantly reduced cell proliferation compared with LEN in a panel of 12 HMCLs. LEN showed no activity in POM-resistant HMCLs. The combination of POM-DEX was strongly synergistic in both LEN-sensitive and -resistant HMCLs, inhibiting cell proliferation and inducing apoptosis. Importantly, this was recapitulated in an *in vivo* xenotransplant SCID mouse model, whereby POM-DEX synergistically reduced tumor growth in LEN-resistant HMCLs. Gene expression studies revealed a unique gene signature in POM-DEX treated samples. Key gene expression events, such as downregulation of IRF-4, c-Myc, and BCL-2, and upregulation of BIM and cleaved PARP1 were confirmed at the protein level.

The combination of POM-DEX induced strong synergistic tumoricidal effects in LEN-resistant HMCLs *in vitro* and *in vivo* suggesting that this will be a formidable therapy in the LEN-refractory setting. Defining the molecular mechanisms behind these effects will enable the generation of predictive biomarkers of patient response and better defined use of this powerful combination in the clinic.

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Cytotoxic Effect of Nuclear Import Receptor Inhibitor Importazole on Multiple Myeloma

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Background: Multiple myeloma (MM) accounts for more than 10% of total hematological malignancies. Nuclear factor-kappa B (NF-κB) has been regarded to play a prominent role in the tumorogenesis and progression in MM. Importin β, function as import protein, is required for the nuclear import of myeloma-related "cargo" proteins including NF-κB. Importazole (IPZ), a highly specific inhibitor of importin β, readily blocks importin-α/β-mediated NF-κB nuclear import. Methods: MM cell lines and primary cells were treated with different concentrations of IPZ. Cell cytotoxic effects were detected through MTT and flow cytometry. The expression level of nuclear NF-κB protein was measured using western blot and immunofluorescence. The DNA binding activity was examined by electrophoretic mobility shift assay. Results: IPZ inhibited cell growth in a dose and time-dependent manner, with IC50 values of 4.43 and 4.78 μM on RPMI8226 and NCI-H929 cells after 48 hours incubation. Exposure of cells to 8 and 12 μM IPZ for 48 hours exerted apoptosis, $14.53 \pm 0.9\%$ and $32.57 \pm 1.8\%$ in RPMI8226, $19.46 \pm 0.7\%$ and $46.02 \pm 1.1\%$ ($P<0.05$) in NCI-H929, respectively. Treatment with 8 μM IPZ could inhibit NF-κB nucleus translocation and reduce its DNA binding. In contrast to primary myeloma cells, IPZ induced cell cycle arrest but not apoptosis in normal bone marrow mononuclear cells. Conclusion: IPZ is a potent agent that selectively targets MM cells, and may be of value in the treatment of MM. Keywords: multiple myeloma; IPZ; NF-κB signaling pathway; cytotoxicity

P-297

NK Cell Activation and Cytotoxicity in Human PBMC/Myeloma Cell Co-cultures Induced by Elotuzumab, Lenalidomide, or Both

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Background: Elotuzumab (Elo) is a humanized anti-CS1 antibody that enhances Natural Killer (NK) cell mediated antibody dependent cellular cytotoxicity of CS1 expressing myeloma cells. Lenalidomide (Len) is an immunomodulatory agent that activates NK cells. Elo+Len enhanced anti-

myeloma activity in xenograft models. Mechanisms of NK cell activation and myeloma cell killing with Elo+Len were investigated. Methods: Human PBMC and myeloma cells (OPM-2) were co-cultured with Elo, Len or Elo+Len for 24-72h. Expression of activation markers and adhesion receptors were evaluated by flow cytometry, cytokines by Luminex and ELISpot assays and cytotoxicity by myeloma cell counting. Results: Co-culture production of IFN-γ increased with Elo and was significantly higher with Elo+Len. OPM-2 cell surface expression of ICAM-1 increased synergistically with Elo+Len compared to each agent alone. NK cell expression of CD25 (IL-2R α) was enhanced by Elo but not Len, and Elo+Len was synergistic. IL-2 levels were increased by Len, but decreased by Elo due to increased consumption by CD25 expressing NK cells as blocking IL-2 uptake with anti-CD25 resulted in higher IL-2 levels than with Len. The number of IL-2-producing cell colonies was increased with Elo, Len and Elo+Len was synergistic. NK cell dependent myeloma cell killing was induced by Elo and to a lesser extent Len and Elo+Len was synergistic. Conclusions: Elo alone and synergistically with Len activated NK cells and enabled NK cell mediated OPM-2 myeloma cell killing via mechanisms involving increased IFN-γ, ICAM-1, IL-2 and CD25.

Treatment	IFN-γ (pg/mL) n=8	ICAM-1 on OPM-2 (MFI) n=4	CD25 on NK cells (MFI) n=8	IL-2 (pg/mL) (Luminex) No blocking (control mAb) n=6	IL-2 (pg/mL) (Luminex) Anti-CD25 blocking mAb n=6	#IL-2 positive colonies (ELISpot) n=9	OPM-2 killing (%) n=4
Control*	48	427	155	21	-	30	1
Len**	94	2040	131	50	-	71	15
Elo + Len	386	42.259	1546	14	134	191	67
Elo	65	3068	975	7.8	52	80	39

*cIgG1 (isotype)
**plus cIgG1

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From CLL to Multiple Myeloma - Spleen Tyrosine Kinase (Syk) Influences Multiple Myeloma Cell Survival and Migration

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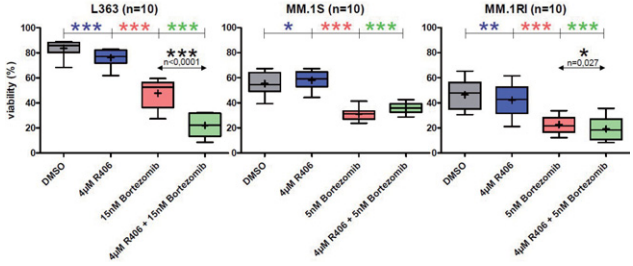
Introduction: Spleen Tyrosine Kinase (Syk) is crucial in various B-cell malignancies and recent results show a relation to the CD31/CD38 pathway. Since CD38 is present on MM-cells, we sought to elucidate the importance of Syk in MM compared to CLL as published (Buchner M et al. Blood 2010). Methods: MM cell lines (MMCLs, L363, MM.1S, MM.1Rl, RPMI8226, U266) and bone marrow samples of MM patients (pts) were compared to that of healthy donors (HD) and CLL pts. Syk expression was determined via immunoblotting. Flow cytometry was used to evaluate cell viability after Annexin/PI-staining and to detect cell migration. Results: MMCLs displayed varying expression (0.5 - 2-fold) of Syk compared to CLL pt samples. 24hr-treatment with R406 (Syk-inhibitor) led to significantly reduced viability in 2 of 3 MMCLs (Fig. 1). In combination with bortezomib, cumulative apoptotic potency was observed (L363, MM.1Rl). Subsequent evaluation of downstream targets revealed downregulation of pAKT and Mcl-1. Syk inhibition did not significantly change the CD38 expression on MMCL as detected on CLL pts. Migration of L363 to BM supernatant from HD significantly decreased as Syk was targeted. Compared to CLL pts, MM BM pt specimen expressed lower Syk and pSyk levels. Conclusions: Syk expression in MMCLs partly resembled that in CLL pt controls. Inhibition of Syk via R406 led to potent cytotoxic and antimigratory effects on MMCLs influencing the AKT pathway. Considering the inhibitory effects, despite low levels of activation in vitro, Syk may represent a therapeutic target in MM.

Figure 1. Apoptotic effect of 24h-R406 treatment on MMCL (L363, MM.1S, MM.1Rl) in vitro and cumulative effect when combined with bortezomib (colored * shows significance of equally colored bar compared to control (DMSO), *P<0.05, **P<0.01, ***P<0.001)



P-299

Pharmacologic Inhibition of c-Myc Kills Myeloma Cells

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The oncogene c-MYC is deregulated in multiple myeloma. Importantly, the activity of c-MYC is elevated in plasma cells in patients with myeloma compared to the premalignant state monoclonal gammopathy of undetermined significance, indicating a prominent role for c-MYC in myeloma pathogenesis. We earlier found the Bone Morphogenetic Proteins induce apoptosis in myeloma cell lines and primary cells by SMAD-dependent downregulation of c-MYC. Repression of c-MYC by short hairpin RNA has also been shown to induce apoptosis in myeloma cell lines. Transcriptional regulation by c-MYC requires heterodimerization of c-MYC and its obligate partner MAX. The small molecular inhibitor 10058-F4 disrupts the formation of such heterodimers and was used in vitro to test the dependency on c-MYC activity in primary myeloma cells and myeloma cell lines. The inhibitor induced apoptosis in a dose-dependent manner in the 22 primary sam-

ples tested. Apoptosis was also induced in myeloma cell lines except in the U266 cell line, which does not express c-MYC. Likewise, we found that treatment of myeloma cells with the malaria drug artesunate also led to downregulation of c-Myc protein concomitant with induction of myeloma cell apoptosis. Taken together, the results identify c-Myc as a target for treatment of multiple myeloma.

P-300

Targeting MAGE-C1 (CT7) Dependency in Relapse Multiple Myeloma with DNA Vaccines

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In multiple myeloma (MM), disease can be de-bulked by successive therapies but tumor invariably relapses. New therapeutic options are clearly essential, and include immunotherapeutic vaccines. For vaccination, a critical question is which tumor-associated antigens (TAAs) to target in remission. Here, the cancer testis antigens (CTAs) come to the fore, as many are essentially tumor-specific. Of these, MAGE-C1 (CT7) is a type I antigen that we previously reported as expressed in >60% relapse MM cases. Other observations in MM have identified CT7 as an early and high risk marker of relapse; associated CT7 with poor prognosis; and identified CT7 as important for survival. Taken together, these findings delineate a dependency on MAGE-C1 in relapse MM, and define it as a lead candidate for immunotherapy. We have developed DNA fusion gene vaccines (pDOM) able to induce immunity to defined CD8+ cytotoxic T-lymphocyte (CTL) TAA-epitopes, necessary to attack HLA class I expressing MM cells. Pre-clinical evaluations utilize the transgenic HLA-A2 HHD model to test pDOM.epitope vaccines. Using in-silico based algorithms we identified several HLA-A2 MAGE-C1 derived epitopes, and selectively examined these by delivery as pDOM.epitope vaccines in the HHD model. Of these, 2 CT7 epitopes (E1, E2) induced high CTL responses, and E1 revealed marked CTL lysis of human MM cell lines made chimeric for HHD MHC class I, higher than any CTA-derived epitope tested in our laboratory. MAGE-C1 then emerges as an optimal CTA to target with DNA vaccines in MM, and facilitates clinical evaluation.

P-301

Kinase CK2 Inhibitors Boost Bortezomib Cytotoxicity on Multiple Myeloma by Downmodulating Survival and Stress Pathways.

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The molecular determinants mediating bortezomib-induced MM cell death are largely unknown. We previously identified the kinase CK2 as a growth-promoting protein in MM. In this study, we verified whether CK2 regulates MM cell sensitivity to bortezomib. MM cells were treated with bortezomib and CK2 inhibitors. Bortezomib-induced MM cell apoptosis and proliferation arrest were significantly increased by the inhibition of CK2 with CX4945 and the tTBB derivative K27 (up to 2.5 fold for primary MM cells and up to 1.8 fold for U266 and INA-6 cell lines for both inhibitors, $p<0.05$, n=3-8). This effect was present in different experimental settings of MM cell growth. CK2 inhibition also empowered bortezomib-triggered mitochondrial apoptosis (assessed by JC-1 staining, up to 2 fold in CK2 inhibitors-treated cells with downregulation of Bcl2, Mcl1 and upregulation of Bax and Bak). The bortezomib-triggered activation of NF-κB and rise in the levels of the unfolded protein response-associated kinase/endoribonuclease IRE1α - which could antagonize apoptosis - were found to be markedly reduced by CK2 inhibition. Moreover, CK2 inhibition also led to a strong downregulation of STAT3 phospho Ser727 levels and enhanced the accumulation of poly-ubiquitylated proteins consequent to bortezomib exposure. These results indicate that protein kinase CK2 can antagonize bortezomib-induced apoptosis by regulating critical signaling pathways at multiple levels in MM cells. Our findings could be particularly relevant for the development of novel bortezomib-based anti-MM combination strategies.

P-302

Carfilzomib in Combination with HDAC6 Inhibitor ACY-1215 Induces MM Cell Death by Inhibition of Autophagosome Formation.

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HDAC6 plays a major role the fusion of autophagosomes to lysosomes and autophagy. Proteasome inhibitor (PI) treatment results upregulation of autophagy as a survival mechanism in multiple myeloma (MM) cells. Here we studied the anti-MM effect of the PI, carfilzomib (CFZ), in combination with the HDAC6 inhibitor, ACY-1215. ACY-1215 in combination with CFZ triggers synergistic cytotoxicity in MM cell lines, including bortezomib resistant MM cells. CFZ increased LC3, suggesting an accumulation of autophagosomes, as well as p62, a binding protein between ubiquitinated proteins within the aggresome and the autophagosome. Importantly, the combination of ACY-1215 and CFZ increased caspase cleavage and apoptosis, and was associated with a block in aggresome formation, as evidenced by decreased LC3 and p62. Moreover, MM cells treated with CFZ showed accumulation of LC3 and p62 in the cytoplasm with nuclear degradation, suggesting autophagosome formation, which was also blocked by addition of ACY-1215. These results suggest that the combination of ACY-1215 and CFZ inhibit aggresome and autophagosome formation, thereby enhancing apoptosis.

P-303

Selective Targeting of Mcl-1 Induces Myeloma Cell Death and Synergizes with Proteasome Inhibitors

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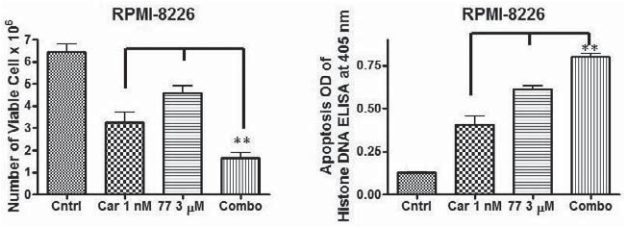
The anti-apoptotic protein Mcl-1 is key to the survival of malignant plasma cells (PCs) in multiple myeloma (MM). We have shown that Mcl-1 is consistently over-expressed in patient-derived MM PCs. Using structure based drug design we have developed high affinity small molecule inhibitors (SMIs) that selectively bind with to the BH-3 hydrophobic groove of Mcl-1. This displaces pro-apoptotic partners such as Bax, Bak, Bok and Bid in MM PCs, ultimately inducing apoptosis via cleavage of caspases 3 and 9. The lead SMI (UMI-77) induced apoptosis of MM PCs at a concentration that does not affect normal lymphocytes (IC_{50} 5 μM). Co-treatment of MM cells with UMI-77 and a proteasome inhibitor (bortezomib or carfilzomib) resulted in synergistic induction of apoptosis (see figure). UMI-77 is tolerated in mice at intravenous doses up to 60 mg/kg, and suppresses tumor growth in a lymphoma mouse model. We are thus evaluating UMI-77 alone and in combination with proteasome inhibitors in a MM mouse xenograft model, with proteomic assessment of treatment effect on MM cells *in vivo*. In summary, we have shown that selective targeting of Mcl-1 induces MM cell death and sensitizes MM cells to the effects of proteasome inhibitors, providing a strong rationale for further evaluation of the SMI UMI-77 as a potential anti-MM therapy.



P-304

CD28: a Pro-survival Signaling Molecule in Multiple Myeloma as a Novel Therapeutic Target

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Multiple myeloma (MM) survival is dependent on the bone marrow microenvironment and is mediated by the receptor CD28, expressed on MM cells. CD28 expression correlates clinically with poor outcomes, and we have shown that CD28 signaling protects MM from chemotherapy. However, the molecular pathway by which CD28 does this is not clear. Since CD28 signals via a PI3K-Akt-FoxO3a pathway in T cells, we interrogated whether this pathway is critical in MM. We observed that blockade of PI3K or Akt abrogates CD28-mediated survival. Upon CD28 activation, transcription factor FoxO3a is phosphorylated and excluded from the nucleus. Being downstream of FoxO3a, we examined whether the pro-apoptotic molecule Bim is regulated by CD28. Indeed, CD28 activation downregulates Bim, blockade upregulates it, and Bim silencing abrogates sensitivity to CD28 blockade. To confirm that stromal cells protect MM, we co-cultured MM and dendritic cells and observed increased survival. However, if CD28 or CD80/86 is blocked, protection is completely abrogated. To examine if this is relevant *in vivo*, we used the murine myeloma model Vk*MYC and a SCID/human model. In either case, treatment with CTLA4-Ig (to block CD80/86) in combination with a sub-therapeutic chemotherapy dose was able to significantly decrease tumor burden and extend sur-

vival. Taken together, these data suggest that CD28 is a direct mediator of chemotherapy resistance *in vivo*, and blockade of CD28 represents a novel target for clinical therapy.

P-305

Individualizing Myeloma Virotherapy Protocols: Oncolytic Picornaviruses, CVA21 and Mengovirus

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Oncolytic picornaviruses are uniformly icosahedral particles of ~30 nM diameter that extravasate efficiently from leaky tumor neovessels and may spread selectively to infect tumor cells throughout the body. MicroRNA targeting was developed to eliminate the undesirable toxicities of these viruses and tailor them for cancer therapy. In this way we have successfully eliminated the muscle toxicity of Coxsackievirus A21 and are in the process of eliminating both the cardiac and CNS toxicities of our oncolytic Mengovirus platform. The targeted Coxsackievirus A21 is rapidly destructive to subcutaneous myeloma xenografts at intravenous doses as low as 103 TCID50, or when administered as naked RNA, while the Mengovirus, attenuated by truncation of the poly(C) tract in its 5' untranslated region, is active in a syngeneic immunocompetent mouse plasmacytoma model. The mode of virus spread that leads to tumor destruction in these models has not yet been histologically characterized, but is associated with sustained secondary viremia during which the circulating virus titer is 3 logs higher than the peak level achieved during initial virion infusion. Our current hypothesis is that this sustained viremia is the key factor in establishing a spreading infection and elimination of disseminated tumor cells. We therefore predict that picornavirus therapy will be equally effective whether the myeloma cells are growing as a subcutaneous plasmacytoma or dispersed throughout the bone marrow in a systemic orthotopic myeloma model. Ongoing experiments will shed further light on this hypothesis.

P-306

Individualizing Myeloma Virotherapy Protocols: VSV-IFNβ-NIS

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Oncolytic VSVs are 70x180nm bullet shaped particles that extravasate from leaky tumor neovessels. Although VSV can enter all cell types promiscuously, propagation occurs only in neoplastic tissues that are not in an antiviral state. Intratumoral spread is contact-dependent and spatially constrained, producing centrifugally expanding infectious centers. Secondary viremia and viremic spread are minimal. In plasmacytomas, virus spread may be terminated rapidly by innate immune responses (antiviral state) or continue unabated until controlled by the adaptive immune system. Based on experimental observations in different myeloma models, we developed a simple spatial mathematical model that calculates the probability of tumor cell survival after intravenous VSV administration. The two key model parameters are (i) density of initially infected cells in the tumor, (ii) average maximum size attained by the infectious centers. Predicted effects of virus dose modification and antiviral immune response modulation were investigated through additional in vivo experimentation, and the results agree with the predictions of the model. Since virus spread is cell contact dependent, myeloma cells are more likely to be killed when embedded in a plasmacytoma than when dispersed through the bone marrow and efficacy is superior for nodular vs diffuse myeloma, where myeloma cell concatenation (or connectivity) emerges as a key driver of the dose-response relationship. This new mathematical model will be useful to guide the further optimization and individualization of myeloma virotherapy protocols.

P-307

The Combination of Dexamethasone and the Mcl-1 Inhibitor, Obatoclax, as a Potential Therapy for Multiple Myeloma

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Glucocorticoids remain crucial in the therapy of Multiple Myeloma (MM), often enhancing even the most powerful novel anti-MM therapies. Despite their usefulness, their effect on this disease is poorly understood. Using a pooled shRNA screening approach, we identified MCL1 as a gene

whose knock-down confers increased sensitivity to dexamethasone (DEX). Mcl-1 is an anti-apoptotic Bcl-2 protein that is often over-expressed in cancers and even MM. It has been linked with resistance to chemotherapy. Obatoclax is a pan Bcl-2 family inhibitor that potently disrupts Mcl-1/Bak interactions and is highly cytotoxic to Mcl-1 dependent cell lines. The combination of DEX with obatoclax results in a synergistic inhibition of MM cell line growth and this is most pronounced when cells are pre-treated for 48h with DEX, suggesting the involvement of gene regulation in this strategy. Bim, a pro-apoptotic Mcl-1 binding partner, is induced in multiple myeloma cells in vitro and in vivo in the Vk*myc murine MM model following DEX treatment. Bim induction is important for Bak oligomerization at the mitochondrial membrane, initiating apoptosis and appears required for DEX mediated cell killing of MM cells. Obatoclax is effective as a single agent in the Vk*myc model and is currently being evaluated in combination with DEX. These results propose a promising new combination therapy that operates through a mechanism involving DEX mediated Bim induction and inhibition of anti-apoptotic Mcl-1, by obatoclax, leading to Bak oligomerization and cell death.

P-308

Terminal Disruption of Secretory Homeostasis by Inhibition of p97 and Proteasome-mediated Protein Degradation in Myeloma

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The toxic effect of proteasome inhibition (PI) in multiple myeloma cells (MMCs) is at least partly due to impaired endoplasmic reticulum (ER)-associated protein degradation (ERAD), which causes overwhelming ER stress. The cytosolic ATPase, p97, plays a key role in mediating ERAD and other protein degradation pathways, and has been suggested as a novel anti-cancer target. The existence of significant non-redundant effects of inhibitors of the proteasome and p97 would open up the possibility that dual inhibition of both ERAD components could be used to terminally disrupt secretory homeostasis in MMCs. We found that separate inhibition of p97 or the proteasome generates quite different effects on the ER and on intracellular protein metabolism. Moreover, concurrent inhibition of both p97 and the proteasome efficiently induced apoptosis in MMCs, caused dramatic vacuolisation of the ER, led to terminal translational shut-down, blocked degradation of ubiquitinated proteins, and deregulated key cellular survival and cell death pathways. While dual inhibition of the proteasome and p97 was highly toxic to MMC lines and primary MMCs, including bortezomib-insensitive MMCs, it showed little toxicity in untransformed cells. Our observations indentify non-redundant roles of p97 and the proteasome in maintaining homeostasis of the ER and of intracellular protein metabolism in MMCs, and provide a conceptual framework for dual targeting of protein degradation pathways as a potential therapeutic strategy in MM.

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HDAC Inhibitor VPA Enhances the Anti-myeloma Effect with PPAR γ Agonist on in Vivo Study

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In spite of the development of new chemotherapy, the multiple myeloma (MM) is still an incurable cancer. The new strategy in chemotherapy is to combine 2, 3 or more molecules of different pharmaceutical classes in order to avoid drug resistance development. Previously we have shown that the combination of two drugs, VPA (Valproic acid, HDAC inhibitor and PIO (Pioglitazone, PPAR γ agonist) potentiates the cytotoxic effect of VPA on MM cell lines and on MM cells isolated from bone marrow of patients at different stages of the disease and even more on PCL patient cells. In order to confirm the cotreatment effect we studied this combination on an *in vivo* model, in NSG mice. We have validated a MM mice model that develops after only 3 weeks of an intravenous injection of MOLP8 MM cell line without previous irradiation of mice. After determining the concentration of VPA and PIO that does not induce cytotoxicity or side effect, we treated the animals with this combination. The treatment of mice with VPA-PIO combination has shown a delay of the MM development of one week whereas the first symptoms of paralysis appear 3 weeks after injection in the control group. In addition the mechanism of the combination is exactly the same as described previously. We have demonstrated that the cotreatment induces an increase of acetylation of Histone 3. Apoptosis demonstrated by caspase 3 and PARP cleavage, is higher in the group of mice cotreated with VPA-PIO. In this

work we confirm that the combination VPA-PIO is promising and could be tested in clinical trials.

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Bendamustine Combination Therapy in Patients Relapsed and/ or Refractory to Bortezomib and Lenalidomide

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Salvage options are limited in patients pre treated with both bortezomib and IMiDs. Bendamustine is a bifunctional chemotherapeutic agent . We report on the use of bendamustine in combination with thalidomide and steroids in a group of patients relapsed and /or refractory to both bortezomib and Lenalidomide. 30 patients were analysed in this retrospective study. Patient characteristics are detailed in Table 1. All patients were pretreated with bortezomib, lenalidomide and were refractory to their last treatment. Bendamustine was administered on days 1, 8 +/- 15 in a 28-day cycle with a cumulative dose of up to 200mg/m2 (range 100to200 mg/m2). Thalidomide was dosed between 50-150mg daily and dexamethasone-dosing equivalent up to 160mgs per cycle as tolerated. 6 patients failed to complete first cycle of therapy and were excluded from the analysis. Median of 5(2-9) cycles of therapy was administered. Median follow up for this cohort is 11.5(3-21) months. ORR of 41.7% (> PR) was observed with a clinical benefit rate (including stable disease) observed in 91.7% of patients. Haematological toxicity rates were high with Grades 1-2/3-4 anemia (50%/40%), neutropenia (15%/65%), thrombocytopenia (20%/47%) respectively. Grades 1-3 non-haematological toxicities were neuropathy (33%), fatigue(13%), diarrhea (16%), vomiting(13%). Average time to first response was 2.3 months. PFS was 2.37 months (0-11) months and OS of 7.6(1.3to20.8) months in this cohort. Bendamustine plus thalidomide and steroids is a reasonable salvage option for double relapsed/refractory myeloma patients.

Patients, n	30	
Median age, years (range)	61.5	(46-80)
Male (%)	18	(60)
Female (%)	12	(40)
Diagnosis, n (%)		
IgG	17	(57)
IgA	6	(20)
LC	6	(20)
Other	1	(3)
Previous lines of treatment, median no. (range)	4	(3-6)
Previous treatment, n (%)		
Thalidomide	24	(80)
Bortezomib	30	(100)
Lenalidomide	30	(100)
Other	15	(62.9)
Autologous transplant	25	(71.4)
ISS stage, n (%)		
III	5	(16.7)
II	6	(20)
I	12	(40)
Unknown	7	(23.3)
Lytic bone disease, n (%)	27	(90)

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Anti-c-Met Nanobody® - A New Potential Drug in Multiple Myeloma Treatment

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c-Met is the tyrosine kinase receptor of the hepatocyte growth factor (HGF). HGF-c-Met signaling is involved in many human malignancies, including multiple myeloma (MM). In recent years, multiple agents have been developed directed to interfere at different levels in the HGF-c-Met signaling pathway. Nanobodies® are therapeutic proteins based on the smallest functional fragments of heavy chain only antibodies, occurring in the Camelidae family. They retain the full antigen-binding capacity of the original antibodies and are highly stable. In this study, we examined the anti-cancer effects of an anti-c-Met Nanobody in vitro. HGF is thought to contribute to the pathogenesis of MM in various ways. We show that the anti-c-Met Nanobody effectively inhibited the proliferation of ANBL-6 MM cells via inhibition of an HGF autocrine growth loop, and the proliferation of INA-6 cells induced by exogenous HGF. HGF-induced migration and adhesion of INA-6 were completely and specifically blocked by the Nanobody. Furthermore, the Nanobody abolished the inhibiting effect of HGF on BMP-2-induced alkalic phosphatase-activity and the mineralization of human mesenchymal stem cells. Finally, we show that the Nanobody reduced the phosphorylation of the c-Met Tyrosine residues, MAPK and Akt. In conclusion, the anti-c-Met Nanobody inhibited MM cell migration, proliferation and adhesion, and blocked the

HGF mediated inhibition of osteoblastogenesis. The anti-c-Met Nanobody might represent a potential novel therapeutic agent in the treatment of MM and other cancers driven by HGF-c-Met signaling.

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Lenalidomide and Pomalidomide Display Different Patterns and Mechanisms of Resistance in a Murine Model of MM

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Second-generation drugs derived from those with proven clinical activity have been developed. Here, we have compared the pattern and mechanisms of resistance of lenalidomide and pomalidomide, using an in vivo model of sc plasmocytoma. Mice were continuously treated with Len-Dex (LD) or Pom-Dex (PD), and after an initial period of sensitivity, tumors became resistant. Time to develop resistance was 34 & 45 days for LD & PD respectively. When mice developed resistance, treatment was changed to the alternative combination, and, interestingly, both LD and PD rescued resistance, indicating the absence of cross-resistance. PD was more potent at overcoming LD resistance than the alternative situation (median TTP of 16 vs 27 days for LD and PD respectively. p=0.004). GEP was also different in LD and PD resistant cells. Using a Q-value < 5%, 56 genes were commonly deregulated, while 395 were exclusive of PD resistant cells and 142 were specifically deregulated in LD resistance. Pathways like MAPK & IL2 signaling were significantly enriched in Pomalidomide group. At protein level, the upregulation of the MEK/ERK pathway was a common mechanism of resistance, although, concordant with the GEP studies, it was more potent with PD. Interestingly, the addition of the MEK inhibitor Selumetinib to IMIDs + Dex in mice bearing resistant tumors induced a decrease of tumor volume and a delay in the TTP of 14 and 18 days for LD and PD respectively. This study supports the absence of complete cross-resistance between LD and PD and the use of MEK/ERK inhibitors to avoid/overcome IMIDs resistance.

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Inhibition of XPO1 Induces a Ribosomal Stress Response in Myeloma Cells

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Ribosome biogenesis requires the coordinate activity of several members of the β-karyopherin family that mediate nuclear import of ribosomal proteins and export of ribosomal subunits. In particular, exportin 1 (XPO1) is required for the export of assembled ribosomal subunits (60s & 40s) from the nucleolus back into the cytoplasm. Inhibition of XPO1 triggers a ribosomal stress response that may result in the death of transformed cells with stressed ribogenesis. We analyzed the effects of the XPO1 inhibitor KPT-330 (Karyopharm) in myeloma cells and in particular the induction of a ribosomal stress response. Treatment with KPT330 induced an apoptotic cell death (caspase 3, PARP cleavage) and suppressed proliferation of MM cells lines with an IC50 ranging from 50-150 nM. In addition, treatment with KPT330 up-regulated the expression of p53, as well as p21, p27 and Puma while it significantly downregulated the expression of c-Myc, XPO1 and Mdm2. These findings are notably consistent with a ribogenesis stress response where unassembled ribosomal proteins RPs (such as RPL11 and RPL5) are released from the nucleolar ribosome assembly factories to bind Mdm2 inhibiting its E3 ligase activity and post-transcriptionally repress c-Myc expression. Indeed, inhibition of XPO1 with KPT330 in MM cells lead to the accumulation of ribosome-free or unbound RPL11 in the nucleoplasm (non-polysome fraction) and its binding to MDM2 (co-IP). We conclude that the inhibition of XPO1 induces a ribosomal stress response in MM cells and therefore may represent a novel druggable target in this disease

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Lenalidomide Induces a Ribosomal Stress in Multiple Myeloma Cells

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The anti-myeloma activity of IMiDs requires their binding to cereblon, an adaptor protein of the Cul4a ubiquitin E3 ligase complex. In order to identify ubiquitylated substrates that are modified by lenalidomide (Len) treatment, we performed a ubiquitin-proteome pull-down using Tandem Ubiquitin Binding Entity (Lifesensors) coupled with quantitative mass-spectroscopy proteomics (iTRAQ) in OPM2 cells exposed to Len (10 μM). Several ribosomal proteins

(RPs) - S25, S26, S20 & S28 - were increased in Len treated samples suggesting that the Cul4a-CRBN complex may regulate RPs stability and hence IMiDs binding to cereblon may trigger a ribosomal stress response. Immunoblot analysis of MM cells exposed to Len lead to a rapid decrease in c-Myc expression (within 60 min) that significantly preceded the downregulation of IRF4 consitent with an IRF4-independent mechanism for c-Myc dowregulation. Furthermore, Len transiently stabilised and subsequently downregulated MDM2 expression with up-regulation of p53 and its downstream targets (p21,PUMA). Under ribosomal stress conditions, polysome-free RPs are reported to be released into the nucleoplasm binding MDM2 and suppressing its E3 ligase activity. Consistent with impaired ribogenesis, in Len treated cells MDM2 co-immunoprecipitated with two RPs RPL11 and RPL5. In addition, a transient increase in the interaction between RPL11 and c-Myc was also observed consistent with the reported role for RPL11 in the post-transcriptional regulation of c-Myc. Our data indicate that lMiDs induce a "therapeutic" ribosomal stress response in MM cells

Section E: Epidemiology, Prognostic Factors, Quality of Life, Disease Complication and Treatment Toxicities

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Lafutidine for Bortezomib-induced Peripheral Neuropathy

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Bortezomib-induced peripheral neuropathy(BIPN) is an important complication of multiple myeloma(MM). Lafutidine is a H2-blocker with gastroprotective activity thought to work via capsaicin-sensitive neurons. Capsaicin has the gastroprotective activity too, by increasing mucosal blood flow via capsaicin-sensitive afferent neurons. Moreover capsaicin selectively blocked afferent sensory neurons. Lafutidine seems to work like capsaicin via the same neurons. The same activity of lafutidine assumed to improve glossodynia and taxoid-induced peripheral neuropathy(PN). We hypothesized that lafutidine might also prevent or improve PN caused by bortezomib. The onsets of PN in previous Japanese trial were reported 47% at median time of 79 days. In other reports, median therapy was less than five courses. So bortezomib was administered in an ordinary way for four courses to compare our data with Japanese studies. Lafutidine was administered 10 mg twice a day. PN was evaluated by some instruments. There were no stop cases because of PN. The occurrence of PN in this study compared with other reports is as follows. Total occurrence of PN;50% vs 47% vs >40% vs >87%, more than grade3; 0% vs 3% vs 13% vs 6.7%. Conclusion: (1) No obvious improvement for occurrence of PN, (2) No PN after the first course, (3) only grade 1 cases and no cases more than grade3, (4) No stop cases caused by PN, (5) This is the first report that lafutidine is useful for amelioration of BIPN.

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Retrospective Analysis of Multiple Myeloma Patients

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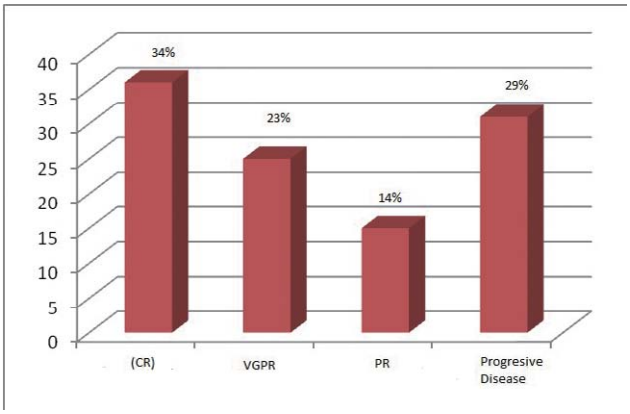
The proteosome inhibition, has emerged as an important treatment strategy of multiple myeloma. Material and Medhod: In this study we included 159 of multiple myeloma

patients with new diagnosed, relapsed or the ones with an active disease between January 2005 and December 2011 according to the international working group.The latest update was done in January 2012. Results:72 patients were women (45.3%), 87 were males (54.7%), mean age was 63(SS:10,5) between 35 and 89. 111 patients who received bortezomib was evaluated after the treatment regimen according to IMWG criteria of response. According to these criteria after the last dose of bortezomib regimen ,since required tests were not available five patients were excluded from the evaluation of response.In the remaining 106 patients; complete response-CR in 36 (34%), VGPR in 25 (23%), partial response-PR in 15 (14%),and progressive disease in 30 (29%) were observed (Figure).There was no difference in response rates between the treatment regimens of bortezomib.Duration of treatment and the number of cycles with bortezomib was found to be in a significant relationship between the response. As a conclusion in this single centre study, bortezomib with effectivity and side effects taken in consideration was found to be an effective and secure treatment modality in patients both with new diagnosed or refracter disease and that are eligiable to transplantation or not.



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Changes in Circulating Blood Level of BDNF are Associated with Bortezomib-induced Peripheral Neuropathy in MM Patients

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Bortezomib Induced Peripheral Neuropathy (BIPN) is a major side effect and dose-limiting factor in multiple myeloma (MM). Brain Derived Neurotrophic Factor (BDNF) is a nerve growth factor which is responsible for the maintenance, and repair of the peripheral nervous system. Aim: In this work we examined alterations in the levels of BDNF in circulating blood of patients with multiple myeloma (MM), that are related with BIPN development. Method: 22 patients with Multiple Myeloma were examined at diagnosis and during receiving Bortezomib based regimen. We used ELISA to quantify soluble BDNF (sBDNF) level in patient's platelets-poor plasma (PPP) and flow cytometry or western blotting to quantify BDNF in platelets. PN was graded according to the cancer Common Toxicity Criteria index. Results: We found higher level of sBDNF at diagnosis in patients who later on developed BIPN. During treatment with Bortezomib the level of sBDNF was significantly reduced in the group of patients that developed BIPN. Analysis of platelets, revealed higher incidence of BDNF expressing platelets as well as higher BDNF content in platelets of patients with BIPN as compared to patients without BIPN. In vitro addition of Bortezomib onto platelets rich plasma increased BDNF accumulation in the platelets and blocked the cleavage of BDNF precursor to its mature form that has the neuroprotective activity. Conclusions: Our results suggest that BDNF may play role in the pathophysiology of BIPN development and may serve as a useful blood biomarker for early detection of BIPN.

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Patient-reported Outcomes in Peripheral Neuropathy in Myeloma Patients Treated with Subcutaneously Bortezomib.

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OBJECTIVE: Peripheral neuropathy (PN) is one of the most important complications of multiple myeloma (MM) treatment. The Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity (FACT) is a useful measurement system of patient-reported PN in MM. We investigated PN using FACT in two treatment regimens, intravenous (IV) bortezomib and dexamethasone (BD) and subcutaneous (SC) bortezomib, cyclophosphamide and dexamethasone (VCD) . METHODS: All patients evaluated PN with FACT everyday during treatment. We assessed the

fluctuation of FACT score from baseline to end of 2nd cycle treatment. Physicians and nurses studied PN according to CTCAE grading system. RESULTS: The data of 26 pts with symptomatic MM were analyzed retrospectively. From Mar. 2008 to Sep. 2009, 18 pts were treated with BD (IV bortezomib, 17 pts used bortezomib twice weekly in 3-week cycle, and 1 pt used weekly, 1.3mg/sqr). From Feb. to Dec. 2012, 6 pts were treated with VCD (5-week cycle, SC bortezomib administrated weekly, 1.3mg/sqr). Grade 3-4 PN occurred 17% in BD and 0% in VCD. FACT average scores in BD group, were 42.2 at the baseline and 36.3 (p=0.004) at the end of second cycle. In VCD group, from 41.6 to 38.2 (p=0.18), respectively. Median cumulative bortezomib dose (during 2 cycles) and response rate after 2nd cycle were 9.15mg/sqr, 10/17 in BD, and 10.4mg/sqr, 2/8 in VCD, respectively. CONCLUSION: Patient-reported outcomes about neuropathy revealed that PN was mild in VCD group. VCD regimen with bortezomib subcutaneously, weekly dose have a potential to improve PN.

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Iron Overload Pattern is Not Infrequent in Multiple Myeloma at Diagnosis

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Iron overload (IO) is expected to occur in hematologic neoplastic disorders associated with ineffective hematopoiesis, such as MDS and AML. In this retrospective study, we have evaluated serum iron test results in MM patients at diagnosis in order to find the frequency of IO. All MM patients followed at our institution between 2002 to 2012 with available serum iron, total iron binding capacity (TIBC), Transferrin saturation (TS) levels and ferritin levels, at diagnosis were included. Patients with known chronic liver disease were excluded. Iron overload pattern (IOP) was described as increased TS (> 45%) in the presence of normal to increased serum iron and ferritin levels. SPSS v17 (SPSS Inc., Chicago, IL) software was used for statistical analyses. Ninety MM (54 male, 36 female) patients and the median age: 61 years (r:31 – 86) fitting to the above criteria were included. Iron parameter abnormalities were: Pure iron deficiency (PID)(1/90, 1%), pure inflammation anemia (PIA) (20/90, 22%), PID or PIA (6/90, 7%), IOP (17/90, 19%), and nonspecific (25/90, 28%). Mean serum ferritin level was 662 (± 634) pg/ml in the MM patients with IO. Most importantly, iron overload was not infrequent in MM.. There was a close association between lambda light chain type MM and IOP (P= .003). Half of the lambda light chain MM patients (7/14) had IOP. We could not observe any difference regarding treatment response, and survival with IO. In conclusion, iron overload is not infrequent MM at diagnosis. The underlying pathobiological mechanisms should further be elucidated.

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The Patients of Age 45 Years and Under with Multiple Myeloma Not Confer Superior Survival

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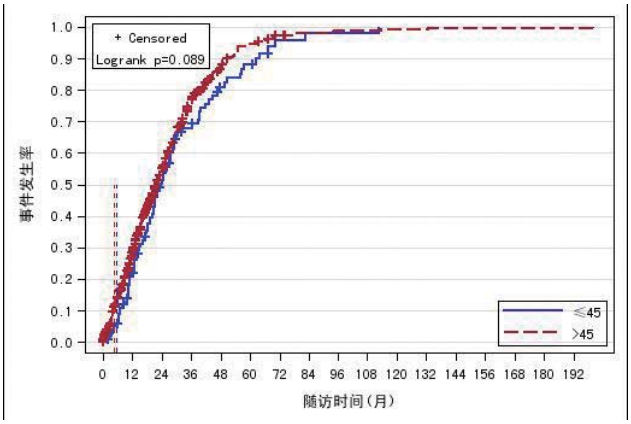
Objective: To describe presenting features and outcomes of patients younger than 45 years of age with multiple myeloma (MM) and compare to an older cohort. Method: 106 patients aged 45 years or less at the time of diagnosis of MM were compared with 893 patients older than 45 years from multicenter. The characteristics, ISS and the Durie-Salmon Staging, laboratory parameters and bone marrow morphology information was recorded. G-banding and Fluorescence in situ hybridization (FISH) was performed. With eight-colour fluorescently labeled antihuman monoclonal antibodies to performed Flow Cytometry (FCM) Analysis. Overal survival (OS) and progression free survival (PFS) was calculated for all patients from date of diagnosis. Results: Compared with the older patients, the younger patients were more frequently Immune gloulin (Ig)D type. All other the characteristics, gender, the ISS staging or D-S staging, increased serum creatinine and the OS(figure 1), DFS did not differ significantly between the 2 groups(table 1), also for peripheral neurophathy (p=0.659) , the number of bone leision(p=0.621) ,FISH fingdings (RB1deletion p=0.424, 1q21amplification p=0.344, IgH recombination p=0.712, P53 deletion p=0.689, D13S19 deletion p=0.203). Conclusion: The patients younger than 45 years of age coexist poor and favorable prognostic factors, not confer superior survival in china mainland. Updated analyses and comparison with Western data will be presented. This retrospective study supported by the Celegene company.



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The Impact of C-MYC Related Aberration and Additional Chromosome 8 in Newly/Relapsed Myeloma in Bortezomib/Dexamethasone

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Multiple myeloma (MM) is characterized by a significant heterogeneity and has multi-step genetic abnormalities. Worse prognostic factors have been reported, although c-Myc gene related abnormalities including translocation and gene amplification (GA) have not been fully studied. The significance of aneuploidy of chromosome 8 has not also been unclear in the use of novel agents. Therefore, we retrospectively analyzed the significance of conventional cytogenetic and Fluorescence in-situ hybridization (FISH) analysis in newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM). Among 53 NDMM, the incidence of non hyperdiploidy (N-HD) by conventional cytogenetic analysis, IgH/FGFR3, del p53, IgH/c-Myc, c-Myc gene amplification, and additional chromosome 8 by FISH was 11.3%, 19.2%, 9.7%, 3.8%,11.5%, and 7.7%, respectively. In the present study, worse prognostic factors were defined as having at least one of the present of N-HD, IgH/FGFR3, delp53, and the incidence was 37.0%. Forty NDMM received bortezomib and dexamethasone (BD) therapy. At the median follow up duration was 399 days, 14 RRMM were recognized, and the number of c-MYC/IgH, c-Myc GA, and additional chromosome 8 at diagnosis were 2, 5, and 2, respectively. At refractory or relapse, 2 obtained c-Myc GA and 4 gained additional chromosome 8 as an additional aberration. In total, 12 of 14 RRMM had both or either abnormalities of c-Myc gene related abnormalities and/or additional chromosome 8. Therefore, these aberrations might be related to worse prognostic factors.

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Adverse Events during Bortezomib-based Induction Therapy Affect the Possibility of ASCT and Outcome in Young MM Patients

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Bortezomib-based induction therapy has elicited high response rate in multiple myeloma (MM) patients. However, some patients can not proceed with autologous stem cell transplantation (ASCT) because of their pre-transplant condition. In Japan, therapy with bortezomib was coverd by health insurance only for refractory MM patients between 2006 and 2011. We retrospectively reviewed the outcomes of 35 consecutive MM patients who were eligible for ASCT before starting induction therapy and received twice-weekly bortezomib and dexamethasone (Dex) after 1-5 cycles of high-dose Dex during this period. The study included 20 men and 15 women, with 38-65 years old at diagnosis. Seventeen patients could not undergo ASCT due to peripheral neuropathy (PN; n = 5), disease progression (n = 3), poor mobilization (n = 3), renal failure (n = 2), or other reasons (n = 4). Compared the ASCT and the non-ASCT group, grade 3/4 adverse events (AEs) during induction therapy were observed more frequently in the non-ASCT group ($p < 0.001$). Overall survival (OS) was significantly higher in ASCT group than in the non-ASCT group (2-year OS, 85.7% vs. 56.5%, $p = 0.01$). Treatment discontinuation before ASCT was associated with inferior OS in both univariate (hazard ratio [HR] = 9.4, $p = 0.04$) and multivariate (HR = 29.5, $p = 0.01$) analyses. Thus, in patients

treated with bortezomib, development AEs, including PN influenced the possibility of ASCT, which affected prognosis. Appropriate management for bortezomib-specific AEs may be important to improve the prognosis of young MM patients.

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Prognostic Value of Expression of CD45 and CD49d in Newly Diagnosed Multiple Myeloma.

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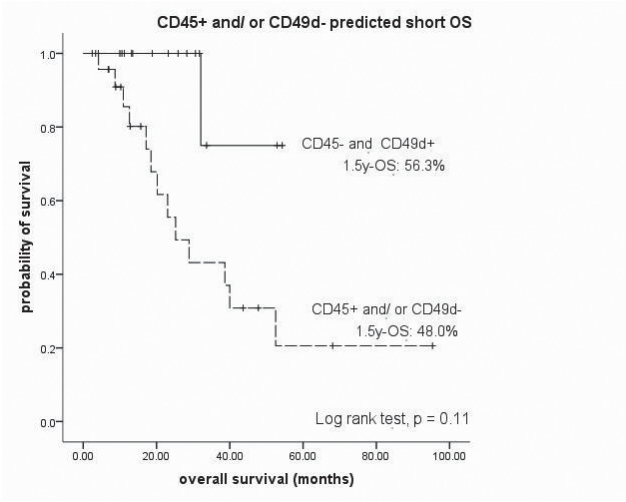
Introduction: Expression of CD45, CD49e, and MPC-1 by flow cytometry (FCM) has reported as a predictor for overall survival (OS) in multiple myeloma before bortezomib (BOR) was available. On the other hands, a predictive value of surfaced marker by FCM was controversial after BOR was clinically available. Patients and Methods: We retrospectively analyzed thirty-eight patients with newly diagnosed multiple myeloma from January 2005 to June 2012 in our institute. We evaluated five kinds of surfaced marker of CD38 positive cells at diagnosis; such as CD19, CD45, CD49d, CD49e, and CD56. We classified patients into two groups based on the numbers of CD45 positive, and CD49d negative. We defined patients with zero prognostic factor and one to two prognostic factors as low risk and high risk, respectively. OS was analyzed by Kaplan-Meier method. Prognostic factors, such as surfaced marker, ISS, and administration of BOR, for OS were evaluated by Cox regression analysis. Result: Median age was 64.6 years. Twenty-four patients received BOR as induction or salvage therapy, and 14 patients had never received BOR. The median follow-up time was 18.9 months. The OS rate at one and half years in high-risk patients was worse than low-risk patients (48.0% vs 56.3%; p = .011). In multivariate analysis, high-risk by FCM was a significant predictor for OS compared with no administration of BOR and ISS 3 (hazard ratio 10.759, 95% CI 1.335 - 86.733; p = .026). Conclusion: CD45 positive and CD49d negative by FCM predicted short OS in newly diagnosed multiple myeloma patients after BOR was available.



P-329

Ascites Formation and Response to Intra-peritoneal Dexametasone in the Course of Refractory Myeloma

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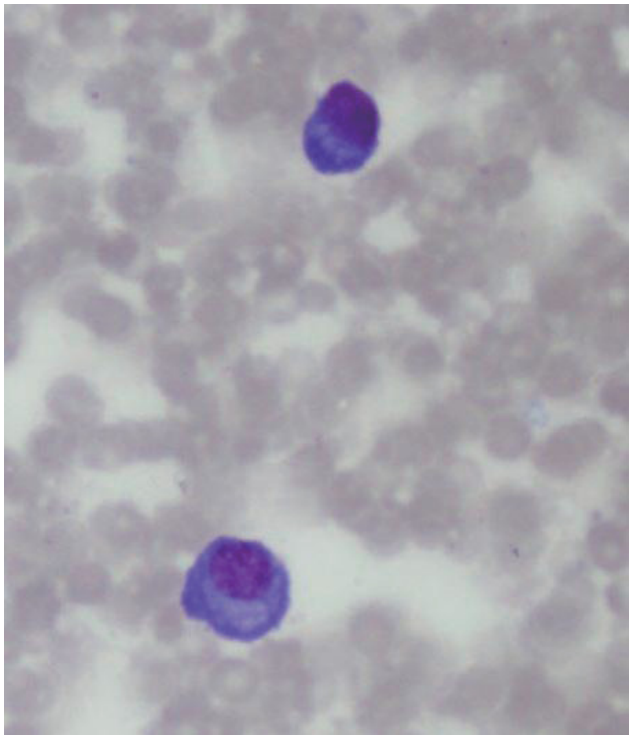
Ascites is a rare complication of multipl myeloma and generally occurs because of portal hypertension due to the infiltration of liver by plasma cells. Infrequently, ascites is detected as a result of peritoneal infiltration by myeloma cells. We, hereby, present a case with sudden ascites due to peritoneal infiltration by malignant plasma cells and responded to intra-peritoneal dexametasone application. Forty-eight years old male was diagnosed with stage 2A non-secretory myeloma in Dec-08 and treated with VAD. He relapsed in July 2009 and treated with bortezomib containing VCD regimen After 8 cycles, renal failure has developed and he was undergone regular hemodialysis programme. He was followed-up with stable disease until development of abdominal distantion and ascites was detected in the abdomen at May 2012. Small lymphocytes, polymorphonuclear leukocytes, mesotelial cells and atypical plasma cells were detected in cytological examination of the ascites. Patient was accepted as peritoneal infiltration of multiple myeloma and regular paracentesis was performed every other day for palliation. But ascites was refractory to regular paracenthesis and forty miligrams of dexametasone was given as intraperitoneal injection after each paracentesis for 3 times. Ascites decreased and plasma cells disappeared. But, patient died due to septic shock. Peritoneal involvement by plasma cells is rare but it should be considered in patients with refractory ascites. When peritoneal involvement detected, intraperitoneal dexametasone injection can be used

as palliation.



P-330

May Hemoglobin Values be an Early Dredictive Indicator for Response to Thalidomide ?

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In this study, we aimed to evaluate myeloma patients under treatment of thalidomide and investigate the potential predictive value of increase in hemoglobin levels as an indicator for response to thalidomide therapy. Thirty-four myeloma patients treated with thalidomidebetween 2001 and 2012 in our center were enrolled to this analyses. The relationship between the variables (age, sex, first and second chemotherapy regimens, daily thalidomide dose, complete blood count with first 3 months after initiation of thalidomide) and OS, PFS were evaluated. After thalidomid prescription, the first 3 months hemoglobin levels were extracted for evaluation. The time from diagnosis to the use of thalidomide was found as 26.1 months. The median thalidomide dose was 285 mg/day and the median duration of thalidomide use was 20 months. The median values of the patients before the use of thalidomide were; Hb: 11.6 g/dl, Htc: 34.8% and third month values were; Hb: 12.0g/dl, Htc: 36.2%. There were no statistically significant difference in hemoglobin levels before and after thalidomidein bot patients cohort with stable and progressive myeloma status. OS was 65.5 months, survival after initiation of thalidomide was 39.2 months and PFS was 20.3 months in our patients' cohort. Although there was no difference in patients with stable and progressive disease status under treatment with thalidomide in terms of hemoglobin levels, it is needed to have longer follow-up period. Hemoglobin levels may be good indicator for evaluation of response to thalidomide therapy.

P-331

Normalisation of Serum FLC Ratio in CR Does Not Improve Progression Free Survival of Myeloma after Upfront SCT

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Introduction: Serum free light chains (sFLC) have been introduced as one of the parameters of stringent complete remission in multiple myeloma (MM). However prognostic significance of normalization of sFLC in patients in CR has been challenged. Goal of our study was to evaluate, whether patients in CR with normal sFLC have longer PFS versus those with abnormal sFLC. Patients and methods: We evaluated 63 patients with MM who reached complete remission after upfront autologous stem cell transplantation (Mel200). Analysis of sFLC using FreeLite kits was done. Primary endpoint of our observation was progression free surival in the group with normalised sFLC ratio versus group without. Results: There were 32 men and 31 women among our patients with median age of 60 years (26-67 years). All patients reached immunofixation negative CR, 35 patients (55.6%) reached sFLC normalization. Median follow-up was 31 months. During the time of observation, incidence of relapse was not different in both groups (p=0.73, log-rank test, median time to relapse was 51 months in abnormal sFLC group versus not reached in normal sFLC group). Conclusion: sFLC normalization alone

after autologous transplantation does not improve progression free survival in our group of patients and therefore is not a benefical marker of progression alone. Other markers such as immunophenotyping of marrow after transplantation are probably needed for more detailed CR description.

P-332

Multiple Myeloma and Infections: A Population-Based Study Based On 9,253 Multiple Myeloma Patients

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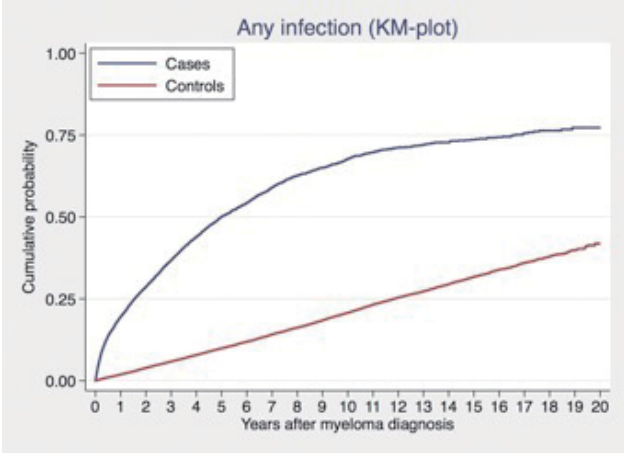
Infections are a major cause of morbidity and mortality in patients with multiple myeloma (MM). We performed a population based study on risk of infections among 9,253 MM patients diagnosed 1988-2004 compared to 34,931 matched controls by using the Swedish Cancer and Patient Registries. Overall, MM patients had a 7-fold (HR= 7.1; 95% CI=6.8-7.4) risk of developing any infection compared to matched controls. The increased risk of developing a bacterial infection was 7-fold (HR=7.1; 95%; CI=6.8-7.4), and for viral infections 10-fold (HR=10.0; 95% CI=8.9-11.4), compared to controls. The risk of infections was highest during the first year after diagnosis; the risk of bacterial infections was 11-fold and the risk of viral infections was 17.6-fold. The risk of infections in MM patients compared to controls increased significantly with time; in the period 1988-1993 the risk was 5.7 fold, in the period from 1994-1999 the risk was 7-fold and in 2000-2004 the risk was 8.9-fold compared to controls. This risk increase was also observed when we restricted our analyses to patients diagnosed after the age of 65 years. Females had a significantly lower risk of infections compared to males (p<0.001). Two months and one year after diagnosis, 22% of the MM deaths were infection-related. Taken together, in this large population-based study, we found that bacterial and viral infections represent a major threat to MM patients. Importantly, the risk of infections increased in more recent years. The effect of novel drugs in the treatment of MM on infectious complications needs to be established.



P-333

High PIM1 Expression Induced by BMSC Cytokines is Associated with Relapse in Patients with Multiple Myeloma

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Background: A proto-oncogene PIM1 is known for its implication in a variety of malignant diseases. Bone marrow stromal cells (BMSCs) appear to play an important role in multiple myeloma (MM) cell growth and osteolytic bone damage. Methods: Using samples obtained from MM patients who received autologous stem cell transplantation (auto-SCT) and U266 and MOLP8 cell lines, we investigated the clinical implication of PIM1 expression and BMSC cytokines and the role of PIM1 expression on p38 MAPK and Wnt/ β-catenin pathways. Results: Real-time PCR analysis revealed that high PIM1 expression was significantly associated with relapse after auto-SCT in MM patients (p=0.01). Patients who relapsed within 6 months after auto-SCT expressed higher levels of BMSC cytokines such as IL-6, sIL-6R, and HGF than the others. In addition, BMSC cytokines activated PIM1-mediated signaling in MM in co-culture. In U266 and MOLP8 cells, IL-6, sIL-6R, and HGF induced PIM1 expression. The

inhibition of PIM1 expression by shRNA decreased IL-6-mediated ERK phosphorylation and HGF-mediated MET phosphorylation, leading to the inactivation of p38 MAPK and Wnt/ β-catenin pathways. In addition, in U266 and MOLP8 cells treated with bortezomib, PIM1 inhibition induced p38 MAPK-mediated apoptosis. Conclusions: High PIM1 expression induced by BMSC cytokines was associated with relapse after auto-SCT in MM patients. PIM1 inhibition regulated p38 MAPK and Wnt/ β-catenin pathways. Our findings suggest that PIM1 could be a predictive biomarker after auto-SCT and a potential therapeutic target in MM patients.

P-334

Prognostic Value of Chromosome 1q21 Gains in Multiple Myeloma: Does the Number of Copies Matter?

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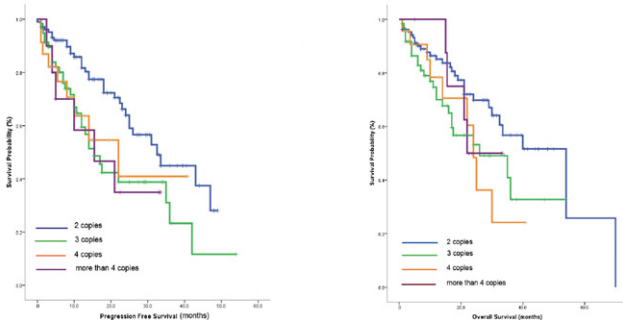
Changes of chromosome 1 are prevalent in multiple myeloma (MM), and gains of 1q are frequently observed. The impacts of copy number variation of 1q21 on the survival of MM are rarely reported and conflicting data exists. It is still unclear whether the copy numbers of 1q21 in positive cells carries any different risk. We explored the prevalence, clinical characteristics and prognostic significance of 1q21 gains in newly diagnosed MM (n=238) and first relapsed myeloma (n=78). Gains of 1q21 were divided into 3 categories: 3 copies of 1q21, 4 copies of 1q21 and at least 5 copies of 1q21. The frequency of 3 copies of 1q21, 4 copies of 1q21 and at least 5 copies of 1q21 in newly diagnosed and relapsed myeloma was 29.6% versus 42.5%(p=0.042), 11.5% versus 20.5(p=0.013), 6.2% versus 8.2%(p=0.547). For the cohort as a whole, gains of 1q21 showed prediction for significantly shortened survival. Median PFS in newly diagnosed patients with 3 copies of 1q21 and at least 4 copies of 1q21 was 14.0 and 21.0 months (p=0.875), and OS was 26.0 and 24.0 months (p=0.875). Our study demonstrated that copy numbers of 1q21 increased with progression of myeloma. However, patients with 4 and more copies of 1q21 at diagnosis had similar EFS and OS compared with those with 3 copies of 1q21.



P-335

Circulating miR-19a and miR-92a in Serum as Potential Biomarkers for Detecting Multiple Myeloma

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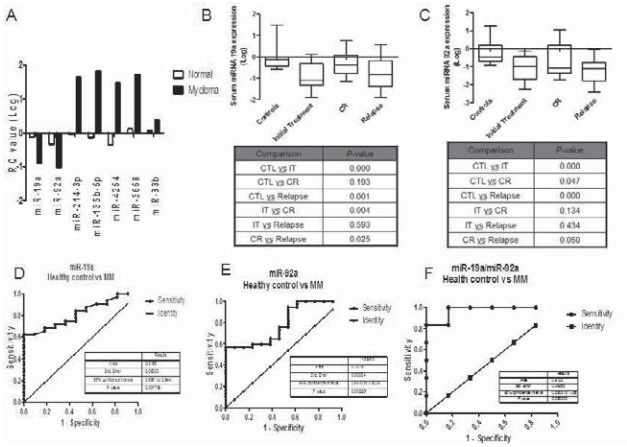
Purpose: Noninvasive and sensitive markers for early diagnosis and better disease classification would be very useful for more effective therapies of myeloma. In this study, we show that circulating miRNAs could work as sensitive biomarkers for the diagnosis, prognosis and treatment evaluation in multiple myeloma. Experimental Design: The exploration phase included 97 patients with 47 symptomatic myeloma in initial treatment, 26 patients in complete remission (CR), 24 patients in relapse and 15 healthy controls. Firstly, the serum miRNA profiles were explored. Ten miRNAs of different expression between myeloma patients and healthy controls were selected from the microarray result (fold change$>$3.0, p$<$0.01). The expression of the miRNAs in myeloma patients with different stage was validated by qRT-PCR. Areas under receiver operating characteristic curves (AUC) were used to determine the feasibility of using serum miRNA concentration as a diagnostic marker for defining myeloma. A multivariate logistic regression analysis was used to evaluate performances of combined serum miRNAs. Results: miR-214-3p, miR-3658, miR-19a and miR-92a, had clinical significance for distinguishing the myeloma patients from normal healthy controls and evaluating treatment efficacy. The combination of miR-19a and miR-92a could provide a more powerful diagnostic tool for distinguishing myeloma patients and healthy control. Conclusions: We have explored the serum miR-214-3p, miR-3658, miR-19a and miR-92a as potential biomarker signatures for diagnosis and treatment evaluation of multiple myeloma.



P-336

Autoimmune Diseases in Course of Immunomodulatory Drugs: Selective Occurrence after Lenalidomide

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Immunomodulatory drugs (IMiDs) have an immunostimulatory activity, more pronounced in Lenalidomide (Len) than thalidomide (Thal). Despite some case reports, a systematic evaluation on autoimmune diseases (ADs) after IMiDs is still lacking. With this purpose, we performed a retrospective study on 135 myeloma patients (pts) treated with Thal, and 113 with Len. Median age at diagnosis of Thal pts was 57 years (range 28-82), and 59 years (range 33-86) for Len pts. ADs were observed before myeloma diagnosis in 7 (5%) Thal, and 6 (5%) Len pts. Median line of treatment at IMiD start was 1 (range 1-4) for Thal pts, and 2 (range 1-6) for Len pts. Thal was administered alone in 5, with steroids in 68, and with chemotherapy in 62 pts, while Len was given alone in 1, with steroids in 99, and with chemotherapy in 13 pts. Overall none of the Thal pts developed ADs, while 8 (7%) Len pts had an AD (p=.002). In particular: one hemolytic anemia grade (G) 3, one autoimmune thrombocytemia G3, one hemolytic anemia G3 plus autoimmune thrombocytemia G3, one polymorphic erythema, one parapsoriasis, one acute thyroiditis, one optic neuritis, and one fatal case of polymyositis. We observed a bimodal pattern, since 6 ADs, including all cytopenias, occurred within the first 3 cycles, while the onset of parapsoriasis and polymyositis were at the 50th and 40th cycle. In 6 out 8 cases Len was part of the first line of treatment. No other correlations were observed. In conclusion Len treatment has a not negligible risk of AD, in particular in the first months of treatment.

P-337

12p Deletion is Heterogeneous in Multiple Myeloma and Associated with Disease Progression and Adverse Prognosis

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Background: Chromosome 12p deletion has been recently reported to exist in about 10% of MM patients and predicts poor prognosis by SNP array. However,the impact of del(12p) on clinical outcome is controversial. The aim of our study is to detect 12p genetic abnormality and analyse its prognostic significance in MM patients. Methods: I-FISH was performed on purified 138+ plasma cells from 253 newly diagnosed, 181 relapsed MM patients, 8PPCL, 6SPCL and 5MGUS patients by using probe covered 12p13.31 region that contains the CD27 gene (BAC clone:RP11-72G18). Cut off value is 10%. Results: del(12p13.31)was detected in 9.5% of newly diagnosed,14.5% of relapsed patients(9.5% vs 14.5%,P=0.045) and 33.3% SPCL (14.5% vs33.3% ,P=0.006; 9.5% vs 33.3%, P=0.000). However, no 12P13.31 abnormality was detected in 8PPCL and 5MGUS patients. With a median follow-up time of 16.5(1-74) months, untreated Patients with del(12p13.31) had significantly shorter PFS (16.5vs 23months)(p=0.018) and OS (21 vs 40months)(P=0.028) compared with patients without del(12p13.31). However, del(12p13.31)had more obvious prognostic significance in relapsed patients with shorter PFS(3 VS 17 months,P=0.000) and OS(11 VS 32 months,P=0.000). Moreover, we found amp(12p13.31) also presented in 5.4% of untreated Patients and 11.8% of relapsed patients(p=0.006),but no prognostic difference between the amp(12p13.31) and without amp(12p13.31) patients. Conclusion: Our results indicate that the chromosome 12p deletion is heterogeneous in multiple myeloma patients and associated with disease progression and adverse prognosis.

P-338

Safety of Autologous Stem Cell Transplantation (ASCT) in Relapsed Multiple Myeloma

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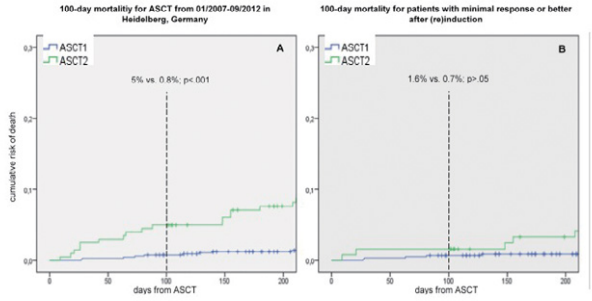
Background: Several studies have supported the role of ASCT for patients with relapsed myeloma (rMM). Reports on safety & early (100-day) mortality of ASCT for rMM are rare & usually include small numbers of patients. Design & Methods: We retrospectively analyzed the outcome of ASCTs for MM at our center from 01/2007 to 09/2012 (n=854). To investigate safety & 100-day mortality, we compared toxicity & mortality data of ASCT in rMM (ASCT2; n=201) with data from upfront ASCT (ASCT1; n=653). Results: Overall mortality of ASCT was 1.8% (n=15) during the first 100 days. Causes of death (CoD) included progression of disease (n=6), infections (n=5) & hemorrhages (n=2). In two cases CoD could not be determined. 100-day mortality of ASCT2 (5%;n=10) was significantly higher compared to ASCT1 (0.8%;n=5; p<.001; A). However, no significant difference in 100-day mortality between the groups was found when comparing patients who achieved at least a minimal response upon (re)induction therapy (ASCT2:1.6%;n=2; ASCT1:0.7%;n=4; B). Comparison of patients >65y with patients <65y revealed no significant difference for 100-day mortality. Analysis of hospitalization data (days in hospital/fever/i.v. anti-infectives) revealed no significant differences between ASCT2 & ASCT1 but showed significantly longer durations of hospitalization & days with fever/i.v. anti-infectives for patients >65y compared to younger patients (C). Conclusions: ASCT for rMM is safe for patients who achieved at least a minimal response after reinduction therapy. For patients >65 years, ASCT is a safe option for primary & salvage therapy.



C

	Type_of_TPL			Age_category		
	upfront	relapse	p	<65	>65	p
Days in hospital	21.1 ±5.2	21.2 ±7.4	>.05	20.6 ±4.5	22.8 ±8.8	<.01
Days in ICU	0.19 ±2.2	0.37 ±2.5	>.05	0.13 ±1.4	0.6 ±4.2	<.01
Days fever	3.57 ±3.4	4.2 ±5.2	>.05	3.5 ±3.4	4.6 ±5.2	<.01
Days iv antibiotics	8.0 ±5.5	8.1 ±5.6	>.05	7.6 ±4.3	9.8 ±8.4	<.01
Days iv antimycotics	0.97 ±4.5	1.4 ±5.1	>.05	0.9 ±3.2	1.8 ±8.0	<.01

P-339

Health Maintenance and Preventive Care Practices of Myeloma Survivors

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Background: Health Maintenance (HM) practices are essential to prevent illness, promote and maximize health. Patients with multiple myeloma (MM) are at risk to develop hypertension, diabetes, cardiovascular disease, and secondary cancers. Each are main causes of death [1-2]. Despite the increased risk of death from modifiable causes, little is known regarding the HM of MM survivors. Data Sources: To identify current knowledge and research in HM and MM, a PubMed search was conducted using the terms: preventive, health maintenance, and multiple myeloma. Data Synthesis: The search yielded limited results. Several studies identified a higher risk for heart disease in patients with hypertension, cigarette smoking, and altered lipid levels [3]. Hyperlipidemia, inactivity, and adiposity can lead to early cancer-related mortality [4-8]. The risk to develop second cancers once diagnosed with MM increases over time [9]. Conclusions: Despite a risk of death from non-MM related conditions, HM practices are not routinely exercised in MM survivors. Research in the area is deficient. Insight into HM is critical to modify risk factors and prevent complications throughout the lifespan. Implications: We have designed an anonymous internet-based survey to assess unmet needs in MM patients. The survey will be distributed through the International Myeloma Foundation and through the Association of Cancer Online Resources. A goal of the research is to incorporate HM practices into the plan of care to decrease mortality from preventable illnesses, and increase cancer surveillance.

P-340

A Placebo Controlled Study to Estimate the Effect Size of Glutamine to Prevent Peripheral Neuropathy in Myeloma

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Background: Bortezomib is used in almost every multiple myeloma (MM) patient. Peripheral neuropathy (PNP) remains a common dose-limiting side effect despite SC or weekly administration which may reduce PNP risk. PNP symptoms range from mild discomfort and loss of sensation, to pain or paralysis.[1] Oral glutamine is an amino acid supplement and has been shown to prevent oxaliplatin and paclitaxel induced PNP in solid tumor patients. [2-4] Anecdotal evidence suggests glutamine may reduce PNP in patients with MM. [1, 5-7] No prior studies have evaluated the efficacy and tolerability of glutamine in MM. Methods: In this double-blind, placebo-controlled trial, patients with MM and treated for the 1st time with bortezomib will receive glutamine 30gm daily in divided doses or placebo for 4 months. Objectives: We plan to accrue 60 patients to estimate the objective effect size of glutamine as a prophylactic intervention to prevent bortezomib-related PNP in MM patients using a placebo control group and an objective neuropathy assessment tool. Secondary objectives include response rate (RR) and clinical benefit response rate (CBR) according to uniform international response criteria and modified EBMT criteria, adherence and QOL at 4 months. [8-10] Conclusions: Identifying supplements to prevent PNP has the potential to improve quality and length of life for MM patients since it would expand therapeutic options. This trial will determine if glutamine may be the first agent to prevent bortezomib-related neuropathy.

P-341

Single Center Experience of Myeloma Patients Treated with Lenalidomide

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We have aimed to evaluate myeloma patients in terms of demographic features and clinical status treated with lenalidomide. Data of thirty-four patients who have been treated with lenalidomide with diagnosis of multiple myeloma in our center between 2010 and 2012 were evaluated. The relationship between the variables; age, sex, first, second and third line chemotherapy regimens, daily lenalidomide dose, overall survival (OS), mortality were analyzed. The median age of the patients was 61.3 years (45-78 years), and of 22 (64.7%) males and of 12 (35.2%) females. Eighteen patients were stage 3A, 10 were 3B, 4 were 2A, 1 (2.9%) was 2B and 1 (2.9%) of the patients was stage 1A. Most of the patients were IgG/kapa myeloma. ASCT was performed in 15 patients before the lenalidomide treatment. Median time from diagnosis to use of lenalidomide was found 33.1 months. In all cases, lenadilomide was combined with dexametasone. Lenalidomide treatment was used as a second line therapy in 9 (26.4%), as a third line treatment in 17 (50%) and as a fourth line therapy in 8 (23.5%) patients. The median lenalidomide dose was 18.3 mg/day (5-25 mg). OS was 44 months. Lenalidomide was ceased in 4 (11.7%) patients because of progression and in 4 (11.7%) patients because of persistent cytopenias. One (2.9%) patient died under lenalidomide. Lenalidomide treatment stil continues in 25 (73.5%) patients. According to our results, lenalidomide was provided to our patients at least after 2 or 3 prior therapies with lesser efficacy and relatively high side effects

P-342

Large Size of Deletion is Common in Chromosome 1P Abnormalities and Predicts Poor Prognosis in Multiple Myeloma

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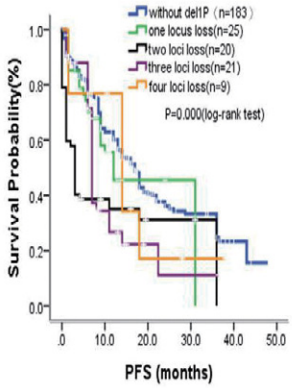
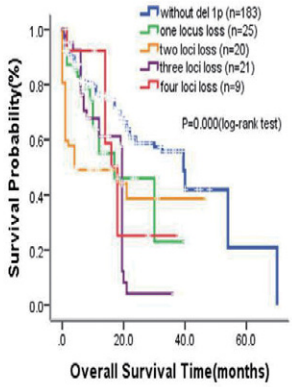
Background: Chromosome 1p abnormalities associated with adverse survival have been recently reported in MM. However, no uniform consensus has been obtained. The aim of this study was to discover characteristics of chromosome 1p abnormalities and the impact of these abnormalities on clinical outcome. Methods: I-FISH was performed on purified 138+ plasma cells from 258 newly diagnosed MM patients. The probes covered the following loci:1p12,1p13.3, 1p21,1p32.3 using BAC clone RP11-418J17,RP11-180N18,RP11-776K10 and RP11-278J17 that contain FAM46C,AHCYL1,Cdc14A and CDKN2C genes. Results: 1p12,1p13.3,1p21 and 1p32.3 deletion rates were 18.8%, 21.9%, 25.1%, 15.6%. Amp(1p12,1p13.3, 1p21 or 1p32.3) were also detected in some patients with amplification rates being 2.8%, 2.8%, 3.5%, 0.2%. Surprisingly,deletion and amplification could coexist in the same patient. 75 patients presented in at least one locus deletion. Among them,77.3% patients had large size of deletion involved two or more loci. Regions involving three loci were mainly 1p12,13.3 and 21,accounting for 82.5%, instead of 1p13.3,21 and 32.3 17.5%. With a median follow-up time of 16.5 (1-74) months, patients with del(1p) had significantly shorter PFS(median:14,3,7,12months) (p=0.000) and OS (median:17,4,19.5,18months) (P=0.000) compared with patients without del(1p) (median PFS:17 months, OS:39.5months). Conclusions: Our results indicate the chromosome 1p abnormalities are complex,various in forms,

mainly large size of deletion,rarely amplification. Del(1p)is a adverse prognostic factor in patients with multiple myeloma.





P-343

Infectious Complications of Bortezomib Regimen in Myeloma

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Bortezomib is a proteasome inhibitor with potent antimyeloma activity in relapsed/refractory multiple myeloma (MM) patients. We evaluated the type and factors affecting the onset of infectious complications and mortality owing to infection in MM patients treated with bortezomib-based regimens. We reviewed 139 patients with MM treated with regimens containing bortezomib in order to assess the type and factors affecting the development of severe infections. Infections occurred in 56 (40.3%) of 139 patients and 83 (7.8%) cases of the 1,069 evaluable cycles. Severe infections developed in 43 (30.9%) patients and ten patients (7.1%) died during bortezomib-based treatment. Multivariate analysis determined lymphocytopenia grade 3-4 (OR 3.17, 95% CI 1.38-7.31, p = 0.007) and number of cycle < 8 cycles (OR 3.91, 95% CI 1.39-11.02, p =0.010) as risk factors associated with increased severe infection. This study showed that MM patients who received bortezomib-based regimens are at a higher risk of severe infections within eight cycles of treatment during especially severe lymphocytopenic period. MM patients treated with bortezomib-based regimens should be closely monitored for the development of infectious complications during lymphocytopenia.

P-344

International Staging System may not be Useful to Predict Prognosis of Multiple Myeloma Patients in the Novel Agent Era.

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Introduction: The international staging system (ISS) is established for patients with multiple myeloma (MM) before the introduction of novel agents for myeloma treatment, and was the most widely used staging system. However, the applicability of the ISS for patients who are exposed to novel agents has not been elucidated. The objectives of this study were to re-evaluate the prognostic factor in MM patients treated with novel agents. Methods: Between July 1993 and June 2012, 187 patients [median age 65.5 (30-87); male/female, 92/95; ISS1 (n=43), 2 (n=64), 3 (n=53), unknown (n=27)] diagnosed as MM were included. Overall survival (OS) was estimated by the Kaplan-Meier method. Results: In all 187 patients, 86 patients (46%) were treated with novel agents (NT group) and 101 patients (56%) with conventional therapy (CT group). The median OS was 64 months, with a significant increase of NT group compared to CT group (68 and 45 months, respectively; p=0.002). The median OS of all patients with ISS 1 and 2 was significantly better than with ISS 3 patients (73, 53, and 48 months, respectively; p=0.03, 0.008). However, no significant differences of OS were observed in NT group by the ISS stage (73, 64 and 68 months, respectively). Multivariate analysis in all patients showed an independent prognostic significance of ISS (p=0.008); however did not show prognostic significance of ISS in NT groups. Conclusions: The findings of our study indicate that ISS is not applicable to prognostic prediction for MM patients in the novel agent era.

P-345

Prognostic Significance of L-type Amino-acid Transporter 1 Expression in Multiple Myeloma

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Background: L-type amino-acid transporter 1 (LAT1) play a key role in the transport of large neutral essential amino acids as well as in cell growth and survival. The expression of LAT1 closely correlates with amino acid PET uptake. This study was conducted to determine the prognostic significance of LAT1 expression in patients with untreated multiple myeloma (MM). Method: One hundred consecutive patients with newly diagnosed MM were retrospectively reviewed. Bone marrow plasma cells (BMPC) expression of LAT1, 4Fc heavy chain (CD98) and Ki-67 at diagnosis was evaluated via immunohistochemistry, and the relationship of these variables with clinical factors was investigated. LAT1 and CD98 expression scores were assessed by the intensity and extent of membrane staining: 0, no staining or <10%; 1+, faint ≥10%; 2+, weak to moderate ≥10%; and 3+, strong ≥10%. The percentage of BMPC expressing Ki-67 (i.e., Ki-67 index) was also calculated by double-staining for CD138 and Ki-67. Results: The LAT1 expression score significantly correlated with the CD98 expression score and the Ki-67 index. Strong LAT1 staining intensity (score 3+) closely associated with ISS stage 3 disease, chromosomal abnormalities and shorter overall survival. Multivariate analysis indicated that LAT1 expression was a significant prognostic factor, independent of ISS. Conclusion: Overexpression of LAT1 is a novel pathological marker for high-risk MM.

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High Serum ICTP is Associated with Short Survival and Future Bone Fractures in Untreated Multiple Myeloma Patients.

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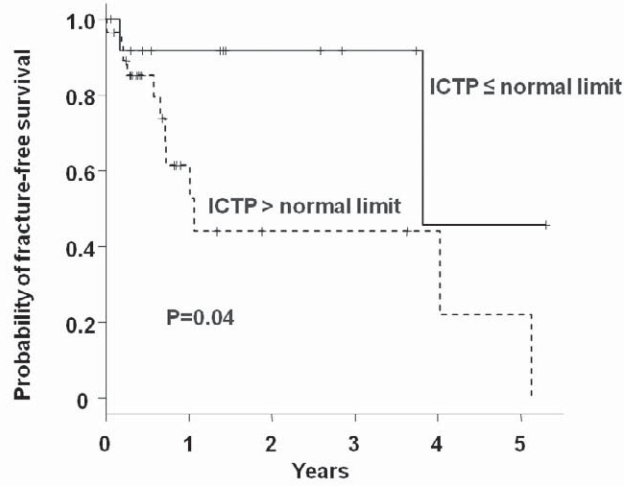
Although various biochemical markers of bone remodeling have been investigated, their clinical impact on bone events and survival in multiple myeloma has not been fully determined. In this single center retrospective study, we evaluated serum C-terminal telopeptide of type I collagen (sICTP), serum bone-specific alkaline phosphatase (sBAP), and urinary amino-terminal collagen type-I telopeptide (uNTx) in 54 previously untreated multiple myeloma patients. These markers were measured before the first treatment to assess the impact on the bone lesions before treatment, future bone fractures, and overall survival (OS). None of these markers were associated with bone lesions at the time of measurements, except for sICTP that tended to be higher in those with bone lesions than those without (10.9 mg/l versus 6.7 mg/l, P=0.14). High sICTP (above upper normal limit: 4.5 mg/l) was associated with marginally worse 2-year OS (59% versus 92%, P=0.08), which was partially attributed to correlation of this marker with well-established prognostic markers (serum albumin; rho=-0.33, p=0.02; figure 1, and serum beta-2 microglobulin; rho=0.75, p<0.001). Furthermore, patients with high sICTP had significantly worse 2-year bone fracture-free survival than those with low sICTP (44% versus 92%, P=0.04; figure 1). Neither sBAP nor uNTx had such correlations. These results suggest that sICTP is a useful marker to predict survival and future bone fractures in untreated multiple myeloma patients.

Figure 1



P-347

Prognosis of ISS Stage I Myeloma

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Background: ISS is a simple and useful system to estimate prognosis. However, by original ISS report, survival time was evaluated after starting of chemotherapy. Our aim was to evaluate the progression and survival time after initial staging of ISS for newly diagnosed, untreated MM patients. Especially, treatment strategy for ISS stage I was received attention. Methods: 127 newly diagnosed, untreated MM patients referred to Nihon University Itabashi Hospital were retrospectively analyzed. ISS stage was determined with the laboratory data at the first visit. Median age of the patients was 62 years

(range 30-88). Median follow-up duration was 32.5 months (range 0-171). Chemotherapy was performed mainly with MP or VAD. Patients treated with thalidomide, lenalidomide, or bortezomib were excluded. Survival curve was censored at the time of transplantation. Results: 50% survival durations after initial diagnosis of stage I (n=54), II (n=26), and III (n=47) patients were 106, 36, and 14.5 months, respectively. 15 stage I patients have not been treated and all of them are alive. 50% progression time from ISS stage I to II in untreated patients was 2 months. For the patients treated at ISS stage I, 50% progression time from stage I to II, and I to III were 61 and 155 months, respectively. Conclusion: We defined prognosis of ISS stage I patients. Certain amounts of MM patients with ISS stage I at diagnosis were not required chemotherapy. Chemotherapy may prolong the progression from stage I to II or III.

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Myeloma Treatment in the Austrian Myeloma Registry:Fast but Cautious Approach to Novel Agent (NA) Based MM Therapies

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Introduction: The AMR was set up in 2008 under the auspices of the austrian haematoloical society (OeGHO) for quality control, pharmacovigilance, research and HTA. It is supported by the COMET Center ONCOTYROL and funded by public grants. Methods: A web based interface was developed and approval of all competent authorities obtained. Retrospective data back to the year 2000, as well as prospective data on all MM pts., which had at least one course of treatment were analyzed as of JAN 06 13. Results: 320 pts. were recruited of which 277 pts. met inclusion criteria. Median age of pts was 64 years (35-88a), median number of treatment lines was 2(1-8) with 48,9% of pts. still alive and median survival was 60 months with 48,2% of pts. reaching a best response of VGPR or better. Cytogenetic data was available for 77% of pts.. 39,3% of pts. received an autologous transplant. While NA based induction therapies totally supplanted MP in elderly pts., and VAD in younger pts. within 2 years from 2005. The use of triplet therapies (PAD, VTD) was adopted as a standard in younger only, while in elderly pts. NA-based doublets (VD, RD) are still more frequently used than triplets (ratio 4:1). Also maintenance therapies up to now have been introduced in only 30% of cases. Discussion: While real life institution of NA based therapies has been fast in Austria, in elderly pts. a cautious approach has been widely adopted with regard to the use of more intensive induction and maintenance therapies. Pros + cons of this attitude, as well as possible reasons for this approach will be discussed.

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Second Primary Neoplasms (SPN) after Autologous Hematopoietic Cell Transplantation (AHCT) for Myeloma: CIBMTR Analysis

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Determining the baseline incidence and risk factors (RF) associated with SPN after AHCT is important to assess the risk of the procedure and evaluate the risk-benefit ratio of therapies pre and post AHCT. The analysis includes 3784 MM pts receiving AHCT between 1990 and 2008. Cumulative incidence (CI) rates of SPN were estimated taking into account the competing risk of death. Incidence rates for cancers in the population were obtained from the SEER database. Poisson regression model was used to analyze RF for overall SPN and MDS/AML. Median follow-up of survivors was 52 mths (range 3 to192 mths).With 12707 person yrs of follow up, 153 new malignancies were reported. Observed to expected ratios for all SPN was 1.0 (99% CI, 0.8-1.2). CI of SPN was 2.5% (95% CI, 2.0-3.0) at 3 yrs. Individual SPN observed more frequently than expected are summarized in Figure 1. In multivariate analysis, RF for development of SPN included: age [HR10.5 (95%CI, 1.5-75.8), p=0.02] for 60-69 yr olds and [HR14.4 (95%CI, 1.9-109.7), p=0.01] for 70+ yr compared to the 18-39 yr group; obesity [HR 1.9(95%CI, 1.2-2.9), p=0.004 for BMI>30 vs. BMI<25]. Specific con-

ditioning regimens or choice of maintenance therapy did not correlate with risk of SPN. Increasing age was associated with development of MDS [HR10.7, (95%CI, 92.1-55.5), p=0.004 for 70+ yrs vs. 40-49 yrs]. Conclusion: In this large cohort of pts with MM receiving an AHCT, the overall risk of SPN was similar but the incidence of MDS/AML, melanoma and other skin cancers was higher compared to age and sex matched general population.

Ratio of observed to expected (O/E) cases of SPN at various time periods post AHCT for MM
(99% confidence intervals)

Time period	2-5 years	5-10 years	10-20 years	Overall
Person-Years at risk	**4502**	**1769**	**158**	**12707**
All SPM	1.0 (0.7–1.4)	1.4 (0.8–2.1)	2.4 (0.6–6.3)	1.0 (0.8–1.2)
MDS	105.6 (43.5–212.5)	109.7 (28.1–286.3)	172.9 (0.9–1284.5)	85.5 (48.5–139.0)
AML	7.4 (1.2–23.4)	8.3 (0.4–38.4)	83.1 (4.3–385.5)	5.5 (1.8–12.7)
Melanoma	1.6 (0.2–6.0)	3.8 (0.4–13.9)	14.1 (0.1–104.9)	3.4 (1.6–6.1)
Other skin cancers	29.4 (4.9–92.5)	81.3 (17.6–231.3)	None	37.8 (16.8–72.4)

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Relapse Pattern after Bortezomib-based Salvage Therapy in Patients with Multiple Myeloma

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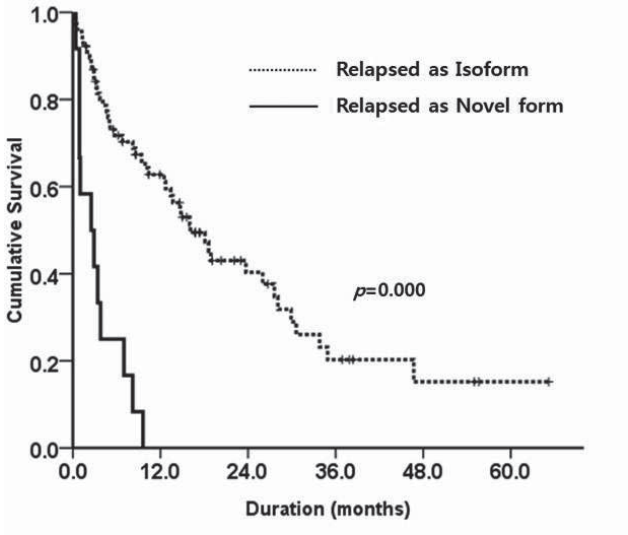
Aims: We retrospectively evaluated relapse patterns after bortezomib-based salvage treatment in patients with MM and analyzed prognostic significance according to relapse patterns. Methods: One hundred thirty-two patients were received by bortezomib-based salvage therapy between Nov. 2004 and Aug. 2011. Eligibility criteria included primary refractory or relapsed MM patients who received at least 2 cycles of bortezomib-based salvage therapy. Results: Of all 132 patients, 91 (68.9%) were relapsed after bortezomib-based salvage therapy. We divided the relapse patterns to the two groups as following: 1) the same relapse pattern (group A) in 77 (84.6%) patients as disease findings at initiation of bortezomib-based therapy and 2) the novel relapse pattern (group B) in 14 (15.4%) patients (plasmacytoma: 7, light chain escape pattern: 5, and plasma cell leukemia: 2) different from initial disease findings. Median overall survivals in group A and group B were 16.1 and 2.5 months ($p < 0.001$), retrospectively (Fig). Of the patients, 27 patients received the retreatment of bortezomib, but 24 of 27 patients showed to the disease progression, including 4 (16.7%) of 24 patients relapsed as novel patterns (plasmacytoma: 2, light-chain escape: 1, and intact immunoglobulin secretion from plasmacytoma: 1) and novel relapse group showed to the trend of poor survival (2.2 vs. 10.0 mon) ($p = 0.3$). Conclusion: This study suggests that the MM patients relapsed as novel pattern after bortezomib-based salvage therapy showed extremely poor prognosis and might be needed by new innovative approaches.



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Older Adults Newly Diagnosed with Myeloma Want to Participate in Treatment Decision Making

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Background: There is growing interest in direct assessment of patient preferences for all components of treatment decision making (TDM). However, the preferred level of participation in TDM for patients with active myeloma has not been previously studied. Research Aims: To describe the preferences for participation in TDM among patients with active myeloma and to explore the association between sociodemographic variables and decisional role preferences. Methods: A cross-sectional survey approach was employed involving administration of the Control Preferences Scale and an investigator-developed interview schedule. The sample consisted of 20 older adults (60 years of age and above) with active myeloma diagnosed within the past 6 months from two large academic cancer centers. Findings: 55% (N=11) of the participants preferred a shared role with the physician and 40% (N=8) preferred to make the decisions after seriously consid-

ering the opinion of their physicians. Only one participant preferred to relinquish the decision to the doctor. Overall, the percentage of the patients wanting participation during TDM is very high at 95% (N=19). Sociodemographic variables have no impact on preferences for participation in TDM. Conclusions: The study findings indicate that older adults newly diagnosed with myeloma want to participate during TDM. More studies that focus on involving patients with active myeloma in the decision-making process are needed in order to influence clinical practice and policy in this direction.

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Treatment, Prognosis and Self-care are Top Information Priorities of Older Adults Newly Diagnosed with Active Myeloma

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Background: In this era of scarce health resources, prioritizing patient's information needs and priorities maximizes efficiency. Research Aims: This study examined the sources of information and priority information needs of a sample of older adults newly diagnosed with active myeloma. Association analysis of whether information needs were influenced by socio-demographic variables such as age, gender, education, marital status, and income was also conducted. Methods: The Information Needs Questionnaire and an investigator-developed interview schedule were administered to twenty older adults diagnosed with active myeloma during a 30-45 minute semi-structured interview. Results: We found that older adults newly diagnosed with active myeloma are able to prioritize information needs. The top three priorities relate to treatment, prognosis, and self-care. Sociodemographic variables did not influence information needs priorities. The Internet, physicians, and family and friends were among the top sources of information. Conclusion: Health care providers could use the top three information needs found in this study as a starting point in eliciting information needs of older adults with active myeloma. Measures that can enhance the patient' s learning process from the top sources of information such as the Internet and physicians are warranted.

P-353

Analysis of Renal Impairment in Newly Diagnosed MM According to the IMWG Consensus Recommendation

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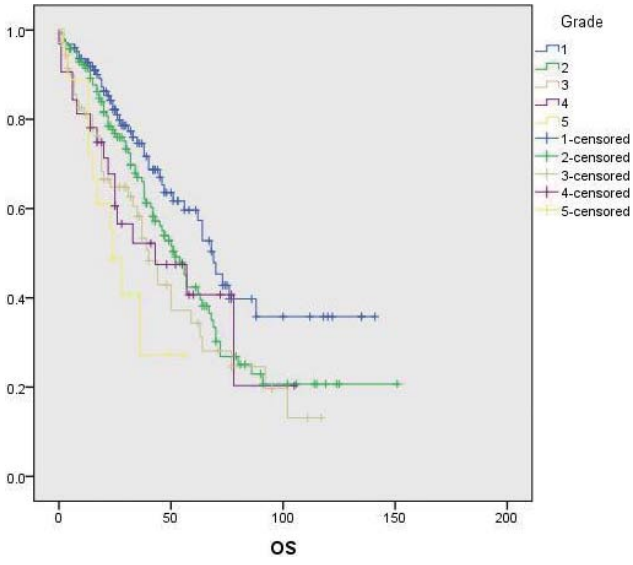
The incidence of renal impairment(RI) in MM and renal response(RR) are variable according to the definition. We analyzed clinical features and prognostic factors related to RI of newly diagnosed MM patients according to the IMWG recommendation. Medical records of newly diagnosed and treated MM patients at a single center from 2000 to 2011 were retrospectively reviewed. Of the 388 patients, 121 patients with renal impairment(eGFR <60 mL/min/1.73 m2) showed significantly old age, less bone lesions, lower hemoglobin, higher beta-2-microglobulin, more hypercalcemia, and high LDH, more plasmacytosis, less plasmacytoma, and advanced ISS stage. Overall survival was significantly different according to the grade of renal impairment (p=0.002, Fig 1). Of the 88 patients who were evaluable for renal response (eGFR <50), RR was 67% and Major RR was 52%. Prognostic factors for major RR were hypercalcemia, plasmacytoma, deletion 13 , eGFR <30mL/min/1.73 m2, use of dexamethasone in the first line treatment, transplantation, and hematologic response(HR). The use of new drugs in the first-line treatment or the use of bortezomib in the first 4 months were not significant. Time to best RR was significantly shorter in patients who used bortezomib in the first-line treatment (66 versus 160 days, p=0.001). OS in patients with major RR was not significantly longer than non-responders (p=0.223). The incidence of RI in newly diagnosed symptomatic MM was 31.2% and OS was significantly shorter. RR was affected by the treatment and HR, but was not translated into significant improvement of OS.



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Multiple Myeloma and Second Primary Malignancy : Results from Single Cohort Study

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Background: Recently, treatment of multiple myeloma (MM) as well as MM itself is considered to be responsible with second primary cancer. We reviewd and analyzed the incidence and characteristics of second primary malignancy in the MM patients. Methods: We collected data of MM patients from multiple myeloma cohort registry of Samsung Medican Center, Korea since 2000. We found patients who were additionally diagnosed of any kinds of primary maligancy other than MM. We analyzed the incidences of second malignancies and their characteristics. Results: Total 436 patients with MM including plasma cell leukemia and solitary plasmacytoma were reviewed and included in the analysis. 36 patients (8.3%) have had both of MM and other primary malignancy. Of these, 14 (3.2%) patients had other cancer priorly, and diagnosed of MM later. 12 (2.8%) patients of MM had second primary malignancy while they were treated or followed-up. These includes two of liver, colon, thyroid, and one of cholangiocarcinoma, prostate, lung, kidney and esophagus, and finally one case of double metachronous cancer of stomach and lymphoblastic lymphoma. 10 patients (2.3%) were found to have synchronous tumors at that time of initial diagnosis of MM. 7 out of 12 patients had been treated with alkylating agent such as cyclophsophamide or melphalan. The median overall survival (OS) between the groups did not statitstial significance. (p=0.24) Conclusion: There was no higher incidence of other primary malignancy among patients with MM. The survival according to having other malignancy did not differ with each other, either.

P-355

Three Hrs Intravenous Administraion of Bor in Myeloma Patients Reduced Severity of Peripheral Neuropathy Induced by Bor

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The proteasome inhibitor bortezomib(Bor) is one of the promising drug for the treatment of multiple myeloma. It has been reported that subcutaneous administration lowering the incidence of peripheral neuropathy(PN) caused by Bor as compared to intravenous. MMY-3021 trial revealed that Bor systemic exposure was equivalent with subcutaneous versus intravenous administration in AUC, and C(max) was lower with subcutaneous administration. We were unable to perform the subcutaneous administration of Bor because they have not been allowed in the health insurance system in Japan. In our hospital, 20 patients(initial tx 15, salvage tx 5) received 21-day cycles of three hours intravenous Bor 1.3 mg/m(2) on days 1, 4, 8 and 11. We retrospectively analyzed the incidence and severity of peripheral neuropathy(PN) induced by Bor. Grade 1 PN occurred in 6 pts, grade 2 PN in 3pts, 11pts did not develop PN. Three hours intravenous administration did not reduce the incidence of PN, however severe PN was not observed. Severe injection site reactions(ISR) were reported after subcutaneous Bor. Three hours intravenous Bor instead of subcutaneous should be considered as one of the administration when ISR induced by Bor become severe.

P-356

Emergence of Oligoclonal Bands after Autologous Stem-cell Transplantation in Patients with Multiple Myeloma

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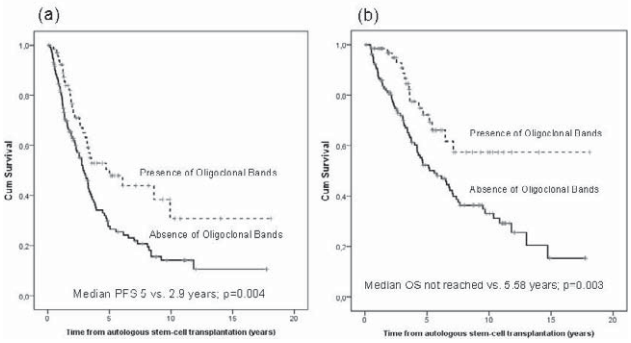
Background: The emergence of oligoclonal bands (OB) is a benign phenomenon frequently associated with complete remission (CR) after autologous stem-cell transplantation (ASCT) in patients with multiple myeloma (MM). The aim of the present study was to investigate the incidence, duration and prognostic value of OB in patients with MM who underwent ASCT at our institution. Methods: 199 patients underwent melphalan-based ASCT at our institution from March 31st, 1994, to December 27th, 2011, and achieved at the least a partial response (PR) after ASCT. A retrospective systematic review of all serum and urine immunofixation studies was carried out. Results: OB were observed in 34% of the patients, with different prevalence according to the use of novel agents vs. conventional chemotherapy in induction (63% vs. 22%; p=0.0001). This phenomena was almost exclusive of patients in CR compared to other degrees of response (92% vs. 8%; p=0.0001) and lasted for a median of 1.35 years. Almost all the OB disappeared before serological and clinical progression. The presence of OB after ASCT resulted in a significantly longer PFS (p=0.004) and OS (p=0.003) (Figure). An oligoclonal humoral response stable more than one year

after ASCT was associated with a significantly longer clinical PFS and OS than those with shorter duration (p=0.008 and p=0.0001, respectively). Conclusions: The emergence of OB after ASCT is a prognostic factor and it is usually observed in patients in CR. Duration of this humoral response is also associated with a significant survival prolongation.

Figure. Progression-free survival (a) and overall survival (b) after autologous stem-cell transplantation according to the presence of oligoclonal bands



P-357

Sensitivity to Batch Effects in Single Array Usage of Multiple Myeloma Gene Expression Survival Classifiers

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Diagnosis and prognosis based on gene expression profiling represents a promising technique for future patient treatment and care. Recently, gene expression classifiers were described which are capable of accurately classifying Multiple Myeloma (MM) patients into high-risk and standard-risk groups. Furthermore, it is clinically necessary to allow classification of single patients, which requires single sample normalization methods such as MAS5 and fRMA. So far, it has not been established how structural differences between datasets, known as batch effects (BEs), need to be countered if single patients are classified. Therefore, we have analysed the EMC-92, UAMS-70 and UAMS-80 classifiers in relation to BEs using MAS5 and fRMA. For this analysis, 5 MM gene expression data sets (Affymetrix U133 Plus 2.0) were available, which were normalized by MAS5 and fRMA. Using Combat, a parametric BE correction (BEC) was applied after which BEC classifier scores were derived. A root mean square value (RMS) of the difference between BEC and non-BEC scores are used as BE related sensitivity measure. The RMS values were determined per batch and signature resulting in 15 values per normalization method (Figure 1). According to the one sided paired Wilcoxon test the RMS was significantly smaller in fRMA in comparison to MAS5 normalized data (p=0.02). This is principally caused by a better RMS for the EMC-92 and UAMS-80 classifiers. Our conclusion is that fRMA is the method of choice for single sample classification.

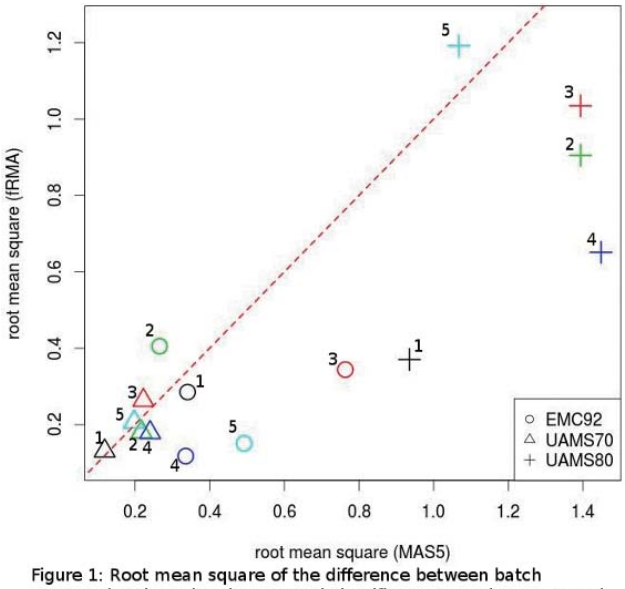

Figure 1: Root mean square of the difference between batch corrected and non batch corrected classifier scores using MAS5 and frozen RMA normalization. This difference tends to be smaller upon using the fRMA method; 1. HOVON-65; 2. MRC-IX; 3. GMMG-HD4; 4. TT2; 5. TT3.

P-358

Analysis of Point Mutations within CCND1 in Multiple Myeloma

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Background: Point mutations within the CCND1 (cyclin D1), which has been recognized as a target of chromosomal translocation in multiple myeloma (MM), were recently reported by whole-genome/exome sequencing analysis. However, its relation to abnormal expression of the gene or clinical significance remains unclear. Materials and methods: After screening of MM samples for expression of CCND1 by RT-PCR and IHC, CCND1-positive ones were subjected

to direct sequencing after amplification of the entire coding region of CCND1. Results: 17 (11 missense and 6 sense) point mutations were identified in 14 (31%) out of 45 cases with strong expression. All missense mutations were present in the region between Rb-binding and cyclin-dependent kinase (CDK)-binding domains. In cases in which genomic DNA was analyzed, mutations were heterozygous and only the mutant alleles were expressed. Missense mutation was also observed in one case with monoclonal gammopathy of undetermined significance. No mutations were detected in 22 MM cases with weak expression of CCND1 and without translocation. No definite correlation between presence of missense mutation and clinical outcome was shown, although received treatments were various. Conclusion: Point mutations within CCND1 were observed in near one third of MM cases with strong expression of the gene and considered to generate from somatic mutations accompanied by chromosomal translocation with immunoglobulin heavy chain gene. Although the location of missense mutation was characteristic, its clinical significance was not established in our study.

P-359

Expression of CREB and VEGF, and Microvessel Density in Multipl Myeloma

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Background: Enhanced angiogenesis is an important step in the growth and progression of multipl myeloma (MM). Cyclic AMP-regulatory element-binding protein (CREB) is a transcription factor, and appears to play a direct role in cancer pathogenesis and prognosis. Vascular endothelial growth factor (VEGF) is a glycoprotein that plays an important role in both pathogenesis and progression of MM. Methods: A total of 76 patients with newly diagnosed MM were studied. Microvessel density (MVD) was examined using immunohistochemistry for Factor VIII antibody. The association between expressions of CREB, VEGF, and MVD by immunohistochemistry and clinical features, laboratory findings, histopathological features, and response to treatment was analyzed. Results: High percentage of plasma cell infiltration was correlated with high-grade MVD and high VEGF expression (p=0.02 and p=0.002, respectively). There was significant association between high CREB expression and high-grade MVD (p=0.01). Both high-grade MVD and high CREB expression showed a trend for higher clinical stage (p=0.2 and p=0.1, respectively). High-grade MVD was significantly associated with poor prognosis and shorter overall survival than low-grade MVD (p=0.04). Expression of high-grade VEGF and CREB showed a trend for poor survival (p=0.2 and p=0.1, respectively). Conclusions: High-grade microvessel density and high expression of VEGF and CREB are correlated with progression of MM. Targeting therapy directed to angiogenesis, VEGF and CREB may be used to improve therapy.

P-360

Risk Factors for Bortezomib Induced Peripheral Neuropathy in Multiple Myeloma Patients

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Bortezomib induced peripheral neuropathy (BIPN) is a common adverse effect in multiple myeloma (MM) patients. We report the incidence, risk factors and outcome of BIPN in 93 MM patients with median age 60(32-81) years. A median of 4(1-9) cycles of Bortezomib was administered for advanced disease (refractory/relapsed) in 68 and early stage in 25 patients, as first-line treatment in 8 and was co-administered with dexamethasone: 38, anthracycline: 16, melphalan-PDN: 8. BIPN prevalence was 55/93(59%) patients after a median of 3(1-7) cycles, grade 1 or 2 in 47/55 (85%), causing sensory neuropathy in all, neuropathetic pain in 50% and motor neuropathy in 14% of them. Four patients presented with bowel autonomic neuropathy. BIPN treatment such as pregabalin was needed in 22 (40%) patients. Patients treated earlier in the disease course (0-2 previous lines) had a similar BIPN incidence with heavily pretreated MM patients (53% and 60% respectively, p=ns). In multivariate analysis, incidence and grade of BIPN did not correlate to factors as sex, age, disease stage, renal impairment or other treatment-related toxicities. However, there was a significant correlation to the number of Bortezomib cycles and the response to therapy. In 26/55 (47%) patients treatment was adjusted and discontinued in 10/55 (18%). BIPN recovered totally in 43/55 (78%) or gradually ameliorated in 10/55 (18%) patients. BIPN is a common, usually mild and self restricting adverse effect but needs prompt treatment adjustments, as there is no specific or highly effective treatment.

P-361

Conventional Cytogenetics and Prognosis in Multiple Myeloma

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The prognostic impact of chromosomal abnormalities was evaluated in 134 newly diagnosed patients with multiple myeloma through classical metaphase bone marrow cytogenetics. A total of 129 patients had assessable metaphases and 42 (32.5%) had cytogenetic abnormalities (CA). The most frequently occurring CA were hyperploidy: 24, complex (three or more CA): 21, del13/13q: 15, hypodiploidy: 10, del17/17p: 7, +1q: 7, del1p: 6, t(11;14): 5, MYC translocations:3. The rate of abnormal karyotype increased with stage (p=0.064 for Durie-Salmon and p=0.04 for ISS) and this was obvious for b2 microglobulin level (p=0.001) but not for albumine (p=0.12). High M component level (>5 g/l, p=0.022) and the presence of renal failure (p=0.012) were also statistically significant. Patients with abnormal karyotype had a higher percentage of bone marrow infiltration (median 64% vs 36% for normal karyotype). Overall survival, progression free survival and the response rate were not influenced by abnormal karyotype. Hyperdiploidy was not correlated with a favorable survival as it was accompanied by other adverse CA as del13, complex, del17p and add1q in 21/24(87.5 %) of cases. A group of 31 patients with adverse CA (complex, hypodiploid, -13, -17p and add1q) had reduced (yet not significantly) OS from the rest: median 25 vs 77 mo, 5year OS 42% vs 63% respectively, p=0.087. In multivariate analysis only age and ISS were significantly associated with shorter survival. Conventional cytogenetics provide usefull prognostic information for MM patients.

P-362

Cytogenetic Findings of Multiple Myeloma in Taiwan: 2-year Experience from a National Referral Center

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Multiple myeloma (MM) is a heterogeneous plasma cell disorder characterized by genetic abnormalities, including chromosomal translocations, deletions, duplications and genetic mutations. Fluorescence in situ hybridization (FISH) with specific DNA probes has become a valuable tool for diagnosing cryptic rearrangements that may not be visible by standard cytogenetics. In this study, we collected 133 MM patients and detected of chromosomal abnormalities by karyotypic tests. 30 of the 133 patients (22.6%) showed chromosomal abnormalities in the conventional chromosome examination. The positive rates of chromosomal aneuploidy, loss of Y chromosome, structural anomalies of chromosome 1, 14q rearrangements and 11q rearrangements were 9.8% (13/133), 6.8% (9/133), 7.5% (10/133), 6%(8/133), and 3.8%(5/133), respectively. Furthermore, interphase FISH was performed in 12 patients with normal karyotype by 4 specific DNA probes, including RB1 gene, p53 gene, IGH/FGFR3 for t(4;14), and IGH/MAF for t(14;16). The IGH/FGFR3 fusion was found in 33.3%(4/12) and RB1 deletion was seen in 16.6%(2/12). These two are the most common chromosomal abnormalities in the FISH assay. The overall abnormal rate of the FISH examination was 41.7% (5/12), indicating FISH is more sensitive than conventional karyotyping and can be used as an index in prognostic evaluation for MM. Since the patients with IGH/FGFR3 fusion manifest a poor prognosis that is only partially mitigated by the use of the novel agents, the FISH screening may pave the way for personalized medicine in patients with this incurable disease.

P-363

Sixteen Cases of Asymptomatic Multiple Myeloma

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Patients with asymptomatic smoldering multiple myeloma have an indolent course for years without therapy. The primary therapy was preserved until disease progression to symptomatic myeloma. We performed the retrospective analysis for natural course of patients who diagnosed asymptomatic multiple myeloma in our hospital. We diagnosed the sixteen cases of asymptomatic multiple myeloma in our hospital from 2008 to 2012. Age at diagnosis was 40 to 83 years old (median age was 76). Male/female is 9/7. The type of M protein, IgG is fourteen cases, and IgA is two cases. For International

Staging System (ISS), Stage 1 is ten cases and Stage 2 is six cases. The average of M protein is 3902mg/dl. At Des. 2012, ten cases progressed to the symptomatic myeloma, six cases are still asymptomatic. For the cases of ISS stage 2, five of six cases progressed to symptomatic myeloma, progression rate is 83.3%. By contrast, on the cases of ISS stage 1, five of ten cases progressed to symptomatic myeloma, progression rate is 50%. The time to progression to symptomatic myeloma form diagnosis is 3 to 39 month (median time was 14 month). For the cases of ISS stage 2, the time to progression is 3 to 16 months, on the other hand, the time to progression on the cases of ISS stage 1 is longer, 12 to 39 months. For the observation of asymptomatic multiple myeloma, especially cases of the ISS stage 2, more carefully follow up or early intervention may be needed.

P-364

Unusual Isolated Intracranial Relapse of Multiple Myeloma

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Intracranial involvement is a rare extramedullary complication in multiple myeloma (MM), resulting from osteodural plasmocytoma or leptomeningeal involvement. Primary parenchymal brain lesions occurred sporadically, usually as part of a systemic disease, although solitary tumors without sign of MM have also been reported. A 43-year-old man presented with bilateral pleural effusion and acute renal failure, related to an IgD- λ plasma cell leukemia (PCL) with diffuse infiltration on spinal MRI. FISH on bone marrow (BM) PC showed a non-hyperdiploid status without 14q32, 17p aberrations nor trisomy 1q21. Complete remission was achieved after 5 cycles of bortezomib-cyclophosphamide-dexamethasone, and confirmed after HD melphalan and autologous SCT followed by 3 consolidation cycles of bortezomib-dexamethasone. Eighteen months later, he complained of dizziness, visual impairment and hemiparesis. Brain MRI showed multiple intraparenchymal enhancing lesions with edema. Lumbar puncture was not carried out because of intra-cranial hypertension. BM biopsy showed no PC infiltration. Skeletal lesions were not identified. Neurosurgical stereotactic biopsy confirmed the diagnosis of plasmocytoma, with a λ chain restriction. Following autologous SCT, MM infiltration of cerebral parenchyma without contiguous bone lesions is very uncommon. Origin could be hematogenous, explaining that PCL is considered a risk factor. No therapeutic guidelines have been established. The activity of new agents (i.e. lenalidomide) and their ability to cross blood-brain barrier are largely unknown.

P-365

Low Testosterone is Associated with Shorter PFS in Multiple Myeloma

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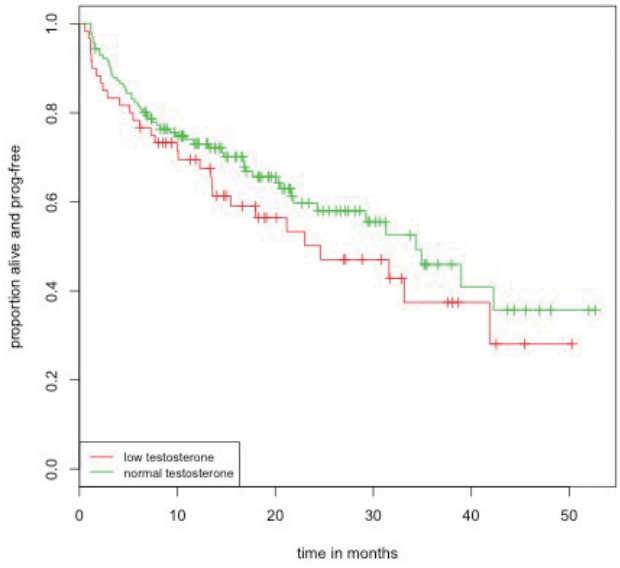
Introduction: Testosterone (T) is important for maintenance of bone mineral density and muscle mass, stimulation of erythropoiesis, energy level, mood, and libido. Androgen deprivation therapy increases risk for diabetes and MI. Obesity increases T in women, with an associated increased breast cancer risk, and lowers T in men while raising estradiol levels. Methods: We retrospectively reviewed 343 patients consecutive patients with plasma cell dyscrasias with either a total or free testosterone level available at the time of referral, 171 patients with active myeloma. Results: 168 patients had a diagnosis of active myeloma and low or normal T 44/171 (25%) were receiving opiates, 29/171 (17%) were taking antidepressants, and 135/171 (79%) were male. 37/171 (22%) had type 2 diabetes and 92/171 (54%) had hypertension. The BMI median was 28.9 (range 16.9-53.1) with 32 (19%) patients normal, 48 (28%) overweight, and 60 (35%) obese. The median time from diagnosis to T assessment was 49 days. We designated two groups of male patients: 44 with low T and 91 with normal T. There was a difference between the presence or absence of lytic bone disease ($p<0.036$), less detectable bone disease on skeletal survey in the normal testosterone group. The median PFS in the low free T group was 23 months (16 events) and 35 months in the normal T group (27 events), $p<0.28$ (see figure). Conclusions: Approx 30% had severe secondary hypogonadism with a trend towards shorter PFS in patients with low free T.



P-366

Comorbidity is an Independent Predictor of Survival in Patients with Multiple Myeloma

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Purpose: Patients with cancer often experience comorbidities that may affect their prognosis and outcome. The objective of this study was to determine the effect of comorbidities on the survival of patients with multiple myeloma (MM). Patients and Methods: In the present study, the influence of comorbidity on survival was analyzed retrospectively in 101 patients with newly diagnosed MM patients from 2005 to 2012 in our institution. Comorbidities were evaluated by using two different scoring systems, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) and the Charlson comorbidity index (CCI) . Results: The median age was 70 years (range, 36-87 years). 34.6% were ≦ 65 years, and 37.6% were ≧75 years. 48 patients (47.5%) had ISS stage= Ⅲ, and 3.9% had chromosome 13 deletion by G-banding. 68% of patients were treated with new drug-based therapies such as thalidomide (17.8%), bortezomib (57.4%), and lenalidomide (27.7%). 24 patients (23.7%) underwent autotransplant. In univariate analysis both the HCT-CI and the CCI were found to be of prognostic significance for overall survival (OS) (p<0.001). In multivariate analysis using Cox proportional model, parameters having independent adverse significance for OS were: HCT-CI≧2 (p=0.01, HR=2.51), PS≧2 (p=0.001, HR=3.32) and ISS=3 (p=0.01, HR=2.51). In addition, high HCT-CI group (score ≧2) was significantly inferior to low HCT-CI group (score＜2) for 3-year OS (43% vs. 82% p=0.0001). Conclusions: Our data proved that comorbidity is an important prognostic factor for survival in patients with MM.

P-367

Pattern of Relapse/Progression after Autologous Stem-cell Transplantation in Multiple Myeloma

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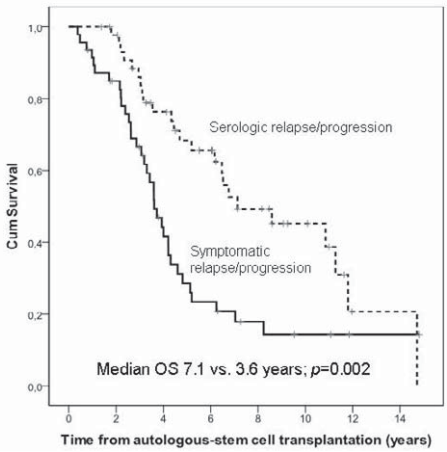
Background: Serological versus clinical relapse requiring treatment and the pattern of relapse or progression after autologous stem cell transplantation (ASCT), are important issues in multiple myeloma (MM). The aim of this study was to investigate the relapse or progression pattern in patients with MM who received ASCT as part of a first-line treatment. Patients and Methods: 170 patients who achieved at the least a minimal response at our institution during the last 18 years after no more of two induction lines before ASCT were studied. Extramedullary plasmacytomas (EMP) were observed in 22% of patients at diagnosis. Results: 93 patients (54.7%) had relapsed or progressed after ASCT: 40% had relapsed from CR and 60% had progressed from PR. A serological or asymptomatic relapse/progression was as frequent as a symptomatic one (49.5% vs. 50.5%). Patients with serological relapse/progression had a significantly longer OS than those requiring immediate treatment (p=0.002)(Figure). The presence of EMP at diagnosis was significantly associated with extramedullary disease at relapse (p=0.001). Median time between asymptomatic serological relapse or progression and treatment requirement was of only 5.6 months. However, 12 out of 46 patients (26%) with asymptomatic relapse/progression did not require treatment within the first 2 years. Conclusion: After ASCT, serological or asymptomatic relapse/progression is observed in about one half of the patients. Extramedullary involvement is frequent, being the highest risk in patients with EMP at diagnosis.

Figure. Overall survival in relapsed/progressing patients with multiple myeloma after autologous stem-cell transplantation, according to serologic/asymptomatic vs. symptomatic relapse/progression.



P-368

Humoral Response against HSP60, HSP70 and HSP90 after Autologous Stem-cell Transplantation in Multiple Myeloma

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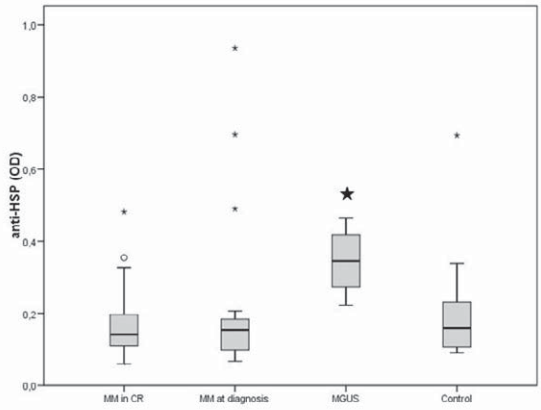
Background: Heat-shock proteins (HSP) are important molecules in the pathogenesis of multiple myeloma (MM). Their blockages by drugs or cellular immune response have been investigated, and a possible association with the presence of oligoclonal bands (OB) has been postulated. The aim of the present study was to describe the serum antibody levels against three HSP (60, 70 and 90) in patients with MM in complete remission (CR) after autologous stem-cell transplantation (ASCT), with or without OB. Methods: We analyzed serum samples from patients with MM in CR (38) or at diagnosis (19), healthy controls (12) and cases with stable MGUS for more than 5 years (8). Total levels of anti-HSP60 and 70 were measured by a commercial ELISA, and an anti-HSP90 assay was standardized in our laboratory. Results: None difference was observed among the measured antibody levels in patients in CR with or without OB, except a trend for anti-HSP70 (p=0.116). Along the different groups studied, only anti-HSP90 showed a differential higher expression in MGUS cases in front of patients with MM (p=0.004; Figure). For this reason, no MM-cases (MGUS and controls) had significantly higher levels of anti-HSP90 than MM patients, both at diagnosis and at CR (p=0.007). No prognosis value of any antibody levels was found after ASCT in patients in CR. Conclusion: Higher levels of anti-HSP90 are found in patients with stable MGUS in comparison with MM patients, suggesting a potential humoral immune response for long-term control of malignant plasma cells.

Figure. Serum levels of total anti-HSP90 in patients with multiple myeloma (MM) in complete remission (CR) or at diagnosis, stable monoclonal gammopathy of undetermined significance (MGUS) and healthy controls.



P-370

Determining the Clinical Significance of MGUS: A Population-Based Study

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Background: We sought to determine whether or not MGUS follow up preceding the diagnosis of multiple myeloma, Waldenstrom's macroglobulinemia, and lymphoplasmacytic lymphoma (collectively MM) results in fewer major complications at cancer diagnosis and longer survival. Methods: Data were obtained from the US Surveillance Epidemiology and End Results (SEER) database linked to Medicare claims from 1994-2005. MGUS follow-up was defined as having a diagnosis claim 4-15 months prior to MM diagnosis. Major complications within 3 months of MM diagnosis were included. We excluded patients with smoldering MM (no treatment/complication claims and no MM death within 3 and 12 months of diagnosis, respectively) in the complication analyses. Results: 17,457 MM patients were included in our study. 51% were males and the median age was 77 years. 6% of the patients had MGUS follow-up preceding MM diagnosis. Unadjusted complication rates at MM diagnosis were mostly lower in the group with MGUS follow-up compared to those without: any (49 vs 58%; P<.001), acute kidney injury (20 vs 24%; P=.01), dialysis (6 vs 8%; P = .28), cord compression

(6 vs 8%; P=.09), fracture (26 vs 33%; P<.001), and hypercalcemia (12 vs 19%; P<.001). After multivariate modeling, MM patients with prior MGUS follow-up had significantly fewer major complications at the time of diagnosis (OR=.68). They also had better disease-specific survival (median 38 vs 29 months, P<.001; HR=.85) as well as overall survival (median 23 vs 19 months, P<.001; HR=.87). Conclusion: Our study supports the clinical significance of MGUS.

P-371

A Case of Relapsed Multiple Myeloma with Central Nervous System Involvement; Longer Survival with Novel Agents

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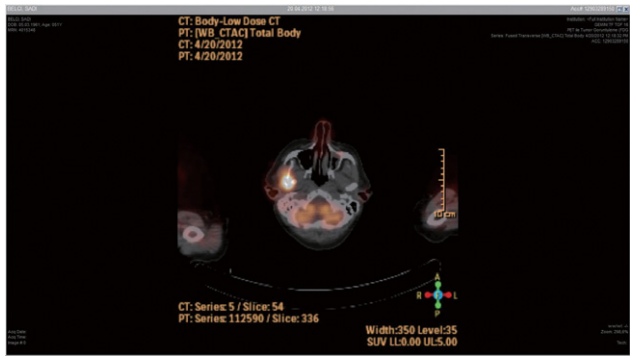
A 51 year old man presented with multiple soft tissue plasmocytomas and diagnosed as IgG kappa multipl myeloma. After achieving a partial response with induction therapy, autologous stem cell transplantation was performed at the 4th month of diagnosis. Very good partial remission (VGPR) was obtained. After 11 months, the patient was admitted with sudden transient loss of vision, headache and temporomandibular mass and myeloma relapse. Magnetic resonance imaging (MRI) revealed a dural and leptomeningeal infiltration and a mass lesion occupying right infratemporal fossa and another mass lesion occupying left petrous apex, extending through the sphenoid sinus and infiltrating cavernous sinus involving the 6th cranial nerve. There were plasma cells in the cerebrospinal fluid . Deletion 17p and 13q were negative. Radiotherapy and chemotherapy (cyclophosphamide, bortezomib, doxorubicin and dexamethasone) and intratechal methotrexate was initiated. After 3 cycles of therapy and obtaining a partial reduction in temporamandibular mass the patient was put on to lenalidomide and dexamethasone.Lesions in MRI disappeared and a VGPR was obtained with three cycles of lenalidomide therapy. At the end of 6th cycle,disease relapsed with central nervous system involvement and progressive cytopenias and the patient died of sepsis. Our patient survived for 9 months after relapsing with leptomeningeal infiltration altough literature reports a median survival of only 2 to 3 months in similar patients. Novel therapeutic drugs may prolong the survival presenting with extramedullary disease.



P-372

Clinical and Genetic Factors for Venous Thromboembolism in Myeloma Patients Treated with Lenalidomide-based Regimens

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IMiDs (thalidomide, lenalidomide and pomalidomide) have proven antimyeloma activity but they are associated with a significant risk of VTE. We analyzed 200 consecutive, unselected MM patients who were treated with lenalidomide-based regimens in order to assess clinical and genetic risk factors that may predispose to VTE: 12(6%) patients developed a VTE (9 DVT and 3 pulmonary embolism). All VTEs occurred in patients on aspirin prophylaxis; no patient on LMWH or acenocoumarol (with a target INR 2-3) had a VTE. VTEs occurred in 9.4% in previously untreated and 4.5% in previously treated patients and were more frequent in patients >65 years (8.1% vs. 1.6%) especially among patients receiving aspirin (10.4% for patients >65 years vs. 1.8% for =<65 years). In patients who received prophylaxis with aspirin a SNP in NFkB1(rs3774968) gene was associated with increased risk of VTE(OR 3.76, 95%CI 1-16, p=0.051). None of the patients who developed VTEs carried common genetic variations, such as FVLeiden and FIIG20210A , which are associated with increased risk of VTEs. Levels of markers of inflammation (hsCRP) and of the serum levels of thrombomodulin were not associated with increased VTE risk. In conclusion, in unselected patients with either newly diagnosed or relapsed/refractory MM who were treated with lenalidomide-based regimens, LMWH or acenocoumarol effectively reduced the risk of VTEs. In patients who received aspirin prophylaxis, genetic variants of genes that are involved

directly or indirectly in inflammatory response may be associated with increased risk of VTE.

P-373

Conditional Survival (CS) Analysis in a Large Cohort of 816 Multiple Myeloma (MM) Patients (pts)

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Survival estimates are typically presented as the probability of surviving a given length of time after the diagnosis. In contrast, CS describes the probabilities of surviving y additional years given pts survived x years, taking into account, how long someone has already survived. We assessed in 816 MM pts age, gender, disease stage (D&S), time of death and last follow-up treated at our department between 1997-2011 with almost complete long-term follow-up. We determined 5-year CS (5y-CS) as the probability of surviving at least 5 more years as a function of years a pt had already survived since diagnosis and stratified 5y-CS according to disease- and pt-specific risks. The OS probabilities at 5-/10-years were 50% and 25%, respectively. The 5y-CS- remained constant over the years (Fig. 1). As expected, D&S stage I vs. II+III showed different 5y-CS estimates of 75% vs. 42%, respectively for those who survived 1 year after diagnosis. Age subgroups revealed substantially different 5y-CS-estimates and remained constant over time (Fig.1). Age and disease stage were significant risks via multivariable Cox model (Table 1). Additional risks were >2 osteolyses, hemoglobin<10g/dl, β 2-MG>5.5mg/l, LDH>200U/l and impaired performance status. Cytogenetics are currently included in our risk assessment (according to Moreau P. ASH 2012:#598 and Avet-Loiseau H. JCO 2012). CS analyses constitute an attractive tool to predict outcome, supplements existing measures and may guide cancer survivors in planning their future. Ongoing risk assessment aims to define long- vs. short-term survivors.

Fig. 1. 5-year-CS stratified by age groups (with 95% confidence intervals)

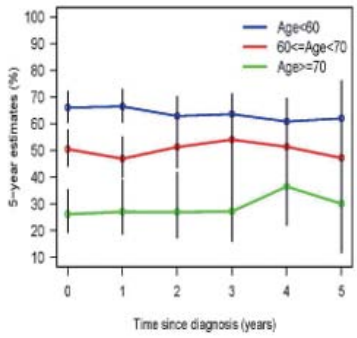

Table 1. Multivariable Cox proportional hazard model

Variables	HR	95%- CI	*p-value*
Female	1	-	*0.89*
Male	1.00	0.83-1.20	
Stage I	1	-	*<0.001*
Stage II+III	2.19	1.76-2.74	
Age <60 years	1	-	*<0.001*
Age 60-70 years	1.72	1.37-2.16	
Age ≥ 70 years	3.46	2.70-4.44	
Admission before 2001	1	-	*0.56*
2001-2007	1.13	0.90-1.42	
after 2007	1.12	0.83-1.50	

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Extensive Bone Marrow Infiltration and Abnormal Free Light Chain Ratio Identifies High Risk Asymptomatic Myeloma

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Asymptomatic multiple myeloma(AMM) is characterized by a constant risk of progression to symptomatic myeloma. In order to identify those patients with AMM at higher risk of progression to symptomatic MM requiring therapy we analyzed 102 patients with AMM and at least 18 months of follow up. The progression rate at 1-,2-, & 3 years was 8%, 15% & 26% respectively and the projected 5-year progression rate was 38%. Extensive BM infiltration, abnormal FLC ratio and serum monoclonal protein>=3 gr/dl were the most significant factors for progression; the type of heavy(IgG vs IgA) or light chain or immunoparesis of the uninvolved immunoglobulins were not. Abnormal mar-

row signal of MRI of the spine was associated with a significant risk of progression(median 15 months,p=0.001). Extensive BM infiltration >=60%(HR:13.7,p<0.001) and FLC ratio>=100(HR:9,p=0.003) independently identified a "very high risk" group which included 12.5% of patients with AMM and who progressed =<18 months from initial diagnosis. Development of anemia and/or lytic bone lesions were the most common features of symptomatic progression. The survival after progression to symptomatic MM was 66 months and it was similar for patients who progressed early(=<18 months) after diagnosis of AMM or those who progressed after a longer period of observation. In conclusion, there is a subgroup of patients who have a substantial risk of progression to symptomatic disease that can be detected at diagnosis (either by extensive BM infiltration>=60% or FLC ratio>=100) and may be considered for immediate treatment

P-375

Cost-Effectiveness of Treatments (Tx) for Newly-Diagnosed Multiple Myeloma Patients (NDMM pts)

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Background: Lenalidomide (LEN) and bortezomib (BORT) have shown clinical benefit for NDMM pts based on primary endpoints involving progression, generating interest in the economic impact.

Methods: Results from phase 3 trials (MM-015 for LEN; VISTA for BORT) were analyzed using a US payer perspective over a comparable period. Drug cost, drug administration, and adverse event (AE) costs were calculated in 2011 US dollars using US payer reimbursement rates and the literature. Pt cohorts were modeled based on median duration of treatment (DOT) and median months (mo) of progression-free survival (PFS). Due to the longer PFS of LEN (31 mo vs 22 mo for BORT), a period of BORT re-Tx was appended to the BORT cohort at progression, using DOT and PFS gain from the APEX trial, bringing the cohorts to a comparable elapsed time.

Results: PFS gain vs study control was 18.3 mo for LEN and 9.2 mo for BORT in the comparable time period. DOT was similar. AE costs for both Tx were <$5,000. LEN had approximately half the cost per PFS mo gained vs BORT, with or without appended post-relapse BORT re-Tx.

Conclusions: Aggregate costs in the comparable time period were similar for the 2 Tx; however, LEN provided more mo of PFS gain, at a lower cost per mo of PFS gained, vs BORT.

	BORT (VISTA)	BORT Full Elapsed Time (VISTA+APEX)	LEN Full Elapsed Time (MM-015)
PFS mo gained (vs within-trial comparator)	6.5	9.2	18.3
DOT (mo)	10.6	14.7	14.4
Cost of Tx (USD)	75,499	112,619	120,975
Cost per PFS mo gained (USD)	11,615	12,241	6,611

P-376

Incidence of Varicella Zoster Virus (VZV) Infection after Lenalidomide (Len) Treatment in Multiple Myeloma Patients

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Introduction: Multiple Myeloma (MM) patients (pts) have shown a risk of VZV infection of 1-4%. Therapy with e.g. bortezomib increases the risk by 4 times. Whether other anti-MM agents also increase the risk of VZV/complicated HSV infections (e.g. VZV-encephalitis [VZV-E], disseminated VZV-infection [d-VZV-i] or conus-cauda-syndrome [CCS]) has not been elucidated. Methods: We analyzed 93 MM pts treated with Len at our department between 2008 and 2011. We determined pt- and MM-disease characteristics, Len usage and cellular and humoral immune surveillance parameters (ISP). Results: 10 pts (11%) showed VZV infections: 7 typical VZV-infections and in 1 pt each, VZV-E, d-VZV-i and CCS, leading to Len discontinuation in all 10 of them. The median therapy duration was 6 months. Potential risk factors for VZV seemed: male gender, age over 70 years, prolonged MM disease duration, extensive or doxorubicin-/bortezomib containing regimes, ASCT or allo-SCT, MM progression and previous VZV infection (Table 1A). Of note, our assessment of the VZV rate in ASCT-receiving MM pts was even similar (8%) than in Len-treated pts. ISP revealed subnormal leukocytes and NK-cells, suppressed T4-, T4/T8-ratio and immunoglobulin titers (Table 1B). Conclusions: Based on these results, we have established an aciclovir prophylaxis in Len-treated MM pts and have noted no VZV/complicated HSV infections thereafter. We postulate that this prophylaxis will minimize the risk of VZV/complicated HSV infections and prevent early discontinuation of Len-treatment in MM.

Table 1A. Baseline characteristics of patients developing VZV, VZV-encephalitis, disseminated VZV-infection and conus-cauda-syndrome under or after lenalidomide therapy

	#	Median (range)
Number of patients	10	
Patient age (years; range)		64 (46-81)
Sex: male / female	7 / 3	
MM type: IgG / IgA / κ-LC only	5 / 4 / 1	
κ vs. λ-LC-type	8 / 2	
Lenalidomide alone / Rd / RCD	4 / 5 / 1	
Lenalidomide dose		10 (10-25)
21 vs. 28-day schedule		21 (21-28)
Len-duration (months)		6 (1-13)
# anti-MM therapy lines before lenalidomide treatment		4 (1-6)
MM-disease duration (months from initial diagnosis to VZV)		39 (20-71)
VZV / VZV-encephalitis / disseminated VZV-infection / conus-cauda-syndrome	7 / 1 / 1 / 1	
Infection under vs. after lenalidomide-therapy	6 / 4	
Infection occurrence after lenalidomide-therapy (months)		4 (1-6)
Specific patient characteristics and potential VZV-risks		
PD MM	5	
Prior VCD-therapy	4	
auto-SCT or allo-SCT	7 / 2	
RAD-pretreatment	2	
Age > 70 years	3	
Prior history of herpes zoster	2	
Secondary tumor occurrence (head-and-neck cancer)	1	
Outcome		
Lenalidomide-therapy interruption/discontinuation	10	
Lethal (generalized dermatitis[1] and MOF / VZV-encephalitis)	2 (1 / 1)	
Conus Cauda Syndrome	1	
Secondary tumor search and detection of head-and-neck cancer	1	

Abbreviations: Dex: dexamethasone; Rld: lenalidomide plus low-dose dexamethasone; RAD: lenalidomide, doxorubicin, dexamethasone; RCD: lenalidomide, cyclophosphamide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; auto-SCT: autologous SCT; allo-SCT: allogeneic SCT; VZV: varicella zoster virus; [1]Stevens-Johnson-fasia epidermal necrolysis overlap syndrome following lenalidomide treatment for multiple myeloma relapse after allo-SCT; MOF: multi-organ failure

Table 1B. Immunosurveillance characteristics of patients with VZV, VZV-encephalitis, disseminated VZV-infection and conus-cauda-syndrome under or after lenalidomide therapy

	# of affected patients	Median (range)
Leukocytes (4027 - 10278 / µl)	10	3800 (1600-13700)
Lymphocyte subpopulations (norm values)		
T4/T8 Ratio (1.0 - 3.3 / µl)	6 / 10	0.55 (0.1 - 0.8)
T-4 cell numbers (424 - 1137 / µl)	6 / 10	192 (75-484)
NK-cell numbers (150 - 600 / µl)	6 / 10	152 (91-335)
Lymphocyte count (20 - 50 %)	6 / 10	30 (7-53)
Immunoglobulin (Ig) titers		
IgG (7 - 16 g/l)	4 / 10	3.64 (3.04 - 6.83)
IgA (0.7 - 5.0 g/l)	1 / 10	0.14
IgM (0.4 - 2.5 g/l)	2 / 10	0.13 (0.12 - 0.14)
1 low non-myeloma immunoglobulin	2 / 10	
2 low non-myeloma immunoglobulin	2 / 10	

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Increased Incidence of Myeloma Patients Aged Less than 35 Years - a Single Center Study

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Multiple myeloma is a malignancy affecting mostly elderly patients with median age of 65 years. Diagnosis is rare in patients under the age of 30 years, the incidence referred is about 0,3%. In the General University Hospital in Prague 5 new patients with multiple myeloma, aged 18, 25, 27, 32 and 35 years, were diagnosed during period 2006 - 2012. All patients had massive axial skeleton involvement, one female patient (27 years) presented as acute renal failure, while two other patients had massive extramedullary plasmocytoma. Regarding cytogenetics just only one patient had completely normal finding. All of patients were treated with AutoSCT, one patient with tandem Auto-AlloSCT.This patient died 9 months after AlloSTC due to relaps of myeloma, the remaining patients survive. Conclusion: The data from Czech Myeloma Group (CMG) do not demonstrate an increase of the incidence of young myeloma patients in the Czech Republic. In the period 2007 - 2011 45% of patients diagnosed in the Czech Republic were younger than 65 years (886 from 1,953), 3.3 % of the patients were younger than 45 years, and 0.9 % were younger than 35 years. The incidence of younger patients (less then 35 years) in our center was 1,25% Possible explanation could be a/centralized care for myeloma patients and concentration in one center b/increase of young patients in some regions of Czech republic c/chance (hopefully).

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Multiple Myeloma & Thrombosis

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Thromboembolic complications are a major morbidity and mortality factor in multiple myeloma(MM). MM itself and most of the myeloma drugs are thrombogenic. We wanted to find out if thromboembolic events are a major concern of myeloma patients at our center and if an increase during IMID era has occured. We went retrospectively through over 500 patients presented between 1998 and 2012 and chose 352 files with complete information. We assessed age, gender, disease type and treaments. Acquired hypercoagulable states (immobilisation, surgery, fracture, diabetes, obesity, previous thrombosis) were but hereditary thombophilic factors not evaluated. There were 45 (38 venous(VT) , 7 arterial) thromboembolic events. Arterial thrombosis was associated with high atherosclerotic burden except for one patient with amyloidosis and congestive heart failure. The major factor contributing to venous thrombosis was immobolisation due to fatigue or fractures All VT were deep vein thromboses or pulmonary embolism except two catheter thromboses during ASCT and one retinal vein thrombosis. Patients who have received IMID therapy were given also adequate thromboprophylaxis according to the current guides and most of thromboses did not ocur under IMID therapy (5 thalidomide, 2 lenalidomide). No significant or spesific risk factor could be withdrawn from our survey except MM being a major risk factor for thromboembolic events. IMID therapy dosen't seem to affect the incidence of thrombosis, maybe because prophylactic measures were applied carefully.

Table: patient characteristics

	venous	arteriel
Age (mean)	59 (38-72)	61 (42-76)
male	n=18	n=3
female	n=20	n=4
thalidomide	6	-
lenalidomide	7	-
Thal / lenalidomide	7	-

P-379

Is P16 and Dapk Genes Hypermetilation Relevant in the Progression of MGUS to Multiple Myeloma?

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INTRODUCTION AND AIMS: DNA methylation status is related with cancer and its role in the pathogenesis of monoclonal gammopathies (MG), namely in the progression from MG of uncertain significance (MGUS) to multiple myeloma (MM) is unclear. Our aim was to evaluate p16 and DAPK genes methylation status in MGUS and MM patients (pts) at diagnosis and to correlate with presentation features and prognosis. MATERIALS AND METHODS: Bone marrow samples from 68 pts at diagnosis, 42 MGUS (60% male, median age 72y, range 41-86) and 26 MM (42% male, median age 73y, range 39-86) and from 8 healthy donors were studied, p16 and DAPK genes promoters methylation status was performed using a methylation-specific polymerase chain reaction (MSPCR). RESULTS: Overall, 38% of MG pts presented at least one hypermethylated gene (58% of MM pts and 26% of MGUS pts, p<0,05). No aberrant methylation was detected in healthy donor' s bone marrow. The frequency of hypermethylation in MGUS and MM pts was, respectively: p16, 12% and 35% (p<0,05) and DAPK, 17% and 39% (p<0,05). Pts with DAPK hypermethylation were more likely to have higher serum Beta2-microglobulin levels (p<0,05) and ISS 2 or 3 (p<0,05). Aberrant p16 methylation was also associated with higher ISS 2 or 3 (p<0,05) in MM pts and with DNA hyperdiploidy (p<0,05) in MG pts. No correlation was found between methylation status of any gene and cytogenetic aberrations as well as overall and progression free survival in MM pts. CONCLUSIONS: Hypermethylation of p16 and DAPK genes might have a relevant role in the progression of MGUS to MM.

P-380

Change in Patient-reported Outcomes in the First Year Post-diagnosis of Multiple Myeloma (MM) in CONNECT® MM

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Objective. To understand patient-reported outcomes (PRO), including health-related quality of life (HRQOL), of multiple myeloma (MM) patients (pts) receiving treatment in the United States (US), PRO of pts meeting CRAB criteria for active/symptomatic MM was assessed at baseline and at 1 year post-baseline.

Methods. Data were collected in Connect® MM, an ongoing prospective US disease registry of MM pts. Clinicians reported pt demographics and clinical characteristics. Pts reported PROs at baseline, within 2 months of diagnosis, and at 1 year post-baseline by completing Brief Pain Inventory (BPI), EQ-5D, and Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM). Mean [standard deviation (SD)] BPI, EQ-5D and FACT-MM change scores were analyzed. Statistical significance was assessed.

Results. 636 pts (189 centers) meeting CRAB criteria provided data at baseline and 1 year post-baseline. The majority of pts were male (58%), white (84%) with mean age 66 years (SD 11). Pts were seen in academic (17%), community (81%) or government (2%) centers. Evaluable International Staging System stage was: I-29%; II-35%; III-35%. Average pain improved over 1 year. HRQOL/functional ability improved in 4 of 5 EQ-5D domains and 4 of 5 FACT domains. Overall HRQOL, as shown by the FACT-MM and FACT-G total scores, also improved.

Conclusions. Connect® MM findings indicate that most PROs improve between baseline and 1 year post-baseline. Data will be examined to identify which disease- and treatment-related factors are associated with HRQOL improvement in this MM population.

	Change Score (N = 636)	
	Mean(SD)	P Value[1]
BPI-average pain	-0.4 (3.0)	.0005
EQ-5D		
Morbidity	-0.1 (0.6)	.0142
Self-care	-0.1 (0.6)	< .0001
Usual activities	-0.1 (0.7)	< .0001
Pain/discomfort	-0.0 (0.7)	.2204
Anxiety/depression	-0.1 (0.6)	.0074
FACT-MM		
Physical	1.0 (5.6)	< .0001
Social/family	-0.4 (4.6)	.0462
Emotional	1.0 (4.1)	< .0001
Functional	1.8 (6.5)	< .0001
MM subscale	1.7 (9.9)	< .0001
FACT-G total	3.5 (14.6)	< .0001
FACT-MM total	5.2 (22.4)	< .0001

[1] P value for change score (H_0: change score = 0).

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Initial Response, Re-attaining ≥VGPR and Late Relapse Correlate with Improved Survival in Relapsed AL Amyloidosis

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Little data is available on outcomes in relapsed AL amyloidosis after frontline therapy. Knowledge of this is urgently required given emphasis on surrogate endpoints in trials for this disease. Here we examine predictors of overall survival (OS) and post-relapse survival (PRS) in the 39 relapsed patients, initially responding to front-line treatment, from the first 250 subjects enrolled in the ALchemy study. Factors examined included clonal response to first and second line therapy, depth of response to second line therapy relative to initial response and relapse within 12 months as a marker of clonal aggressiveness. Median follow-up was 27.5m (12.8m from second line treatment). 90% received a thalidomide-based regimen as frontline therapy with a ≥VGPR rate of 36%. 62% received a bortezomib-based regimen at relapse with a ≥VGPR of 59%. Depth of response improved to ≥VGPR after second line therapy in 48% of patients only achieving a PR to frontline treatment. Depth and durability of response to frontline therapy, re-attaining ≥VGPR and later relapse correlated with better OS (Figure 1). No significant difference in OS was seen based on depth of response to second line therapy (Figure 1B). Interestingly, similar outcomes are seen in those who improved their depth of response from PR to ≥VGPR after second line treatment compared with those re-attaining only a PR; further emphasizing the importance of clonal control with initial therapy (Figure 1C). No factor predicted for improved PRS although the cohort is small and follow-up post-relapse is short.

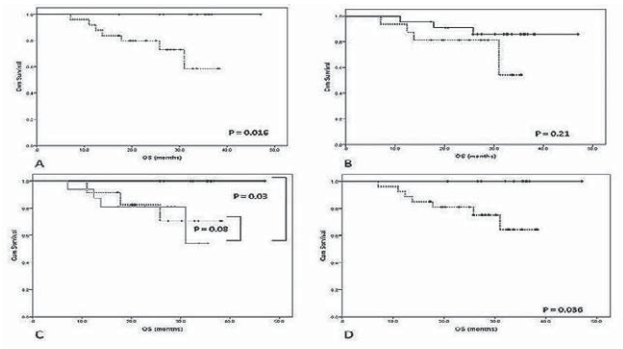

Figure 1: Overall survival of relapsed patients by response to frontline therapy, depth of response relative to initial response and timing of relapse. Compared with those who only achieved a PR (dashed line) to front-line treatment those who achieved ≥VGPR (solid line) had an improved OS (A). In contrast, compared with achieving a PR or less to second-line therapy (dashed line) those attaining a ≥VGPR (solid line) had a similar OS (B). However, those who re-attained ≥VGPR (solid black line) after second-line treatment had an improved survival compared with those who re-attained only a PR (grey line) with these patients having a similar outcome to those who upgraded their response to ≥VGPR (dashed line) from a PR (C). Patients with early relapse (<12 months, dashed line) had inferior OS (D).

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Second Primary Malignancies in Patients with Multiple Myeloma

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Purpose: Second primary malignancies (SPM) in multiple myeloma (MM) patients may be attributable to previous treatments, multiple myeloma related factors, host genetic factors, environmental factors or behavioral factors. Longer patient survival in this patient population can lead to overestimation of the risk of second malignancies. The current study evaluated the incidence of SPM in MM. Methods: From more than 500 MM patients diagnosed at Istanbul University Cerrahpasa Medical Faculty, Turkey between 1998 and 2012, adequate follow-up data were available for 352, with characteristics representative of the whole group. Data of the patients with SPM are summarized in table 1. Twelve patients (3.4%) were diagnosed with a SPM. Briefly, these were 3 females and 9 males with a median age of 64 (range 48-87) years. SPM occurred before the diagnosis of MM in 4 cases, or concomitantly in 5 patients. One patient developed two different solid tumors. Only 1 patient had a history of immunomodulatory agent use before SPM diagnosis. Conclusion: Data describing SPM in MM patients either receiving immunomodulatory agents or not are scarce. Concomitant diagnosis of SPM was documented in many patients during assessment for MM. Further studies are needed to define the

role of treatment or disease related factors for SPM development in MM patients.

	Age at MM Diagnosis	Sex	MM Type	Second Malignancy Diagnosis in Relation to MM	Type of Second Malignancy	Immunomodulatory Drug Exposure	Stem Cell Therapy	Radiotherapy
Patient 1	64	m	IgG/λ	7 years before MM	Prostate adenocarcinoma	No	No	No
Patient 2	61	m	IgA/λ	1 year and 2 months after MM	Peritoneal metastatic adenocarcinoma	No	Yes	No
Patient 3	64	m	IgA/κ	2 years and 6 months after MM	Colon adenocarcinoma	No	Yes	Yes
Patient 4	73	m	IgG/κ	Concomitant	Prostate adenocarcinoma	No	No	No
Patient 5	72	m	IgG/κ	Concomitant	Prostate adenocarcinoma	No	No	No
Patient 6	61	m	κ light chain	Concomitant	Prostate adenocarcinoma	No	Yes	No
Patient 7	74	m	IgA/κ	Transitional cell carcinoma 2 years before MM, lung cancer diagnosed concomitantly	Transitional cell carcinoma, squamous cell lung cancer	No	No	No
Patient 8	66	m	IgA/κ	11 years before MM	Prostate adenocarcinoma	No	No	No
Patient 9	53	m	IgG/κ	11 years after MM	Chronic lymphocytic leukemia	No	No	No
Patient 10	48	f	IgG/κ	3 years after MM	Colon adenocarcinoma	Thalidomide for 10 months	Yes	No
Patient 11	87	f	IgG/κ	Concomitant	Transitional cell carcinoma	No	No	No
Patient 12	51	f	IgA/κ	3 years before MM	Essential Thrombocythemia	No	No	No

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Cutaneous Vasculitis during the Course of Multiple Myeloma; A Case Report

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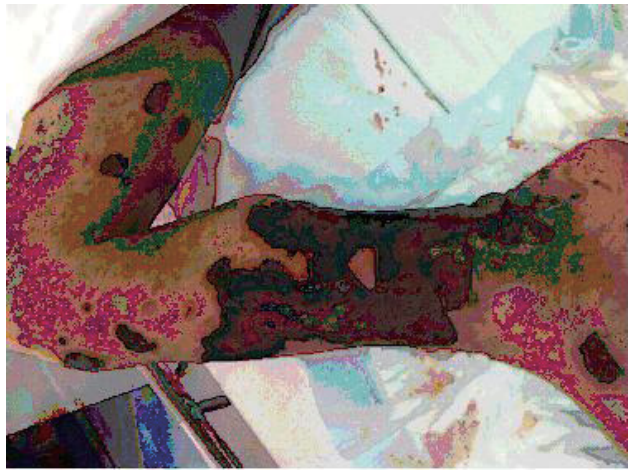
Introduction: Vasculitis can occur in the setting of an underlying process such as a malignancy, more commonly hematological rather than solid. Case Report: In the present study we report a case of a 56-year-old male patient who presented with vasculitis affecting the lower limbs during the course of multiple myeloma (MM). IgG/ λ MM was diagnosed and considered as smoldering. While followed-up without treatment, 6 months after the diagnosis, he complained of tingling sensation in both legs. He was evaluated as Durie Salmon and ISS stage 2 MM. VAD regimen was initiated. On the 3th day of chemotherapy reticular purpuric lesions rapidly progressing to areas of extensive necrotic ulcerations developed (Figure 1). There was no history of recent infection or surgery and no G-CSF or coumarin exposure. Urinary sediment, complement levels and coagulation tests were normal. Rheumatologic tests, cryoglobulin, cryofibrinogen, viral serologies, antiphospholipid antibodies were found (-). Tissue sample obtained by punch biopsy revealed no amyloid deposits and clots and immunofluorescence studies did not demonstrate any deposition. Corticosteroid therapy (three boluses of 500 mg methylprednisolone every two days) was initiated and wound debridement was performed. Treatment was directed at underlying MM and the treatment scheme was switched to CyBorD. Conclusion: Vasculitis can be seen during the course of MM. Prominent response to systemic chemotherapy supported our diagnosis of MM-associated vasculitis.



P-384

Assessment of Quality of Life in Turkish Multiple Myeloma Patients by Using EORTC-QLQ-C30 and EORTC-QLQ-MY20

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Objectives: We evaluated anxiety, depression, quality of life (QoL) in multiple myeloma (MM). We also determined the association between these disorders and patients' demographic characteristics. Methods: We included 89(54M, 35F; age:62.4 ± 10.1) MM patients. Demographic features, laboratory data and treatment modalities were obtained from medical records. EORTC-QLQ-C30, its myeloma module (EORTC-QLQ-MY20), and Hospital Anxiety and Depression Scale (HADS) were answered by all patients. Results: Fatigue was the symptom with the highest mean score(48.7 ± 27.3), followed by pain(40.2 ± 30.3), insomnia(33.3 ± 35.2) and appetite loss(32.9 ± 37.5). Financial function was the function scale with the lowest mean score(23.6 ± 30.6); cognitive function had the highest mean score(80.3 ± 20.7). MM patients with depression had significantly higher pain, fatigue, dyspnea and appetite loss scores ($p>0.001$); lower physical, role, social and emotional function scores ($p>0.001$); lower global QoL scores (64.7 ± 24vs.34 ± 22.3, $p>0.001$);and higher EORTC-QLQ-MY20 scores($p>0.05$).Multivariate linear regression analysis showed that physical function score(OR:4.48;$p=0.028$) and role function score (OR:3.82; $p=0.03$) positively influenced the global QoL score independently.The treatment side effect score of EORTC-QLQ-MY20 (OR:-2.20; $p=0.01$) and the

presence of depression (OR: -1.7; p=0.007) were independent factors which negatively influenced the global QoL score. Conclusions: Independent parameters which negatively influenced the global QoL in MM were the presence of depression in HADS and treatment-related side effect score.

P-385

A Comparison of IgG, IgA and IgM HevyLite Assay with Conventional Techniques for the Detection of Paraproteins

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Conventional techniques to detect and quantify monoclonal proteins can be hampered by the presence of polyclonal immunoglobulins and co-migration of other serum proteins. Use of HevyLite assays (HLC) to quantify heavy chain/light chain pairs may be a useful adjunct to standard laboratory tests. Methods: Consecutive serum samples identified as having an IgA, IgG or IgM M-band by electrophoresis were analysed using paired IgM κ/IgM λ, IgA κ/IgA λ and IgG κ/IgG λ HLC assays and results compared. Results: 164 samples were included in the analysis. 45 IgA M-protein samples (κ=25, λ=20) were compared (myeloma=30, MGUS=13, Other=2). In 22/25 IgA κ and 18/20 IgA λ samples the involved IgA HLC was raised. The IgA HLC ratio was abnormal in 44/45 IgA samples. An IgG M-protein was present in 92 samples (κ=47, λ=45; myeloma=56, MGUS=28, other=8). The involved HLC was raised in 24/47 IgG κ and 40/45 IgG λ samples. The IgG HLC ratio was abnormal in 83/92 IgG samples. An IgM M-protein (κ=17, λ=10) was detected in 27 samples (MGUS=16, LPL=7, other=4). IgM κ samples had a raised involved HLC isotype in 16/17 with abnormal HLC ratio in 17/17. Similarly 10/10 IgM λ samples had a high involved HLC with 9/10 having an abnormal IgM HLC ratio. All 88 myeloma samples analysed had an abnormal HLC ratio regardless of M-protein level. Conclusions: IgM, IgA and IgG HLC demonstrated excellent correlation with conventional methods suggesting a potential role for the HevyLite assay in monitoring of M-proteins.

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Serum miRNAs Add to ISS and FISH to Predict PFS and OS in Phase 3 Trial

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INTRODUCTION: MicroRNAs (miRNAs) are involved in myeloma (MM) pathogenesis and differential plasma cell miRNA expression is associated with distinct patient subgroups. A comprehensive profile of circulating miRNAs for disease prognostication has not been reported. METHODS: On 104 newly diagnosed MM serum samples a screening analysis of 654 miRNAs was performed using nCounter technology (nanoString, Seattle, USA). A candidate set of miRNAs, including miR-92a, miR-30a, miR-19b, miR-16, miR-21, miR-25, miR-126, miR-223, and miR-451 was further validated by qRT-PCR in the serum of 234 newly diagnosed MM patients enrolled on a randomized phase 3 study of VMPT-VT vs. VMP (NCT#01063179). qRT-PCR was performed on ABI7900HT with a 2-ΔCt approach and using synthetic spiked-in miR-759 as endogenous control. High vs. low expression of these markers were evaluated in relation to clinical characteristics and to OS and PFS. RESULTS: Overall 234 pts had evaluable peripheral blood samples of which 33% had high risk FISH [del17, t(4;14), or t(14;16)] and 30% were ISS stage 3. In the univariate setting, 6 miRNA markers were significant for OS; lower expression for miR-92a, -25, -16, -19b, -451, and 126 corresponded to worse OS. When we adjusted for ISS stage and high risk features, circulating miR-19b was significant for PFS and OS while mir-16 and -451 were significant for OS but borderline for PFS (p=0.07 and p=0.088, respectively). CONCLUSIONS: Serum miRNAs add to ISS stage and FISH as new prognisticators in myeloma patients and are independently associated with PFS and OS.

P-387

Aprepitant Markedly Reduces the Emetic Episodes Caused by High-dose Melphalan in Patients with Plasma Cell Dyscrasias

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Background: Autologous stem cell transplantation (ASCT) with high-dose melphalan (HD-Mel) is frequently used for the treatment of patients with multiple myeloma (MM) and other plasma cell dyscrasias. HD-Mel is highly emetogenic and the nausea and vomiting remain as the most distressing side effects. Aprepitant, a selective antagonist of NK1 receptor, provides superior protection against CINV. However, its efficacy in ASCT conditioning with HD-Mel has not been fully evaluated. Aim: To evaluate the efficacy of aprepitant in preventing emetic episodes in patients receiving ASCT conditioning with HD-Mel. Method: A retrospective chart review was performed on patients receiving ASCT conditioning with HD-Mel at Keio University Hospital between January 2008 and December 2012 for nausea and vomiting episodes. Result: Sixty four patients (60 MM, 3 POEMS syndrome, and 1 primary amyloidosis) were identified, and 31 patients received aprepitant. Complete protection from HD-Mel induced emesis was obtained in 51.6% of patients who received aprepitant as compared to 21.2% of patients who did not. This difference lead to a statistically significant decrease of emetic episodes with a relative risk of 0.252 (95% CI 0.085 - 0.752, p=0.013). The severity of nausea and days without any food intake were also significantly reduced with the use of aprepitant. No serious adverse events associated with the use of aprepitant were observed. Conclusion: Aprepitant offers more effective emesis control than currently available approaches in the Japanese population receiving ASCT conditioning with HD-Mel.

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Evaluation of Neutrophil Gelatinase-associated Lipocalin (NGAL) and Cystatin-C in Multiple Myeloma patients

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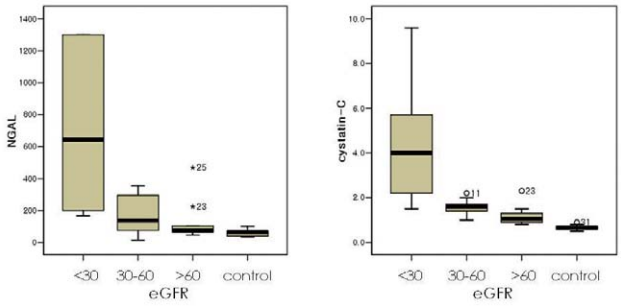
Renal impairment is a common complex of multiple myeloma (MM) patients. Up to 50% of patients revealed increased creatinine level (Cr) and about 9% of patients are needed dialysis. The estimated glomerular filtration rate (eGFR) are generally used methods to evaluate renal impairment, but they are not accurate for acute renal failure. Therefore, new markers are necessary to detect early renal damage because the majority of MM patients have acute renal damage. Neutrophil Gelatinase-associated Lipocalin (NGAL) is overproduced by proximal tubular cells in response to injury. Cystatin-C (Cys-C) reflects GFR than Cr. We evaluated the clinical significance of plasma NGAL and Cys-C in MM patients. NGAL was measured using Alere™ Triage NGAL test and Cys-C was measured by Latex turbidimetric immunoassay (HiSens Cystatin-C, HBI). The eGFR was calculated using the MDRD equation. The NGAL level was different among three eGFR groups (>60, 30-60, <30 mL/min) as 76.0, 137.0, 643.0 ng/mL, respectively). The Cys-C was also different among GFR groups (1.05, 1.60, 4.00 mg/L, respectively). NGAL and Cys-C were correlated (r=0.579, P=0.001) and eGFR was significantly correlated with NGAL and Cys-C with r values -0.614 and -0.786 (P<0.001, P<0.001). Our data suggest that NGAL and Cys-C offers valuable information for the kidney function of MM patients and their measurement may help in the identification of patients with high risk for the development of acute renal function.



P-389

The Prognostic Implication of Parathyroid Hormone in Multiple Myeloma

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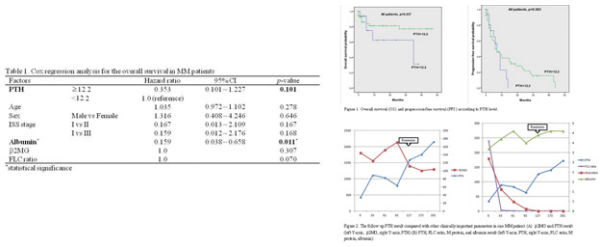
Multiple myeloma(MM) is one of the most common cancer associated with hypercalcemia.Hypercalcemia in cancer is associated with poor prognosis and mainly due to increased bone resorption and release of calcium from bone.Parathyroid hormone (PTH)is reduced through a negative-feedback when calcium is elevated,thus maintaining calcium homeostasis.So we investigated the prognostic implication of PTH in MM and relationship with other risk factors of MM. We ananlyzed 70 patient who diagnosed with MM and checked for PTH between 2009 and 2012.Medical record were reviewed for age,sex,PTH,plasma cell percent,etc.Collected data was analyzed by R 2.13.0 and PASW 18.0.We performed Spearman's correlation analysis,Kruskall Wallis test,survival analysis,etc.PTH level of 70 MM patients was 35.9 ± 40.5 pg/ml.Albumin and LDH were in positive correlation with PTH.Plasma cell percent,M protein,FLC ratio, β2MG,ISS stage,chromosome abnormality showed negative correlation. There was not meaningful difference of PTH according to chromosomal abnormality,bone lesion,progression.Mann Whitney U-test for clinical parameters between low level and normal/high PTH group were as follows;calcium(p=0.0),creatinine(p=0.027), β2MG(p=0.022) was significant.About the prognostic implication of PTH(Tab1),group whose PTH level was below 12.2 pg/ml showed more shorter OS(p=0.237) and PFS(p=0.363,Fig1).We surveyed follow-up PTH with other parameters in several patient;PTH showed correlation trend,considering clinical state(Fig2).In conclusion,PTH suggest the potential of prognostic factor in MM patient.



P-390

A Pilot Study of High Dose Weekly Epoetin Alfa in Patients with Myeloma:Its Effects on Hemoglobin and Quality of Life

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Background: The objectives were to evaluate the effects on hemoglobin and quality of life after treatment with high-dose Epoetin Alfa in patients with multiple myeloma (MM). Methods: In the non-randomized, open-label, single institution pilot study, patients with MM requiring therapy, and a hemoglobin (Hgb) level <11g/dL were eligible. Epoetin Alfa was administered at 80,000 units(U) subcutaneously(sc) weekly.The dose was adjusted based on Hgb levels at day 28. The Functional Assessment of Cancer Therapy Anemia questionnaire was administered to assess quality of life(QOL). Prophylaxis for venous thromboembolic events(VTE) was not mandated. Results: From 9/2003 to 6/2008, 31 patients were enrolled. A Wilcoxon signed rank test was performed to evaluate the change in Hgb and QOL scores from baseline to day 28. Among evaluable patients, the Hgb increased by at least 1gm/dL in 13(57%) pts and by at least 2 gm/dL in 9(39%) pts; baseline Hgb 9.4g/dL(6.8-11.0g/dL) to day 28 10.8g/dL(6.1-14.1g/dL). The median change in Hgb was 1.3g/dL(range-3.0-4.4, p=.02). There was no significant difference in QOL scores(p=.214). 3 pts developed VTE while receiving 1)lenalidomide, high dose dexamethasone and Aspirin 325mg daily, 2)thalidomide and doxil based therapy with Aspirin 81mg daily, and 3)cyclophosphamide and prednisone without VTE prophylaxis. Conclusions: Epoetin Alfa increased Hgb in most patients. In this small study no significant increase in QOL scores was found. The incidence of thromboembolic events was 9% which confirms the need for caution and adjusted VTE prophylaxis with ESA use.

Patient Characteristics (N=31)

Median age, years (range)	61.8 (41-86)
Age <65 / =65 years, n(%)	16(52) / 15(48)
Male / Female N(%)	19(61.3) / 12(38.7)
Durie-Salmon Stage II, IIIa, IIIb (N)	3(9.7) / 25(80.6) / 3(9.7)
Newly Diagnosed n=7	
Concurrent anti-myeloma therapy, n(%)	
IMiD Based (RD, TD, CTD)	7(100)
Relapsed and/or Refractory n=24	
Concurrent anti-myeloma therapy, n(%)	
Alkylator Based (CP, MP)	7(29.2)
IMiD and/or Anthracycline (MTD, TD, DATA, DVD-R, DVD-T)	13(54.0)
Proteosome Inhibitor (VD)	2(8.3)
Other (SGN-40, Interferon Alpha)	2(8.3)

Cyclophosphamide and Prednisone= CP; Cyclophosphamide, Thalidomide and Dexamethasone= CTD; Thalidomide and High-dose Dexamethasone= TD; Dexamethasone, Vincristine, pegyla tedliposomal doxorubicin and thalidomide= DVD-T; Dexamethasone, Vincristine, pegyla tedliposomal doxorubicin and lenalidomide= DVD-R; Melphalan, Thalidomide and Dexamethasone= MTD; Melphalan and Prednisone= MP; Lenalidomide and High-Dose Dexamethasone= RD; Bortezomib and dexamethasone= VD; Dexamethasone, Arsenic, Thalidomide and Ascorbic Acid=DATA.

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Usefulness of Direct Serum Immunoglobulin Heavy/Light Chain Pairs Measurement in Monoclonal Gammopathy

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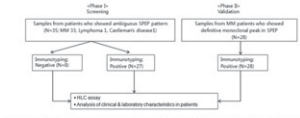
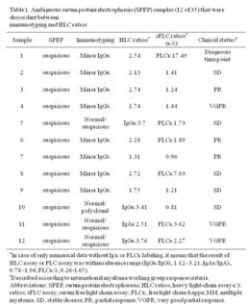
Determination of monoclonal gammopathy by conventional electrophoresis can be obscured by large protein such as haptoglobin,transferrin.Ambiguity in electrophoresis band sometimes gives rise to confusion.Heavy chain/light chain assay by using Hevylite™antibody(The Binding Site,UK) have recently been developed for the accurate measurement of monoclonal protein.We compared immunotyping (IT) profile to immunoglobulin heavy/light chain measurement and observed the ratio between the intact Ig kappa and lambda ratio.We collected 35 & 28 sera from patient with suspicious and definitive peak on serum protein electrophoresis and IT by Capillarys™2(Sebia,USA),respectively(Fig1).Monoclonal protein production was further examined using Freelite™antibody (The Binding Site) and specific Ig(G, A) κ and Ig(G, A) λ Hevylite™ antibody (Binding Site).The result were analyzed using PASW 18.0.Direct measurement of Ig heavy/light chains showed discordant IT results for 12 of 35(34.2%) patient sera with suspicious SPEP pattern(Tab1) and identical IT results for 28 patient sera with definitive peak on SPEP. Overall,good agreement was found between HLC assay and IT (κ=0.718,p=0.000;cross-tabulation Gamma, Kappa analysis).In conclusion,serum Ig heavy chain/light chain pairs measurement was comparable to IT and helpful in making decisions in case of ambiguous monoclonality.The measurement of the heavy chain/light chain pair ratio also allowed precise quantification of monoclonal Ig with ambiguous electrophoresis pattern and identification or discrimination of clonality.





P-392

Evaluation of Immunohistochemical (IHC) Biomarkers of Outcome Using Bortezomib-based Induction in Myeloma (MM) Patients

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There are limited data on the predictive role of proteomic biomarkers in the context of contemporary anti-MM therapies. Aim To conduct an exploratory analysis to correlate the expression of specific MM-related proteins: p53, p16, BCL-2, RelA, XBP1, CCND1, IRF4, NKFB2 and FGFR3 with overall response rate (ORR) after 4 cycles of PAD induction therapy and overall survival (OS) in patients with newly diagnosed MM. Post-hoc analyses were also conducted for progression free survival (PFS). Methods IHC was performed on diagnostic bone marrow trephines and independently scored for staining and sub-cellular localization by 3 haematopathologists. Marrows were scored for the proportion of positive plasma cells (PC) or where PC were uniformly positive, the intensity of positivity (HI vs LO) was recorded. Marrows containing <10% plasma cells were not considered evaluable. Results 91/107 patient samples had >10% CD138 and were therefore evaluated. There was no difference in ORR (post PAD or 3/12 post-ASCT) for RelA, FGFR3, p53, CCND1, NFkB2, IRF4 but positivity for either XBP1 or BCL2 were associated with lower rates of both post-induction and post-ASCT ORR(table). Emergent inferior PFS for patients who were BCL2 HI, RelA HI, XBP1 HI or p53+ was suggested at 2 years. Patients who were CCND1+ versus those who were CCND1- had better OS at 2 years. Conclusion While longer follow-up is required these data from de novo MM recapitulate our previous findings in the relapse context whereby high levels of BCL2 and CCND1 negativity may predict for poorer outcomes with bortezomib-based therapy.

IHC stain	Non-responders post induction		Non-responders 3/12 post-ASCT	
	Positive	Negative	Positive	Negative
XBP1	17/79	0/9	17/79	0/9
BCL2	15/77	2/12	18/77	0/10

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Monocyte Phenotype as a Novel Predictor of Survival in Multiple Myeloma Patients

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Recent advances in development of prognostic biomarkers for multiple myeloma (MM) have focused on tumor-specific characteristics. The aim of this study was to identify patient immune phenotype predictive of survival in MM. Peripheral blood mononuclear cells were collected from 10 healthy donors (NL) and 69 MM patients before and after first-line treatment and examined by flow cytometry. Pre-treatment phenotype predictive of survival by univariate analysis included previously reported and novel phenotype: Treg, CD28+ T cells, CD4/CD8 ratio, and intermediate (CD14+CD16+) monocytes. After multivariate analysis adjusting for ISS, age, gender, and treatment, intermediate monocyte was the only phenotype that remained statistically significant as a predictor of OS (high vs low: median OS 4.6 (85% CI 2.5-6.8) vs 8.7 (6.9-10) yr, p=0.02. HR 2.26 (1.16-4.5), p=0.01). Patients whose non-classical (CD14loCD16+) monocytes decreased with treatments had a prolonged PFS compared to others (median 4.1 (1.6-6.6) vs 2.3 (1.5-3.1) yr, p=0.04. HR 0.35 (0.13-0.89), p=0.03). There was a suggestion of improvement in OS, although this did not reach statistical significance in this limited sample population (median OS 8.7 (4.3-11.0) vs 5.2 (1.8-8.6) yr; p=0.10). An elevated intermediate monocyte population is a novel, independent predictor of OS in MM patients. Declining proportions of non-classical monocyte during treatment improves PFS, and potentially OS. This study supports further study in the role of monocyte subsets in pathobiology of MM and its potential impact on immunotherapy.

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Single Centre Experience on Treatment Outcome in Transplant-eligible Myeloma Patients in Malaysia

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Introduction: High-dose chemotherapy with autologous stem cell transplantation (ASCT) remains standard of care for patients with multiple myeloma (MM) in the era of emerging novel agents. Here we present the treatment outcomes of our transplant-eligible patients for the last 10 years with different induction regimen. Method & Results: We retrospectively analyzed a total of 77 patients who received high-dose melphalan (HD-MEL) followed by ASCT from August 2002 and December 2012 in our centre. The induction chemotherapy prior to ASCT has evolved from VAD regimen (30%) to Thalidomide or Bortezomib (T/V)-based regimen (70%) with time. No significant age different among two groups although T/V-based group had more male patients. Majority was IgG subtype (VAD: IgG 70% and T/V-based: 77% respectively). More patients in the T/V-based group attained CR/nCR (37%) as compared to VAD regimen (22%) prior to ASCT. The median day of neutrophils engraftment was 1 day earlier for T/V-based group (VAD: Day+11 and T/V-based: Day+10 respectively) while platelet engrafted at Day+ 10 in both groups. The incidence of TRM was 3%. The overall survival (OS) of all MM patients post ASCT was 50% at 56 months from the time of transplant. We will present the post-ASCT outcome, the survival curve and event free survival (EFS) of the each group later. Conclusion: ASCT still remains a viable treatment option to deepen the response and prolong survival of MM patients.

	VAD regimen N=23	Thalidomide/Bortezomib-based N=54
PATIENT DEMOGRAPHIC		
Median age (year)	54 (range: 25 – 63)	56 (range: 37 – 69)
Male gender (%)	48	61
Race (%)		
Malay	65	54
Chinese	26	33
India	9	11
Other	-	2
Myeloma subtype (%)		
IgG Kappa	48	40
IgG Lambda	22	37
IgA Kappa	9	6
IgA Lambda	4	7
Light chain kappa	4	4
Light chain lambda	4	2
Non-secretory	9	4
Post-induction outcome (%)		
CR/nCR	22	37
VGPR	74	59
Relapse/refractory	4	4

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The Significance of Isotype Class Switching after Transplantation in Multiple Myeloma in the Era of New Drugs

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Introduction: Multiple myeloma (MM) is a hematological malignancy characterized by production of a single serum monoclonal immunoglobulin of constant isotype (MIG). Switching of the MIG isotype or transient presence of oligoclonal bands detectable by serum immunofixation electrophoresis has been reported following high-dose chemotherapy. We reported positive prognostic significance of these findings in 72 adult patients with multiple myeloma receiving autologous or allogeneic hematopoietic cell transplantation in the past. Currently we wanted to verify this fact in the era of new drugs. Patients and Methods: We carried out a retrospective analysis of 57 MM patients (31 men and 26 women, median age 60 years) who underwent autologous transplantation as a part of upfront treatment of MM from 2006 to 2010. The frequency and clinical significance of the appearance of abnormal protein bands distinct from the presenting MIG was evaluated. Results: Protein band distinct from the MIG present at diagnosis was found in 8 (14%) patients, 4 (7%) patients had oligoclonal bands and 6 (11%) patients had both isotype switch and oligoclonal bands after transplantation. Survival rates were the same in all patient groups. Conclusion: Based on our results, switching of the MIG isotype or transient presence of oligoclonal bands after autologous transplantatation lost its positive prognostic value in the era of new drugs. The possible reason of this difference from our previous results is strong immunological potential involved in their antitumor action.

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Acupuncture Combined with Methylcobalamin for Chemotherapy-induced Peripheral Neuropathy of Patients with Myeloma

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Chemotherapy-induced Peripheral Neuropathy (CIPN) is seriously affecting the quality of life as well as the response rates to chemotherapies and there is no described clear and effective therapy. Acupuncture has a great potential for the treatment of CIPN, but up to now there are not enough cases of randomized clinical research to analyze the effectiveness. 58 MM patients which met the inclusion criteria were randomly assigned into a solely Methylcobalamin therapy group (10 times of 500 μg intramuscular Methylcobalamin injection every other day followed by 3 months of oral Methylcobalamin application) and Acupuncture combined with Methylcobalamin group (Methylcobalamin used the same way as above accompanied by 3 cycles of acupuncture). The evaluating parameters included visual analogue scale (VAS) pain score, FACT/the GOG-Ntx questionnaire scores and electromyographic (EMG) nerve conduction velocity (NCV) determinations. After 3 months of therapy, the pain was significantly mitigated in both groups, with a significant higher decrease in the acupuncture treated group ($P < 0.001$). The patients' activities of daily life evaluated by FACT/the GOG-Ntx questionnaire improved obviously in both groups while more significantly in the acupuncture treatment group ($p<0.001$). The NCV in the acupuncture treatment group improved significantly while amelioration in the control group was not observed. This study suggests that Acupuncture combined with Methylcobalamin for the treatment of CIPN showed a significant better outcome than a solely Methylcobalamin administration.

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Lenalidomide and Related Factors in Myeloma Patients, Single Center Experience

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Almost all patients with multiple myeloma MM who survive the initial treatment, will eventually relapse and require further and a more potent therapy. Treatment options for patients with relapsed refractory MM include hematopoetic cell transplantation, rechallenge with the previous regimen, treatment with a new regimen. There are certain factors to determine the second line treatment such as risk stratification of the disease, prior treatments and response. Lenalidomide has a benefit of not causing neuropathy and is chosen in patients who have been previously treated with neurotoxic regiments including vincristine, bortezomib and thalidomide.We are presenting 14 patients with MM, who have been previously treated with regimens with dexametasone with vincristine, doxorubicin, cyclophosphamide, bortezomib, melfalan, thalidomide and finally Len. Mean age of the patients was 68.7 7 patients were male and 7 female. 5 of the patients had IgA heavy chain while 7 had Ig G, 2 had light chain. Lenalidomide

is indicated in patients who have been previously treated with 2 different regime and have been refractory or relapsed. We observed Grade 3 neutropenia due to len in 6 patients 40% and thrombosis in 2 patients 13.3%. We didn' t observe a relation between the initial stage of the disease or disease duration with response to Len. We didn' t observe a relation between remission durations with prior regimes and response to Len. Overall remission was observed with Len in 9 of the patients. Further predictive factors are needed in determining the treatment in relapsed or refractory MM.

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Bortezomib Induced Herpes Zoster and Acyclovir Prophylaxis in Multiple Myeloma Patients

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Multiple myeloma (MM) patients treated with bortezomib-based regimens are at particular risk of herpes zoster reactivation. We assessed a cohort of 204 patients treated with bortezomib at our department between 2003-2012. 126 patients recieved acyclovir 200mg per day whereas 72 patients (historical cohort) had no prophylaxis. In patients without prophylaxis, the incidence of herpes zoster reactivation was 28%, whereas there was only one case (1%) of herpes zoster reactivation in patients with acyclovir prophylaxis, in a noncompliant patient. Patients with previous herpes zoster history without prophylaxis were at particular risk (3 out of 6, i.e. 50% incidence). The reactivation occured mostly within the first three cycles of treatment (78%), however, in some patients we registered the reactivation even in later phases of the treatment. We conclude that acyclovir prophylaxis is essential for patients with MM treated with bortezomib based regimens, and should be maintained for the duration of treatment. Even low doses of acyclovir are efficient and create sufficient prophylaxis.

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Adverse Event Management of Pomalidomide + Low-dose Dexamethasone in Relapsed and Refractory Multiple Myeloma

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Background: Advanced relapsed and refractory multiple myeloma (RRMM) is associated with compromised bone marrow function, leading to potentially more severe hematologic adverse events (AEs) and discontinuations. Methods: In this multicenter, randomized, open-label phase 2 study, MM-002, patients who had received >=2 prior therapies and were refractory to their last treatment were randomized to pomalidomide plus low-dose dexamethasone (POM+LoDEX; POM 4 mg/day, days 1-21 of a 28-day cycle; LoDEX 40 mg/week) or POM alone. This analysis focused on the management of hematologic AEs during POM+LoDEX treatment by means of dose modifications and supportive care. Results: Amongst the 113 patients randomized to POM+LoDEX, the most common grade 3/4 AEs were neutropenia (41%), anemia (22%), thrombocytopenia (19%), and pneumonia (22%). AEs were managed through dose reductions or interruptions, and with the use of appropriate supportive care (Table). Dose reductions occurred in 29% of patients in the POM+LoDEX arm. Discontinuations due to AEs were relatively low (7%) and discontinuations due to neutropenia and thrombocytopenia occurred infrequently. The most common concomitant therapies were growth factor support, and red blood cell and platelet transfusions (Table). Conclusions: POM with LoDEX was generally well tolerated. AEs were predictable and manageable with appropriate dose reductions, interruptions, and supportive care; rates of discontinuations due to AEs were low.

Table. Management of adverse events in patients receiving POM + LoDEX in the MM-002 study.

	POM + LoDEX (N = 112)
Patients who discontinued POM due to AEs, %	7
Neutropenia	1
Thrombocytopenia	0
Patients with ≥1 POM dose reduction, %	29
Patients with ≥1 POM dose reduction due to AEs, %	26
Neutropenia	4
Thrombocytopenia	5
Median time to first POM dose reduction, mos	1.5
Patients with ≥1 POM dose interruption due to AEs, %	67
Neutropenia	9
Thrombocytopenia	5
Supportive care, %	
G-CSF	46
RBC transfusions	45
Platelet transfusions	14

AEs, adverse events; G-CSF, granulocyte colony-stimulating factor; LoDex, low-dose dexamethasone; POM, pomalidomide; RBC, red blood cell.

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Multiple Myeloma : Treatment and Survival in the Era of Novel Agents

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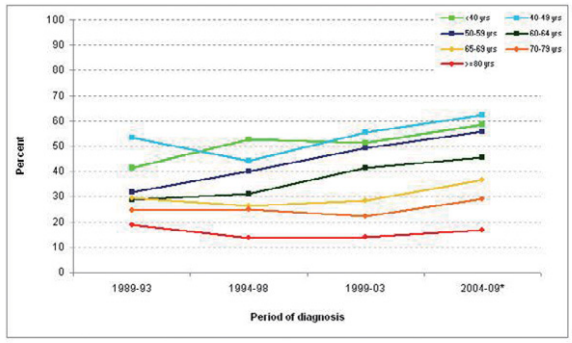
Over the last two decades, the use of High-dose Melphalan and novel agents like thalidomide, lenalidomide and bortezomib has changed the management of patients with multiple myeloma (MM) and extended overall survival. For patients <66 years, efficacy and survival improvement are convincing based on randomized controlled trials in contrast to older patients. To establish the real impact of novel agent on improvement in survival in unselected myeloma patients we retrospectively analysed all MM patients diagnosed in the period 1989-2009 who were recorded in the Dutch Cancer Registry (n =16.822). Survival improved significantly for patients up to 70 years (fig 1). Survival improvement is observed after HDM therapy and AutoSCT became treatment of choice for younger patients and thalidomide- based regimens for the elderly. To explore if treatment efficacy can be translated to treatment effectiveness for patients >65 years we determined the sequence of treatment regimens, effect of treatment regimen on overall survival and the impact of pre-existing comorbidities, WHO-performance status and age on survival using the Dutch PHAROS registry (Population based Haematological Registry for Oberservational studies) (n=427). Choice of treatment regimen is significantly related to age and year of diagnosis. While there is large treatment diversity, we observed patterns of treatment sequence ordering. Age and WHO-performance status are significantly related to overall survival (both P<.001) while number of pre-existing comorbidities at diagnosis has no significant impact (P=0.06).



	Period of diagnosis							
	1989-1993		1994-1998		1999-2003		2004-2009*	
Age group (years)	PE	SE	PE	SE	PE	SE	PE	SE
<40	42	7,3	53	7,9	52	7,8	59	7,3
40-49	53	3,7	44	3,5	56	3,3	62	3,0
50-59	32	2,2	40	2,3	49	2,1	56	1,8
60-64	29	2,4	31	2,4	41	2,5	45	2,2
65-69	29	2,1	26	2,0	28	2,0	37	2,0
70-79	25	1,5	25	1,4	22	1,3	29	1,3
80+	19	2,4	14	1,8	14	1,9	17	1,8

Fig 1: Five year relative survival for multiple myeloma patients stratified by period of diagnosis and age category.
***: estimation based on period analysis**
Abbreviations: PE, period estimate of survival; SE, standard error

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Toll-like Receptor 4 Agonist LPS-induced *CXCL10* mRNA in Peripheral Blood (PB) as a Predictive Biomarker of Bortezomib

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We reported unique predictive biomarkers of responses to bortezomib (Bzb) in ASH2012. As biomarkers exhibit potential utility in personalized treatment of Bzb, the interim report was further validated. A 2 ml sample of PB was prospectively obtained before i.v. treatment (D0) and 2-3 days (D2-3) and 1-3 weeks (W1-3) after the first dose. Triplicate of 0.06 ml each were incubated *ex vivo* with phytohemagglutinin, heat aggregated IgG, lipopolysaccharide (LPS), zymosan A, or solvent for 4 hrs at 37° C and then stored at -80° C. *IL2, IFNG, GMCSF, TNFSF2, CCL4, IL6, CXCL10*, and *ACTB* mRNA were quantified as previously described (J Immunol Methods 363:95, 2010). Of 83 pts enrolled from 6 centers, 80 were assessable for this analysis, including 53 pts in the

ASH report. The number of CR, VGPR, PR, SD, and PD were 5, 7, 33, 33, and 2, respectively. One of the main findings of the report, LPS-induced *CXCL10* was maintained in this analysis; ie, pretreatment fold increase (FI) of CR or VGPR was significantly higher than PR (p=.03), SD (p=.01), and PD (p=.01) by t-test. Moreover, 10 of the 12 pts of CR or VGPR showed a >=3 FI and both of the 2 PD pts showed a <3 FI whereas FI of PR or SD was distributed widely without a clear distinction. LPS-induced *CXCL10* levels in CR/VGPR was significantly and continuously inhibited in D2-3 (p=.001) and W1-3 (p=.008), whereas such inhibition was transient and only found in D2-3, not in W1-3 in PR/SD. The two PD showed no change in D2-3 or W1-3. LPS-induced *CXCL10* mRNA in PB is a promising biomarker for the prediction and monitoring of Bzb treatment.

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Estimation of GFR with Different eGFR Equations in Multiple Myeloma (MM) Patients (pts) Receiving Lenalidomide (Len)

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Renal impairment (RI) in pts with MM is one dreaded end-organ damage. The estimation of glomerular filtration (eGFR) rates is based on different equations, such as Cockcroft-Gault (CG), MDRD or CKD-EPI, currently being assessed and compared worldwide. We enrolled 132 MM pts uniformly treated with Len according to the approved indication between 2006-2012. The GFR for quantifying RI was estimated by the CG-, MDRD- and CKD-EPI-equations. The eGFR was divided into 5 stages as described. The median pt age was 64 years (range 41-90), with males in 62% and predominantly advanced stage II/III D&S and ISS disease (96%+65%, respectively). The median Len dose was 25mg (range 5-25). The median serum creatinine was normal with 1.0mg/dl, whereas the median eGFR showed already CKD stage 2, with substantially different CG-, MDRD and CKD-EPI-equations of 74, 81 and 77ml/min/1.73m2, respectively. Compared with the MDRD equation, more pts were reclassified to lower eGFR values by the CKD-EPI equation and less to higher CKD stages (Fig.1). This indicates that the MDRD overestimates the GFR, especially in elderly pts with normal or less pronounced RI (Table 1). Correspondingly, the CKD-EPI equation reclassified more pts to lower and less to higher CKD stages measured by CG. To the best of our knowledge, we here demonstrate for the first time that the CKD-EPI equation in Len-treated pts best calculates the GFR in all CKD stages and detects more pts with RI than via MDRD. Our results enlarge the arsenal of available eGFR equations by the CKD-EPI equation which seems valuable in Len-treated pts.

Fig. 1. Reclassification of MDRD estimated GFR stages by the CKD-EPI equation

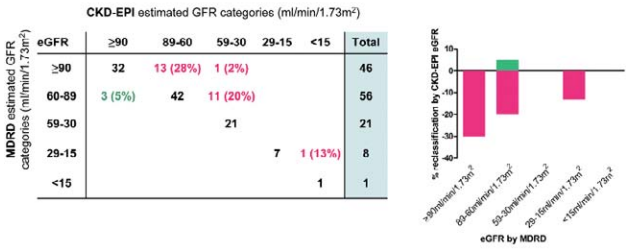

Table 1. Estimated CKD stages and prevalence of CKD stages 3-5 by different eGFR equations

Variables	CKD-EPI		Cockcroft-Gault		MDRD	
	n (%)		n (%)		n (%)	
1: eGFR ≥90 ml/min/1.73m²	35 (26)	68%	49 (37)	70%	46 (35)	77%
2: eGFR 80-60 ml/min/1.73m²	55 (42)		43 (33)		56 (42)	
3: eGFR 59-30 ml/min/1.73m²	33 (25)	32%	32 (24)	30%	21 (16)	23%
4: eGFR 29-15 ml/min/1.73m²	7 (5)		7 (5)		8 (6)	
5: eGFR <15 ml/min/1.73m²	2 (2)		1 (1)		1 (1)	

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The International, Observational EMMOS Registry of Myeloma Patients Treated in Routine Clinical Practice: First Results

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This non-interventional study aimed to provide an accurate 'real-life' picture of practices in multiple myeloma patients,

independent of drugs used, in 22 countries in Europe and Africa. A multi-staged site and patient selection enrolment model was developed to minimize selection bias. Enrolment was stratified by country, region and practice type (academic, regional, local, private). Overall 2428 patients are enrolled and have had retrospective and prospective data collected. In this first interim analysis 1298 patients (53.5% males) are included. Median follow-up was 15 months. At time of inclusion mean age was 64.7 years (+/-10.75). Median Karnofsky score was 80% (range 70-90), 47% of patients had bone lesions, 6% had severe neuropathy and 19% had severe renal impairment. The same baseline characteristics were observed in different site types. Patients had received a median of 1 line of therapy (range 1-10); 144 patients had a transplant history. In the non-transplant group ORRs were 56%, 55% and 48% to 1st, 2nd and 3rd line therapy; in this group 50%, 41% and 40% of patients received a bortezomib-containing combination as 1st, 2nd and 3rd line therapy, respectively, and their ORRs to bortezomib-based therapy were 67%, 65% and 50%. AEs and serious AEs were collected prospectively; no new safety signal was detected. The incidence of nervous system disorders was ~5% with bortezomib-based therapy. Ongoing analyses from this study will allow future health economic, pharmaco-epidemiologic, and outcomes research, and will provide important data from the clinical arena.

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Risks for Different Neoplasms (DNs) in Multiple Myeloma (MM) Patients (pts): Institutional Database of 744 MM Pts

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DNs after first-line- and maintenance-treatment have been reported, questioning whether specific risk factors (RFs) exist in MM. Moreover, 2nd tumors have gained more attention as MM pts live longer and randomized data show associations between newer drugs and excess risk of DNs. Large population-based databases offer powerful sample sizes, but bears the limitation of focussing on primary rather than 2nd tumors. We have conducted a large study designed to define the rate of DNs in a well-characterized clinical MM cohort. We identified 744 consecutive pts treated at our institution 1997-2011 and analyzed the onset of DNs and MM-specific RFs. 118 (16%) showed DNs, whereas 84% had no DNs apart from their MM. Prior/synchronous DNs were observed in 83 pts (63%) and subsequent DNs in 49 (37%). Most (77%) DNs were solid tumors; whereas hematological DNs with 23% were prominently observed subsequently (Fig. 1). MM pts with DNs vs. no DNs were older, predominantly male, had IgG-MM and more CTx-cycles, use of steroids, alkylators, lenalidomide/thalidomide and radiotherapy, but lacked laboratory abnormalities nor had more ASCTs. The risk of dying without subsequent DN was substantially higher than that of developing a 2nd tumor (cumulative incidence at 20 years: 78% vs. 11.2%, respectively; Fig. 2). Matching the SEER database with our data is currently underway and will expand our knowledge on DNs. Our and previous analyses suggest that physicians need to discuss individual risk-benefit ratios with pts and stay updated as more knowledge becomes available on this topic.

Fig. 1. Different neoplasm among 744 MM pts; prior vs. subsequent to MM diagnosis

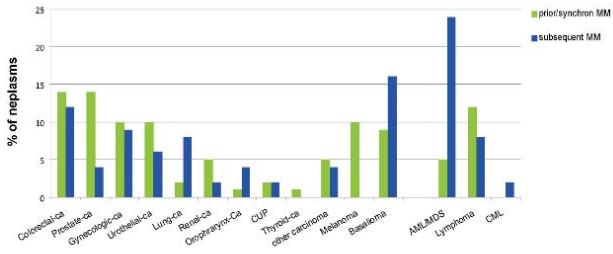
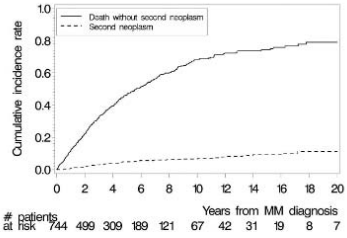


Fig. 2. Cumulative incidence rate (CI) of developing a 2nd tumor and of death without subsequent DN after a diagnosis of MM



P-405

The Frequencies of Cytogenetic Abnormalities by Interphase FISH Compared with Metaphase Chromosomes

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The prognostic role of cytogenetic abnormalities in patients with multiple myeloma is increasingly evident recently. However, the frequencies of the abnormalities in Japanese remain unclear. Fluorescence in situ hybridization (FISH) involving t(4;14), t(14;16), t(11;14), 17p13 deletions, and 13q deletions was performed at baseline in interphase bone marrow

cells as well as metaphase chromosomes from 45 patients. Of all patients, 60% (27/45) harbor aberrant cytegenetics by FISH, whereas 24% (11/45) by metaphase chromosomes. Del(13q) and t(11;14) are the most frequent chromosomal abnormalities, observed in 29% and 22% of the patients, respectively, and a further three, t(4;14), t(14;16), and del(17p), considered poor prognosis were 11%, 2%, and 9%, respectively. Only 4% patients showed chromosome 13 deletion by metaphase chromosomes. Patients with lower percentage of plasma cells (<10%) in bone marrow tended to be negative for FISH analysis (p=0.004). Abnormal cytogenetics associated with high risk group on ISS staging (p=0.011). Two patients were compared bone biopsy with bone marrow aspiration at the same time by FISH analysis; bone biopsy had more concentrated cytogenetic abnormalities. From nine of patients FISH was analyzed both at the time of diagnosis and relapse, their abnormalities were similar. Interphase FISH analysis is sensitive and useful to detect cytogenetic abnormalities, however require a higher number of plasma cells in bone marrow. The further clarification using FISH is warranted in myeloma patients.

P-406

Intravenous (IV) or Subcutaneous Bortezomib (SC) for Multiple Myeloma (MM): A Prospective Time and Motion Analysis

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Background: Bortezomib (1.3 mg/m^2 IV on days 1, 4, 8 and 11 for eight, three week cycles) is effective in MM. A recent randomized trial demonstrated that SC bortezomib is equally effective, but with reduced side effects. A prospective time and motion study was undertaken to evaluate the efficiency and cost savings of the SC route over the IV one. Methods: Time and resource use data were collected from MM patients being treated with bortezomib IV (n=20) or SC (n=20) in seven U.S. community oncology clinics. Outcomes were presented as a total cost per dose of bortezomib administered IV or SC and compared using parametric and non-parametric statistical tests (± 95%CI). Results: The mean total time for IV and SC delivery was 76.3 and 39.8 minutes (p = 0.005), with the associated cost of bortezomib being $189 and $90.84 respectively. With the inclusion of costs for drug wastage (i.e. mean of 1.2 mg for both IV and SC bortezomib, which is 34% of a 3.5 gram vial) and premedication, the total cost was $808 (95%CI: $603-1011) and $596 (95%CI: $334-856) per dose for IV and SC bortezomib. Over a full cycle of therapy, the total cost for drug delivery including wastage would be $3,232 and $2,384 for IV and SC bortezomib. Conclusion: The SC route resulted in a savings in drug delivery costs. However, drug wastage remained substantial. In contrast, an orally administered agent such as lenalidomide, with at least comparable efficacy, has the potential to save health care resources, avoid drug wastage and be less of a burden for patients in terms of weekly clinic visits.

P-407

High Level Decorin in BM Plasma Associated with Better Response of Novel Agent Induction in Newly Diagnosed MM Patients

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The growth of myeloma cells depend on bone marrow (BM) stroma consisted of stromal cells, cytokines and extracellular matrix (ECM). Decorin (DN) is abundant in the ECM, which was found to down regulate the EGFR by post ligand binding endocytosis, suggesting its potential anti-tumor effect. A total of 113 newly diagnosed MM patients who received either thalidomide (THA) or bortezomib (BTZ)-based induction were enrolled. Patients' BM plasma at diagnosis were collected, and which were obtained from 10 non-MM persons as a control. DN in the stored BM plasma were measured by the DuoSet ELISA kits. Among the 113 MM patients, 62 (55%) had THA-based regimen, 13 (11%) had BTZ-based regimen, and 38 (34%) had combined THA and BTZ-based regimen. The mean DN level was 17.2 ng/mL with IQR:11.4-21.6 for the MM patients, and which was 15.9ng/mL (IQR:11.2-18) for the control. Using DN 15.9 ng/mL as a cutoff, there were 59 MM patients had high DN (DN-h) and 54 had low DN (DN-l). Comparison on clinical features between DN-h and DN-l group showed no differences. The overall response rate (ORR), terms of partial response or better, was significantly higher in DN-h (81%) than in DN-l (57%), P=0.015. Multivariate analysis confirmed high DN was an independent factor (odds 3.289, 95% CI:1.035-10.455). The median progression-free survival was longer in DN-h (not reached) than in DN-l (19 m), P=0.05. These findings supported the anti-myeloma effect of DN. High DN in BM plasma associated with better ORR and longer PFS in newly diagnosed MM patients who had received novel agents-based induction.

P-408

Tolerability of Velcade (Bortezomib) Subcutaneous Administration Using a Maximum Volume of 3 mL Per Injection Site

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Until recently, intravenous (IV) injection (inj) has been the standard for bortezomib (Bor) administration with adoption of subcutaneous (SC) inj based on no difference in efficacy, decreased neuropathy and ease of administration. SC dosing was validated at a 1 mg/mL concentration which leads to many patients (pts) requiring more than one SC dose as standard SC administration is to a maximum of 2mL per inj site. In this prospective study evaluating a change to SC administration, Bor 1mg/mL was administered SC to consecutive myeloma pts to a higher maximum of 3mL per inj site. Pts were new to Bor or switched from IV. We evaluated systemic and inj site reactions (rxns). For 56 individual pts, 314 doses were administered over 3 months. Assessment of previous inj sites were documented as per patient history and clinical exam on next treatment day in 250 visits; baseline and post-administration blood pressure documented in 298 and 281 visits respectively. Skin rxns were noted in 103 doses (41%) with all rxns being grade 1 or 2. Pts tolerated SC injections well and only 3 pts were switched back to IV due to grade 2 skin rxns. One patient was switched back to IV due to nausea, and another due to preference. This is the first time that SC Bor of a volume up to a maximum of 3 mL (or 3mg of Bor) per inj site has been reported. This higher single dose is well tolerated with limited skin rns, no significant hypotension and facilitates ease of administration with only 5 pts needing 2 injections per visit versus 32 pts with standard 2mL dosing.

P-409

Lenalidomide in Myeloma Treatment- Impact of Treatment Persistence on Disease Control & Healthcare Resource Utilization

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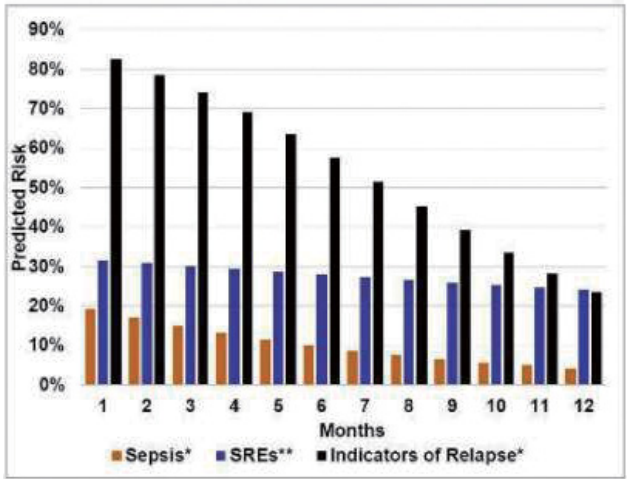
Background: While persistence to drug therapy is essential to achieve optimal patient benefits, poorly controlled multiple myeloma (MM) results in more rapid disease progression, related complications, impact on quality of life, and premature death. The aim of this study is to evaluate the real-world persistence with lenalidomide (LEN) treatment in MM patients (pts), and assess the relationship between treatment persistence with (1) indicators of poor disease control and disease-related complications, and (2) the total healthcare costs for MM pts. Methods: Commercial & Medicare Advantage enrollees of a large US health plan were studied (2007-2011). Treatment discontinuation, disease-related complications (sepsis, indictors of relapse or disease progression (e.g., addition or switch to bortezomib), skeletal-related events (SRE), and healthcare resource use and costs, were analyzed. Results: Among the 605 MM pts meeting the inclusion criteria, a one month increase in persistence was associated with a lower probability of SREs (OR=0.96; p=0.078), sepsis (OR=0.86; p<0.001), and relapse/progression (OR=0.78; p<0.001). The probability of an inpatient hospitalization (OR=0.68; p-value<0.001) and additional ER visits (OR=0.83; p=0.002) were both lower with longer duration. A one-month increase in persistence was associated with, on average, an 8% decrease in medical care costs (p=0.007). Conclusions: Longer persistence with LEN therapy was associated with improved patient outcomes and consequently leads to cost saving due to fewer hospitalizations and ER visits.

Figure 1. Predicted risk of disease progression as a function of LEN persistence – 1 year follow-up.



P-410

Cereblon Detected by Immunohistochemical Staining in Myeloma Cells Associated with Treatment Response of Lenalidomide

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Recently, cereblon (CRBN), the primary teratogenic target of thalidomide, was found to be required for the anti-myeloma activity of other immumodulatory drugs (IMiDs), like lenalidomide, which might be served as a biomarker for the clinical assessment of its anti-myeloma effect. We retrospectively analyzed 42 myeloma patients who had lenalidomide and dexamethasone (LD) as their salvage treatment. Expression of CRBN in myeloma cells (MC) were demonstrated by immunohistochemical (IHC) staining on the paraffinized bone marrow tissue sections taken before the commencement of LD. The results of IHC were interpreted by two independent reviewers. The overall response rate (ORR), terms of partial response or better, was significantly higher in the patients whose MC were positive for CRBN staining (71%) than those who were negative (35%), P=0.05. Another two cohorts of patients, one had thalidomide and dexamethasone (TD; n=50) and another one had melphalan and prednisolone and bortezomib (VMP; n=24) as their induction regimen. Interestingly, in the TD and VMP cohorts, the CRBN expression in MC determined by the IHC method was not able to tell who responded to the treatment from who did not respond (TD cohort: CRBN+ vs. CRBN-, ORR 61% vs. 68%, P=0.759, PFS 35m vs. 26m, P=0.8542, respectively; VMP cohort: CRBN+ vs. CRBN-, ORR 93% vs. 78%, P=0.583, respectively). Our data suggested that expression of CRBN in MC shown by the IHC was primarily associated with the treatment response of LD.

P-411

Three Cases of Multiple Myeloma Resembling Solid Tumors: Presentation, Treatment, Outcome

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Plasmacytomas are frequently a presenting feature of multiple myeloma. We report 3 cases with multiple myeloma presenting with unusual plasmacytoma localizations that resembled solid tumors. Case 1: Female, 54, presented with persistent pain in the left lower quadrant. CT scans revealed a large mass arising from the left ovary extending to the sigmoid colon. Biopsies performed during operation revealed a plasmacytoma and further investigation was consistent with multiple myeloma. The patient was treated with bortezomib and dexamethasone and then autologous transplantation and achieved a durable complete remission. Case 2: Male, 82, presented with anorexia, weight loss, night sweats and low grade fever. Physical examination showed significant liver enlargement. Imaging studies revealed multiple focal lesions in the liver and biopsy showed plasma cell tumors. Trephine biopsy confirmed multiple myeloma and the patient received cyclophosphamide, bortezomib and high dose dexamethasone with excellent results. Case 3: Female, 62, with an 8 year history of multiple myeloma in CR for the past three years presented with severe headache, convulsions, aphasia and delirium. A brain CT scan showed multiple large foci located at the temporal and frontal lobes. CSF examination revealed 15-20 monoclonal plasma cells/m3. The patient received 5-drug combination chemotherapy with rapid disappearance of the plasma cells but succumbed due to neutropenic infection. Conclusion: Bizarre presentation of multiple myeloma with unusual location of plasmacytomas does not confer an adverse prognosis.

P-412

GCSF Therapy and Treatment Outcomes in Neutropenic in Relapsed Myeloma Patients Treated with Lenalidomide Based Therapy

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Background: There are several options for managing relapsed multiple myeloma including lenalidomide based combinations.Grade 3-4 neutropenia in present in 35% of patients. Objective: To determine the prevalence of severe neutropenia and treatment outcomes of lenalidomide/low dose dexamethasone combination in 3 cohorts of patients (N=283) in 3 provinces (Manitoba, Ontario, British Columbia) with relapsed-refractory myeloma who developed grade 3-4 neutropenia with different GCSF use policies on outcome measures. No primary prophylaxis was used in BC, use to maintain neutrophil >1 x 109/l in MB and 2-3 doses for the last 2 weeks of each 28 day cycle x3/ week) in ON. Results:

Grade 3-4 neutropenia was present in 27%, 61% and 48% of the MB, ON cohort and BC cohort. Progression free survival at one year (PFS1) among patients with severe neutropenia for MB was 31%, 39% for ON and 64% in BC. Overall responses (complete, very good or partial) were seen in 50% of MB neutropenic cohort, 67% of the ON cohort and 91% of the BC cohort. Neutropenia developed within 2 months of starting therapy. No statistically significant differences were found between neutropenic "GCSF" and "non-GCSF" users in ON on PFS (p= 0.710) or overall response (p=0.822). Conclusion:The prevalence of severe neutropenia varied between the 3 provinces unexplained by lines of therapy and stage of disease. Although BC had a low rate of GCSF use, they had higher rates of PFS and ORR. We could not show that GCSF use during lenalidomide based therapy in severely neutropenic patients affected treatment outcomes.

Table 1. Demographic characteristics of patients with neutropenia.

Variable (Total=283)	Manitoba (N=37)	Ontario (N=200)	British Columbia (N=46)
Grade 3-4 Neutropenia	27%	61%	47.8%
Age in years (Q1-Q3)	61.5 (60-67)	61.5 (54-66)	63.5 (59-73)
Male Gender	40%	55.74%	54.6%
ISS Stage I	10%	55.74%	31.8%
ISS Stage II	90%	27.1%	22.7%
ISS Stage III	0%	2.46%	22.7%
No. of Prior Therapies			
1	10%	15.6%	31.8%
2	20%	35.3%	22.7%
3 or More	70%	48.4%	45.5%

P-413

Discordant Response to Novel Agents from Site to Site in Multiple Myeloma with Multifocal Extramedullary Disease.

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Multifocal extramedullary disease (EMD) is an uncommon complication of Multiple Myeloma (MM). We report a series of 30 MM patients, observed at our Institutions between 2004-2011, with more than one EMD. Overall, 13 cases presented with EMD at diagnosis (EMD-1) and 17 cases developed EMD at progression or relapse after 1st line therapy (EMD-2). The median number of EM sites per patient was 3. The most common sites (78%) of EMD-1 were soft tissues surrounding the skeleton (STSS). The sites of EMD-2 were airways, skin, subcutaneous tissues, lymphnodes, pericardium, pleura, breast, central nervous system, orbit, gastrointestinal tract, thyroid, pancreas, liver, kidney, abdomino-pelvic masses in 55% of cases and STSS in 45% of cases. After 4 cycles of treatment, Bortezomib based or Lenalidomide based, irrespectively of the treatment, the EM masses showed discordant response or progression, from site to site and between various sites in each patient with multifocal EM lesions. In particular, 73% of EM masses arising from the bone with a soft tissue component showed a response to treatment whereas only 27% of EM masses involving other sites showed a response. The discordant response of EMD to treatment according to the site, observed in our case series, suggests that the progression of myeloma cells homing in different tissues may affect the outcome of EMD either because of EM myeloma cells could became more tolerant to novel agents in some sites rather than in others, either because of novel agents could have a different efficacy in different microenvironments.

P-414

Adverse Prognostic Impact of Bone Marrow Microvessel Density in Plasma Cell Myeloma

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Angiogenesis has an important role in proliferation and survival of plasma cell myeloma (PCM). Bone marrow (BM) microvessel density (MVD) is a useful angiogenesis marker, which can be detected by anti-CD34 immunohistochemical stain. Here we investigated the prognostic impact of MVD. A total of 108 PCM patients were included. Of the patients, 64% (n = 69) were male and the median age was 64 (32-83). MVD was assessed by screening three hot spots of CD34 positive vessels and counting the number of vessels (X400, 0.24mm2) on BM of diagnosis. Two different persons estimated MVD respectively in a blind manner. The prognostic impact of MVD was assessed by Cox proportional hazard ratio (HR). The median of MVD was 33.7 (3.7-98.2). The patients were divided into three MVD groups (median 16.8, 33.9 and 54.7) for analysis. Initial treatment regimen received including thalidomide and dexamethasone (33%), vincristine and dexamethasone (25%), and melphalan and prednisolone (28%). Autologous peripheral blood stem cell transplantation was performed in 31 patients (29%). The median overall survival (OS) was 26 months (2-270). Hemoglobin, beta-2-microglobulin, plasma cell count and the cellularity of BM were associated with MVD ($P < 0.05$). High MVD group showed a significant HR of 3.06 (95% CI 1.64-5.71, $P = 0.0005$) for progression free survival (PFS) but not for OS. Performance status and albumin were associated with PFS and OS. MVD

of BM in patients with PCM represented a poor prognostic marker. Thus, MVD measurement may be considered as a routine BM study at initial diagnosis.

P-415

Does Stringent Complete Response (sCR) Criteria Represent a Deeper Level of Remission as Compared to Conventional CR?

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sCR criteria appears to represent a deeper level of remission as compared to conventional CR but this remains controversial. We compared the impact on PFS and OS of achieving sCR vs. conventional CR on 102 patients included in the GEM05>=05 trial studied after induction by immunofixation, serum free light-chains (sFLC), and flow cytometry (FC). According to the IMWG criteria for sCR, an abnormal clone is defined when the κ/λ ratio is >4:1 or <1:2 for κ and λ patients, respectively, and counting >=100 PCs. Thus, we have defined clonality by FC when >=0.5% PCs were present in the BM and >80% (κ patients) or >50% (λ cases) of those PCs were phenotypically aberrant. Conventional CR was defined according to the IMWG criteria. Among the 102 patients (all in >=PR), 44 (43%) were in conventional CR and 28 (27%) in sCR after induction. Patients in conventional CR showed superior PFS vs those failing to achieve it (53 vs 26 months; P=.0004, HR=2.4), Achieving sCR also predicted for extended PFS (53 vs 28 months; P=.001, HR=2.6). No significant differences were noted for OS. We then investigated the individual contribution of sFLC and cellular clonality (as above defined) for risk stratification. No significant differences were noted for PFS or OS between patients with normal (n=57) vs. abnormal (n=45) sFLC ratio. By contrast, patients with absent (n=81) vs. detectable clonal PCs (n=21) showed superior PFS (40 vs 21 months; P=.0001, HR=3.1), but identical OS (P=.373). Our results highlight the drawbacks of the sCR criteria and urge the need of a more accurate definition of sCR.

P-416

Bortezomib (Btz)-induced Peripheral Neuropathy (BiPN) in Previously Untreated MM: Impact of Dexamethasone (Dex) Schedule

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BiPN may arise due to various mechanisms including inflammation. Recent analyses have shown inflammatory genes associated with late-onset BiPN; reducing the inflammatory component with concomitant Dex may reduce BiPN incidence/severity. We analyzed PN/sensory PN rates from studies of regimens incorporating IV Btz (1.3mg/m^2, d 1, 4, 8, 11; 21-d cycles) and differing Dex schedules in >=20 untreated MM patients (pts). Studies were categorized based on Dex schedule: A-partnered, day of/after Btz (d 1, 2, 4, 5, 8, 9, 11, 12); B-weekly (d 1, 8, 15); C-other (eg d 1-4, 8-11). Pooled PN rates were calculated for each schedule. We identified 10, 3 and 14 studies (10, 6 and 15 arms), with 994, 191 and 1030 pts, using schedules A, B and C, respectively. Pooled overall PN rates were 46.1%, 61.3% and 48.7%; grade >=3 PN rates were 5.4%, 11.0% and 9.6%, respectively. Grade >=3 PN rates were >50% lower with schedule A vs B (rate difference -5.6%; 95%CI:-10.2% to -0.9%, indicating statistical significance), and also significantly lower with A vs C (-4.2%; 95%CI:-6.5% to -1.9%) and A vs B+C (-4.4%; 95%CI:-6.7% to -2.2%). No differences in response rates were seen across schedules. Exploratory analyses accounting for potential confounding factors will be presented. This initial pooled retrospective analysis suggests the hypothesis that partnered Dex dosing (schedule A) may result in less severe BiPN. The impact of Dex on inflammatory cytokines and the relationship to BiPN is being explored; additional PGx analyses of a phase 3 trial of Btz-based induction will be presented.

P-417

Standardisation of Analysis of Basic Biochemical Parameters in Monoclonal Gammopathies

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Introduction: Due to rising importance of free light chains analysis (FLC), we focused on interlaboratory comparison of FLC analysis. In the next step we tried to evaluate if the methodological unification is a correct step towards improving the standardisation. Methods: We focused on evaluation of FLC, ratio of kappa/lambda, heavy/light chains, beta-2-microglobulin (B2M) and immunoglobulin (Ig) levels. We used SPA Plus analyser with kits Freelite and Hevylite (Binding Site, UK). For B2M and Ig ´ s, different methods according to each laboratory were used - 3x SPA Plus (Binding Site), 1x AxSym (Abbott), 1x Immulite (Siemens), IgA, IgG, IgM 2x SPA Plus (Binding Site), 1x Immage (Beckman), 1x Cobas (Roche), 1x BN ProSpec (Siemens). Samples: 12 native sera from patients with monoclonal gammopathies (MG) were distributed as frozen aliquotes into 5 hematological centers in the Czech republic. Results: All laboratories did M-protein typing (success rate 87.5%). There was a highly positive impact of interlaboratory unification of diagnostic algorithms and all diagnostic procedures as well as predefined algorithms of sample dilution. B2M and Ig ´ s analysed with different instrumentation brought different results, however with the same interpretation in all cases. Conclusion: We consider unification of diagnostic methods as success in MG diagnosis. SPA Plus contributes to correct result interpretation. Supported by grants IGA MH CR NS/10387-3, NS/10406-3 and by project for conceptual development 00179906.

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Age Dependency of Reference Values of Immunoglobulin Heavy/Light Chain Pairs and Free Light Chains Serum Levels

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Introduction: HevyLite is a relatively new method used for qualitative and quantitative analysis of HLC (Heavy/Light-chain pairs) in patients with monoclonal gammopathies. The reagent antibodies have specificity for unique epitopes that form at the junction between heavy- and light-chain constant regions of each immunoglobulin molecule. Methods: The analysed set comprised 50 serum samples from 37 women and 13 men, age 79 to 89 years, without previous evidence of monoclonal gammapathy. The serum HLC levels were evaluated by the SPA Plus turbidimeter, system HevyLite (The Binding Site, UK). The same method was used for investigation of FLC (Free Light Chains) levels. The presence of M-Ig and renal function (creatinin) were assessed and we excluded persons with M-Ig positivity (2 subjects), persons with M-Ig not assesed (9 subjects) and persons with abnormal renal function (9 subjects). Results: Reference values of FLC and HLC were evaluated in 30 subjects and 23 subjects, respectively (table 1). Conclusion: The current reference values provided by manufacturer do not correspond with the results of our age-based study group. Proper reference values are needed for all age groups in order to take full advantage of possibilities the HLC and FLC systems provide. Further multicentre studies may be useful in defining cut-off values.

Parameter	Reference value of our group	Unit	Reference value provided by manufacturer	Number of subjects
FLC kappa	11,030 - 44,27	mg/l	3,3-19,40	30
FLC lambda	8,650 - 29,86	mg/l	5,71-26,30	30
FLC kappa/lambda	1,05 - 2,56	–	0,26-1,65	30
Hevylite IgG kappa	3,513 - 12,738	g/l	3,84-12,07	23
Hevylite IgG lambda	1,251 - 6,81	g/l	1,91-6,74	23
Hevylite IgG kappa/lambda	0,962 - 4,34	–	1,12-3,21	23
Hevylite IgA kappa	0,298 - 4,180	g/l	0,57-2,08	23
Hevylite IgA lambda	0,246 - 2,614	g/l	0,44-2,04	23
Hevylite IgA kappa/lambda	0,809 - 2,16	–	0,78-1,94	23

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Evaluation of Symptom Assessment and Health-related Quality of Life in MM Patients Followed in Simultaneous Care

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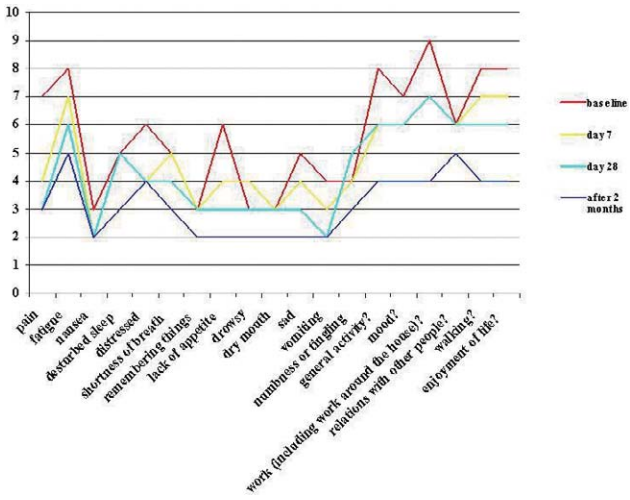
We have set up a multi-disciplinary team aimed at introducing early supportive/palliative care integrated with standard hematologic care (simultaneous care). The team consists of a palliative care physician, a hematologist, a counselor, a psychologist and a social worker. We evaluated the effect on health-related quality of life (QoL) and symptom assessment using the MD Anderson Symptom Inventory (MDASI: scores from 0-better to 10-worse symptoms) at baseline, on days 7 and 28, and every month. Specific attention was paid to pain, by assessing both physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of patients (pts). Sixty MM pts were followed 40 pts were in 1st line therapy, 5 in relapse and 15 in advanced stage. The symptoms reported at baseline were: pain (83%), fatigue (92%), anxiety (67%); 54 pts were treated with opioids/NSAIDs (37%) and with strong opioids (63%), 35% was treated for breakthrough cancer pain. Psychosocial interventions were carried out in 18 pts. Among the 15 pts with advanced phase, 10 were assigned to early palliative home care. The MDASI showed a significant reduction in the median value of all symptoms after 2 month (Fig1). Our study demonstrates the feasibility of simultaneous care through a multi-professional team dedicated to the management of symptoms in patients with MM. Based on the reduction in the intensity of symptoms and improvement of the QoL score, the effectiveness of this type of organization should be emphasized



P-420

Predictive Value of Free Light and Heavy Chain Analysis in Multiple Myeloma Patients Treated with Bortezomib

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The new biomarkers useful to evaluate the immune production as free light chains (FLC) and heavy/light chain (HLC) ratios and the uninvolved isotype, are potentially risk factors to predict the response to therapies that included Bortezomib. Patients and Methods: We have analyzed retrospectively FCL, HLC and their ratios in stored serum of 65 patients (45 IgG, 20 IgA) diagnosed with multiple myeloma and treated with Bortezomib, between 2004-2010. The analysis of FCL and HCL has been performed at diagnosis, and follow-up (after 4 and the last Bortezomib cycles, according The Binding Site Ltd assays. The data have been recorded in a SPSS data base, the response has been defined according IMMWG criteria. Concentration of involved immunoglobulin has been compared with the M-component; FCL HCL ratios and immunoparesis have been correlated with the intensity of response, progression-free survival (PFS) and overall survival (OS). Results: 35 females and 30 males, mean age of 68 y has been included. In 12 patients a hematopoietic stem transplant were performed and were analyzed separately. Considering the original immunoglobulin isotype concentration, our results show that to obtain a strict response after Bortezomib therapy and the increase of HLC ratio of uninvolved isotype is associ-

ated with a longer PFS and OS, the follow-up of HCL ratio is a more sensitive procedure that monoclonal component. HLC ratio is a satisfactory marker of follow-up response and probably the uninvolved isotype concentration as marker of immunoparesis is correlated with the PFS and OS .

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Multiple Myeloma Associated Necrobiotic Xanthogranuloma: Treatment Response Monitoring by Means of PET/CT Imaging

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Necrobiotic xanthogranuloma is a rare chronic destructive granulomatous skin disease often accompanied by monoclonal gammopathy. Because of its rare incidence, the optimal treatment strategy remains unknown. Herein we present the case of a patient diagnosed with multiple myeloma associated necrobiotic xanthogranuloma. To the best of our knowledge this is the first documented case in the Czech Republic. The 86-year-old male patient was followed up with multiple myeloma. Painful cutaneous indurations developed in the lower legs. Histological examination revealed an extensive necrobiotic xanthogranuloma. Positron emission tomography/computed tomography (PET/CT) scan imaging showed multiple cutaneous and subcutaneous infiltrates with Standardized Uptake Values (SUV) reaching up to 10. Considering his comorbidities, the patient was eligible only for an oral combination treatment with cyclophosphamide and prednisolone complemented by analgesic radiotherapy of the painful soft tissue lesions. The therapy resulted in size regression of the infiltrates as well as substantial pain relief. Furthermore, a decrease of pathological tracer uptake on a restaging PET/CT examination was documented. In conclusion, as a rare complication of multiple myeloma, necrobiotic xanthogranuloma may decrease a patient's quality of life significantly. PET/CT scanning is a useful diagnostic modality in disease activity evaluation, while combination of systemic treatment with local irradiation of myeloma infiltrates represents an attractive treatment possibility. Supported by NT12130 and NT11154.

P-422

Progress in the Treatment of Multiple Myeloma: A 19-year Experience at Chiba Cancer Center Hospital

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Background Novel agents have conducted a remarkable progress in the treatment of multiple myeloma (MM) in the past decade. In Japan, however, because of delay in approval of such agents (bortezomib in 2006, thalidomide in 2008 and lenalidomide in 2010), the published data showing clinical benefits of novel agents are limited. To confirm the role for novel agents in Japanese patients, we retrospectively analyzed the clinical outcome of MM patients in single institute. Patients and methods From 1991 to 2009, 249 patients were newly diagnosed as MM in Chiba Cancer Center Hospital; 31 MGUS, 18 asymptomatic myeloma, 168 symptomatic myeloma, 5 non-secretary myeloma, 13 solitary plasmacytoma of bone, 10 extramedullary plasmacytoma and 4 plasma cell leukemia. Median age was 65 (26-89) and 130 males and 119 females were included. Conventional chemotherapies were administered as an initial treatment in 182 patients. Novel agents were introduced in 39 patients with refractory or recurrent disease. Results After the median follow-up of 41.0 months, median overall survival (OS) and 3-year survival rate of 182 patients were 44.5 months and 56.2%, respectively. Median OS was superior when novel agents were administered (76.1 vs 38.7 months, $p<0.001$). Survival benefit of novel agents were evident not only in younger patients (under 65, median OS not reached vs 46.5 months) but also in elder patients (over 66, median OS 47.6 vs 30.8 months). Conclusions It is confirmed that novel agents produced considerable improvement in the treatment outcome in Japanese MM patients.

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Risk Stratification of Multiple Myeloma (MM) Patients by Using Freiburger Comorbidity Index (FCI)

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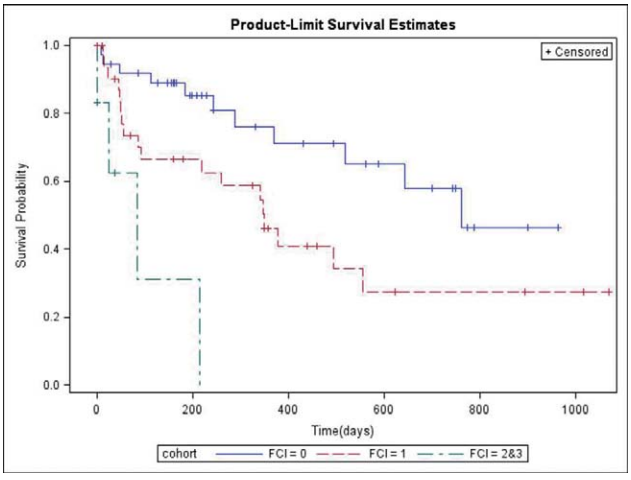
Introduction; Many elderly patients are vulnerable because of comorbidities that complicate the management of MM. Although tailored therapy is implicated to be inevitable for

these patients, no data are available that account for assessing vulnerability of MM patients. In order to explore a useful index to screen patients with MM leading to a proper individualized therapy based on our daily practice, we analyzed our local urban area patients. Method; Overall survival (OS) and progression free survival (PFS) of patients with MM who presented consequently between September 2009 and August 2012 in two core hospitals in Kitakyushu city were retrospectively analyzed. Patients were classified into three groups (0, 1, 2&3) using Freiburger comorbidity index (FCI) consisting of renal impairment, pulmonary disease and performance status. Results; In total, 78 newly diagnosed patients were enrolled. Median age was 72 years. 40 were male. Thirty seven patients were subdivided into FCI=0, thirty five into FCI=1, and six into FC=2&3. Combination of three risk factors identified significantly different median OS between FCI=0 and FCI=1 (P =0.0084). And significance was found in median PFS between FCI=0 and FCI=1 (p=0.0265) and between FCI=0 and FCI=2&3 (P =0.0005). Conclusion; This retrospective analysis revealed an efficacy of FCI that clearly stratified patients with MM. FCI could be an easy and useful device to screen vulnerability before choosing and starting therapy of MM. Prospective studies with stratification groups should be implemented to establish personalized therapy of MM.



P-424

Low Serum IgM Levels at Diagnosis are Associated with Time to First Treatment and Overall Survival in MM and CLL

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Background:Low serum IgM levels were proposed to be unfavorable prognostic factor in B-Chronic Lymphoproliferative Disorders. Aim:To investigate the impact of IgM on the outcome in Multiple Myeloma(MM) and Chronic Lymphocytic Leukemia(CLL) patients. Patients and methods:103 MM patients and 69 CLL at diagnosis were studied. In the MM-group 36%, 30% and 34% were in ISS stages 1, 2, 3 respectively. 80% were or become symptomatic during follow up and median follow up was 33 months(1-131). In the CLL-group 65%, 26% and 19% were in Binet stages A, B, C respectively. 55% percent were or become symptomatic during follow up and median follow up was 62 months(5-157). IgM was determined at diagnosis by classical nephelometry and by HevyliteTM methods; the first measures total IgM while the second the immunoglobulin fractions bound to either kappa or lambda light chains (IgMkappa and IgMlambda).Survival curves according to IgM levels were drawn by Kaplan-Meyer method and compared by the log-rank test Results:In the MM-group total serum IgM ranged from 0.07-1.8g/L(median 0.28). Low total IgM levels(below 0.5g/L) correlated to shorter TFT(p=0.001) and to shorter OVS(p=0.001)(Fig 1A). In the CLL-group total serum IgM ranged from 0.03 -2.46g/L(median 0.53). Low total IgM levels(below 0.5g/L) did not correlated TFT or to OVS. With Hevylite measurements the sum of IgMkappa plus IgMlambda ranged from 0.12-3.69g/L (median 0.60). Low sum of IgMkappa plus IgMlambda levels(below 0.5g/L) correlated to shorter to OVS(p=0.016)(Fig.1B). Conclusions:Low IgM levels correlates to TFT and OVS.

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Significance of The Quality of Response on Progression Free Survival in Multiple Myeloma-Effect of sCR

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Background: In Multiple Myeloma (MM) the depth of response has been associated with longer Progression Free Survival (PFS), thus prolonging overall survival.Stringed Complete Response (sCR) was defined by the International Consensus Response Criteria. Only a few studies exist to date on the impact of sCR on PFS. Aims: To investigate the effect of sCR on PFS. Patients-Methods: 51 intact immunoglobulin MM patients were studied from diagnosis to last follow up (38-IgG, 13-IgA). ISS stages were equaly distributed (34%, 34% and 32%) All patients were symptomatic at diagnosis.

Median follow up was 33 months (7-145). Results: During patients' follow-up, 145 lines of therapy were studied. Treatment lines were initiated according to standard criteria and median lines of therapy were 2 (1-11).Treatments included VAD (20%), bortezomib- (25%), lenalidomide- (15%), thalidomide- (8%), melphalan- (7%) containing regiments and various drug combinations (25%). The median PFS for the first line of therapy was 13,5 months (mo), 10 mo for the second line, 8,5 mo for the third and 9 mo for the forth. The was no statistical correlation between the PFS medians of the 4 lines of therapy (Fig 1A). Eleven percent of responses were sCR, 34% CR and nCR while 55% were PR or less. The depth of response correlated to PFS and patients in sCR, CR and nCR had longer PFS than the others (p<0.001)(Fig. 1B). Also patients in sCR had longer PFS than patients in CR+nCR (p=0.021) Conclusion: The achievement of sCR provides the longest PFS.

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5-years Follow-up Study for Frequency of MGUS in a Korean Elderly Urban Cohort

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We previously reported the prevalence of MGUS in a Korean Elderly Urban Cohort recruited from 2005 to 2006 (First Wave, Park HK Am J Hematol. 2011;86:752-5). Their plasma samples were screened using immunofixation and free light chain (FLC) assays. Age and gender-adjusted prevalence rates of MGUS were estimated as 3.3% (95% CI=2.0-4.6%), and the age-adjusted prevalence of MGUS was 4.3% in men (95% CI=1.9-6.6%) and 2.6% in women (95% CI=1.0-4.2%). We followed them and collected their serum between 2010 and 2011(Second Wave). Among 1,000 participants of First Wave, 419 agreed with the donation of serum for protein electrophoresis, immunofixation and FLC assays. The frequency of MGUS in Second Wave was 3.10% (95% CI=1.44-4.76%) in all, 4.27% (95% CI=1.54-6.99%) in men, and 1.92% (95% CI=0.06-3.79%) in women. Among 35 MGUS patients in First Wave, 11 were followed. Eight of 11 had persistent MGUS and other 2 showed the disappearance of M protein. The last one showed mild anemia with persistent M protein of 1.4g/dL suggestive of progression to MM, but was not confirmed because of early death just after Second Wave. Additional 4 MGUS newly developed in Second Wave. The mean amount of M protein in 13 patients with MGUS was 0.55g/dL (range: 0.2～1.4). Subtypes of M protein were predominantly A and G in 8 and 5 patients. Light chain was lambda, kappa and none in 8, 4, and 1 patient. Abnormal ratio of FLC was correlated with the presence of MGUS (p=0.000). In conclusions, the frequency of MGUS is persistently lower in elderly Koreans (3.1%) than other races.

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Molecular Genetic Epidemiology of Multiple Myeloma: the IMMEnSE (International Multiple Myeloma rESEarch) Consortium

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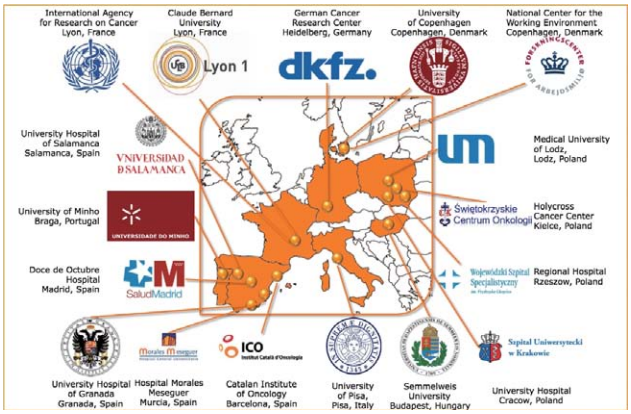
We established the IMMEnSE (International Multiple Myeloma rESEarch) consortium, to increase our understanding of the genetic determinants of multiple myeloma (MM) risk, response to therapy and survival. At present we have DNA samples of over 1600 MM cases and almost 3000 healthy controls from 7 European countries. For the majority of the cases we also have clinical data on known prognostic factors, therapy outcome and survival. We already performed

several association studies in the context of the IMMEnSE consortium. In particular, we found associations between MM risk and SNPs in the ABCB1 gene, which encodes for an efflux pump that has a key role in protecting cells from chemical damage, and with a SNP in the 8q24 region, which has been shown to harbor multiple loci of susceptibility to various cancers. Finally, we genotyped in the IMMEnSE cases and controls three MM risk SNPs from a recently published genome-wide association study (GWAS), and confirmed the association of two of them. We will study additional SNPs from ongoing GWAS, as well as SNPs of key genes involved in the pathogenesis of MM. Additionally, we are measuring telomere length and genotyping SNPs of key telomere-related genes in MM cases and controls. Finally, we plan to study methylation status of key genes involved in MM etiology , and mitochondrial copy number. We will investigate the role of all these factors in relation to MM risk and prognosis. We continue to collect samples and data of MM cases and controls, as well as of subjects with monoclonal gammopathy of undetermined significance (MGUS).



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Characterization of Death <=6 Months of Enrollment for Newly Diagnosed Multiple Myeloma in the Connect MM US Registry

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Connect MM is a prospective observational registry designed to document real-world management and outcomes in newly diagnosed multiple myeloma (NDMM) patients (pts). The study was initiated in 2009 and enrolled 1,494 pts in 228 centers in the USA. Early death in pts with NDMM is becoming more of an issue, but little evidence currently exists about pt factors that may contribute to this. The characteristics of pts who died <=6 mos of enrollment vs pts who survived >=6 mos were compared. Logistic regression analysis assessed the significance of associations of pt's characteristics on likelihood of early death (odds ratio [OR] 95% CI). Of the 103 (7%) pts who died <=6 mos, 52% were male and 83% Caucasian. Median age for pts who died <=6 mos was 72 vs 66 yrs for pts surviving >=6 mos; ISS stage III classification at baseline was 35% vs 22% of pts, respectively. The causes of death in pts who died <=6 mos were: multiple myeloma progression (39%), cardiac failure (13%), infection (7%), pneumonia (6%), renal failure (4%), sudden death (3%), other (15%), and unknown (13%). History of MGUS or smoldering myeloma was similar between both pt groups (16% vs 17%). Univariate and multivariate analyses on baseline characteristics are shown in the table. Analysis of Connect MM registry provides real-world evidence of characteristics of pts with NDMM who die <=6 mos, and may lead to the identification of previously unidentified prognostic factors. Further analyses are needed and planned.

Table. Logistic Regression Analysis of Baseline Characteristics Associated with Early Death (≤6 mos).

Characteristic	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age[a]	1.53 (1.26, 1.84)	<0.001	1.29 (1.05, 1.58)	0.015
ISS Disease Stage[b]	2.68 (1.87, 3.85)	<0.001	1.67 (1.15, 2.40)	0.007
ECOG Status[b]	2.40 (1.82, 3.18)	<0.001	1.69 (1.26, 2.25)	<0.001
Cytogenetic High Risk[c]	1.56 (0.95, 2.55)	0.077	1.32 (0.82, 2.13)	0.255
History of Diabetes	2.12 (1.37, 3.30)	0.001	1.45 (0.89, 2.37)	0.137
History of Hypertension	2.55 (1.58, 4.11)	<0.001	1.71 (1.01, 2.90)	0.047
Myeloma Bone Involvement[d]	0.75 (0.48, 1.17)	0.209	--	--
Hypercalcemia (Serum Calcium ≥11.5 mg/dL)	2.52 (1.31, 4.84)	0.006	1.78 (1.01, 3.13)	0.046
Renal Insufficiency (Serum Creatinine > 2 mg/dL)	1.67 (1.00, 2.80)	0.051	--	--
Anemia (Hemoglobin < 10 g/dL or >2 below LLN)	1.34 (0.87, 2.07)	0.185	--	--
Clonal Bone Marrow Plasma Cells ≥10%	0.49 (0.27, 0.89)	0.020	0.31 (0.16, 0.62)	<0.001
β_2 Microglobulin[a,e]	1.01 (0.97, 1.05)	0.701	--	--
Platelet Count[a,e]	0.45 (0.33, 0.60)	<0.001	0.53(0.39, 0.72)	<0.001
Creatinine Clearance[a]	0.89 (0.83, 0.94)	<0.001	--	--

Characteristics for which multivariate data are not presented are those which were screened out either because they had univariate *P*-values greater than 0.15 or did not enter significantly in the variable selection step. The multivariate analysis involved variable selection using stacked multiple imputations (Wood et al., 2008) and the final model was analyzed using Rubin's method for combining imputed analyses.
[a]Odds ratio and confidence intervals are computed for 10-year, 100 mg/L , 100 x10^{A9}/L and 10-point increases for age, β_2 microglobulin, platelet count and creatinine clearance respectively.
[b]Odds ratios, on average, are for 1-category increments.
[c]Cytogenetic high risk is defined as those with FISH del(13)/rb 1 locus and elevated β_2 microglobulin (>2.4 mg/L), FISH del(17p)/p53, FISH t(4.14), FISH t(14.16), cytogenetic hypodiploid, cytogenetic del(13), cytogenetic del (13)/rb 1 locus, cytogenetic 17p/53p, and cytogenetic t(4.14).
[d]Per CRAB criteria.
[e]Unusually high observations to be queried were excluded.
ECOG, Eastern Cooperative Oncology Group; ISS, International staging system; LLN, lower limit of normal.

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Cereblon Protein Expression is a Predictor of Response to Lenalidomide in Multiple Myeloma

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IMiDs cytotoxicity in myeloma cells is mediated through their binding to Cereblon (CRBN). In this study, we validated CRBN as biomarker of clinical response to Lenalidomide. At the mRNA level, using qRT-PCR (n=26, amplicon overlapping exons 8-9) or chip microarray analysis (n=32, Affymetrix probe 222533_at), low CRBN was significantly associated with shorter PFS (p=0.008) and lack of response to Lenalidomide. At the protein level, using fluorescence immunohistochemistry coupled with automated digital imaging (HistoRx PM-2000) and analysis (AQUA software), we quantified CRBN expression using a TMA constructed from marrow biopsies of MM patients (n=42) collected prior to initiating Lenalidomide. Staining for CRBN was performed with a polyclonal anti-CRBN antibody (HDA045910, Sigma-Aldrich) and revalidated with a monoclonal antibody (CRBN-65, immunogen CRBN aa 65-76, provided by Dr R Chopra). CRBN protein expression (AQUA scores) ranged from -1.419 to 3.895 after Z standardization. PFS was significantly shorter in CRBN-low (bottom quartile) versus CRBN-high (top quartiles 1-3) (5.6 vs 19.7 mos, p=0.008). Similarly, OS was also reduced in CRBN-low patients (11.4 vs 30.4 mos). In multivariate analysis including ISS and cytogenetics, CRBN was retained as an independent predictor of PFS (HR 0.161; p=0.01) but not for OS. In contrast, no association between CRBN protein expression and survival was observed in an independent cohort (n=37) treated with bortezomib. In conclusion CRBN protein expression may guide the selection of MM patients who benefit from IMiDs-based therapeutics.

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Quality of Life Improvements for Pomalidomide + Low-Dose Dexamethasone (POM+LoDEX) in Relapsed and Refractory MM (RRMM)

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Background: RRMM pts who have exhausted novel agent therapy (LEN and BORT) have poor prognosis. In MM-003, POM+LoDEX (n=302) significantly improved PFS and OS vs high-dose dexamethasone (HiDEX; n=153) in RRMM pts who failed LEN and BORT. This analysis assessed Quality of Life (QOL) changes in MM-003.

Methods: To assess pt-reported outcome responsiveness between arms, Minimal Important Differences (MIDs) for 3 clinically relevant EORTC QLQ-C30 domains (Global Health Status, Physical Functioning, and Fatigue) were calculated as clinically meaningful change thresholds (1 standard error of measurement) from baseline through cycle 5. Kaplan-Meier analyses of time to first clinically meaningful worsening were performed using these 3 domains.

Results: Pts receiving HiDEX demonstrated clinically meaningful worsening in Global Health Status and Physical Functioning scores by cycle 2 (*P*=.04) and cycle 3 (*P*=.02), respectively. Similarly, POM+LoDEX substantially extended the median time to meaningful worsening vs HiDEX for Global Health Status and Physical Functioning (Table); a lower proportion of pts receiving POM+LoDEX demonstrated a clinical meaningful worsening in Fatigue scores vs HiDEX. Median time to meaningful worsening in Fatigue scores was also significantly extended with POM+LoDEX vs HiDEX (Table).

Conclusions: This analysis suggests that POM+LoDEX improved QOL vs HiDEX. Specifically, POM+LoDEX resulted in lower proportions of pts experiencing clinically meaningful worsening and extended time to meaningful worsening for Global Health Status, Physical Functioning and Fatigue.

Table: Time to First Worsening of Selected EORTC QLQ-C30 Domains of Clinical Interest

Domain	Treatment Arm	Median Time to First Worsening, Days (95% CI)	Log-Rank *P* Value
Global Health Status	POM + LoDEX	114 (71-143)	.058
	HiDEX	85 (37-140)	
Physical Functioning	POM + LoDEX	174 (123-288)	.088
	HiDEX	106 (57-NE)	
Fatigue	POM + LoDEX	113 (71-169)	.038
	HiDEX	60 (57-113)	

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide.

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Renal Impairment as Prognostic Marker in Myeloma Care. A Population Based Study Including 1538 Patients

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Background: Renal impairment (RI) is a relatively common feature of multiple myeloma (MM) and it has been shown in several studies that RI at the time of diagnosis correlates to inferior survival. Aim: To understand the impact of RI on survival in the era of novel agents. The primary endpoint of this retrospective study was overall survival (OS). Time to next treatment (TTNT) was the secondary endpoint. Methods: The study population included all patients diagnosed with MM since earliest January 2000 until latest June 2011 at 14 Swedish sites. The estimatet glomerular filtration rate was calculated using the MDRD-formula and RI was defined as eGFR <60 mL/min/1.73 m^2. Multivariate Cox model analysis was made to adjust for age, hypercalcemia haemoglobin and albumin levels at time for MM-diagnose. Results: The study population consisted of 1538 patients. Patients with RI at diagnosis (n=680) had a significantly worse median OS of 33 months 95% CI[28;36] compared to those without RI (n=858), with a median OS of 52 months 95% CI[48;56]; (p<0.001). HDT and novel treatment improved median OS in patients with RI (72 vs 26 months, HR 0.30 (0.22-0.41), p<0.001 and 60 vs 27 months HR 0.49 (0.37-0.65), p<0.001 respectively). This difference was also significant in the multivariate analysis. RI implied a shorter median TTNT after 1st line (13 vs 20 months, p<0.001). HDT prolonged TTNT (30 vs 11 months, p<0.001). Conclusion: RI is still an important prognostic marker in MM. HDT and novel treament regimens can partly overcome the negative impact of RI with improved median OS.

P-432

Immunoglobulin Same Isotype Immunoparesia: a New Biomarker in Patients with MGUS.

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The IMWG has established guidelines for MGUS risk stratification based on the size and type of monoclonal protein (MP), and serum Free Light Chain ratio (rFLC). Nowadays the quantification of specific immunoglobulin heavy/light chains pairs is possible, and this project aims to study specific heavy/light chains (HLC) alterations in MGUS patients. 137 newly and previously diagnosed MGUS patients were studied by serum protein electrophoresis, immunofixation, serum free light chains (Freelite) and specific heavy/light chains pairs (Hevylite, Binding Site). Systemic immunoparesis (SI) was defined as decreased levels of one or two of the non monoclonal immunoglobulins (Ig), and Immunoparesis of the Same Ig Class (ISC) as decreased levels of the uninvolved HLC pair from the monoclonal Ig class. The correlation between M-spike and monoclonal HLC pair was also established. Data is presented in table 1. In the IgG cases there was a trend towards higher rHLC alterations and stronger uHLC suppression with increasing MGUS risk of progression. SI is a marker of disease progression and is often seen in MGUS patients progressing towards MM or in patients progressing from a complete remission after treatment. In this population, ISC is more frequent than SI (52% vs 33,1%), suggesting a promising role for HLC in MGUS prognosis. Also, due to the SPE limitations for small MP and MP that migrate with other serum proteins, the Hevylite specific quantification may be a helpful tool for MP quantification. More studies are needed to confirm the Hevylite role on MGUS patients risk stratification

	Low Risk	Low-Intermediate Risk				Intermediate-High Risk				High Risk		
	IgG cases	IgG cases	IgA cases	IgM cases	all cases	IgG cases	IgA cases	IgM cases	all cases	IgA cases	IgM cases	all cases
% abnormal rHLC	76,5	94,3	100	100	96,4	100	100	100	100	100	100	100
(n)	26/34	33/35	10/10	10/10	53/55	11/11	17/17	17/17	45/45	1/1	2/2	3/3
% uHLC suppressed	38,4	69,0	66,7	14,3	55,5	100	62,5	26,7	59,5	100	50	66,7
(n)	12/33	20/29	4/9	1/7	25/45	11/11	10/16	4/15	25/42	1/1	1/2	2/3
% iHLC increased	75,8	62,1	100	100	75,6	100	100	100	100	100	100	100
(n)	25/33	18/29	9/9	7/7	34/45	11/11	16/16	15/15	42/42	1/1	2/2	3/3
% SI	14,7	34,3	30	40	34,5	54,5	62,5	28,5	45,4	0	0	0
(n)	5/34	12/35	3/10	4/10	19/55	6/11	10/16	4/17	20/44	0/1	0/2	0/3

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Extramedullary Spread of Multiple Myeloma Cells and Expression of Adhesion Molecules: a Study of 91 Autopsy Cases.

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Background: The extramedullary disease (EM) progression of myeloma was frequently observed in heavily treated patients and it is well known that adhesion molecules play a role in disease progression and drug resistance. Methods: We reviewed autopsy reports and medical records of 91 multiple myeloma cases between 1979 and 2012 in our institution. The sites of myeloma cell invasion were studied gross and microscopically. Factors associated with EM were statistically analyzed. NCAM, VCAM, ICAM, and CD138 immunostaining in the bone marrow was performed. Results: In 91 autopsy cases, 18 patients were treated with novel agents. EM progression of myeloma cells was observed in 67 patients (73.6%). Frequent sites of EM were spleen, liver, kidney, lymph nodes, lung, pancreas, and gastro-intestinal tract. The incidence of EM was significantly higher in patients treated with novel agents than in patients without novel agents (100% vs. 67.1%, p=0.005). The risk factors of EM were novel agents, longer duration of illness, and adverse cytogenetic abnormalities. In the cases with novel agents, the expression of NCAM was significantly low (18.8% vs. 53.8%, p=0.048) compared to the cases without novel agents. However, the expression of VCAM was significantly higher in the cases with novel agents than the cases without novel agents (31.3% vs. 0%, p=0.0027). Conclusion: Multi-organ involvement of myeloma is not rare in autopsy cases of the disease. Exposure to novel agents may contribute to extramedullary spread of myeloma cells and altered expression of adhesion molecules.

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Prognostic Implication of Aberrant CD33 Expression of Myeloma Plasma Cells

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Flow cytometry provides information on immunophenotypes of plasma cells (PCs) in myeloma patients. Clinical significance of the aberrant expressions has not been fully evaluated. Thus, we analyzed antigen expression (CD19, CD20, CD28, CD33, CD38, CD45, CD56, CD117, and CD138) of plasma cells in total of 46 myeloma patients using multicolor flow cytometry (MFC). The association of aberrant expression of CD33 or CD117 on myeloma cells with laboratory and clinical parameters such as therapeutic response, disease progression, and survival was investigated. The median age of patients was 62 yrs (38-78) and treated by regimen including thalidomide plus dexamethasone, vincristine, doxorubicin-dexamethasone, and melphalan-prednisolone. Expression of CD33 and CD117 was observed in 8 (17.4%) and 4 (8.7%) patients, respectively. The antigen expression and laboratory parameters did not show significant correlation except marginal association of CD117 with decreased platelet count (p=0.098). For overall survival, CD33 expression showed significant hazard ratio of 1.04 (p=0.013, 95% CI: 1.01-1.08), but not for progression free survival. MFC is an effective method to detect various antigens present in myeloma PCs, enabling diagnosis and prognostic determination. This study suggests association of myeloid expressions such as CD33 and CD117 with clinical outcomes or laboratory parameter, supporting the idea that immunophenotypic characterization of myeloma PCs might be useful in evaluation and management of the disease.

P-435

Advanced Presenting Features and Short Survival among Thai Patients with Multiple Myeloma

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BACKGROUND: Thai myeloma patients seem to have more advanced disease. Our objective was to investigate the clinical features and outcomes of Thai myeloma patients. METHODS: From 2002 to 2007, 1207 patients with newly diagnosed MM were enrolled from 25 centers RESULTS: Fifty two percent were male with a median age of 62 years (range, 20-96). The majority are under the universal coverage (UC; 60%) and government funding (29%).Types of M-protein were IgG (68%), IgA (19%) and light chain only (12%). Most of them were ISS stage II (30%) and III (56%). The clinical features included poor performance status(PS) (ECOG > 2; 53%), anemia (85%), renal impairment (39%),

multiple osteolytic lesions (68%) pathological fractures (33%) and hypercalcemia (46%). The first-line regimens were melphalan-prednisolone (MP; 54%), VAD (29%), dexamethasone (10%) and novel agents based regimens (4%). Forty eight patients (4%) underwent ASCT. The median event free survival (EFS) and overall survival (OS) were 8 months (95% CI: 6.9-9.0 months) and 18 months (95% CI: 15.7-20.2) months), respectively. Median OS according to ISS stage I, II and III were 62, 29 and 17 months, respectively. Male gender, age over 65 years, poor PS, medical reimbursement from UC, anemia, thrombocytopenia, renal impairment, hypercalcemia, hypoalbuminemia and systemic infection were independently associated with poorer survival. CONCLUSIONS: Thai patients with MM presented with more advanced disease. The improvement of public awareness and referral system in addition with novel agents therapy may improve their outcomes.

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The Incidence and Severity of Autonomic Neuropathy after Bortezomib Induction

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Background

Peripheral neuropathy (PN) is an important complication of multiple myeloma (MM). As a sub-type of PN, autonomic neuropathy (AN) can be difficult to diagnose. Furthermore the presence and progression of AN in MM is not fully characterised.

Aims

To determine the presence of AN in patients with myeloma exposed to bortezomib induction followed by autologous stem cell transplant (autSCT).

Methods

Patients given bortezomib based induction therapy for MM were invited to participate in a set of autonomic tests at a time point post auSCT and pre maintenance or 2nd line therapy. A single set of autonomic function studies were carried out, including vagal and adrenergic cardiovascular reflex testing and thermoregulatory sweat test. NCI CTCAE neuropathy scores, neuropathy disability score (NDS) and neuropathy symptom score (NSS) were also completed.

Results

Seven out of 9 patients exhibited some autonomic dysfunction. Two patients showed cardiovagal, adrenergic and sudomotor failure characteristics of significant AN. Four patients had distal sudomotor and mild cardiovagal or adrenergic failure indicative of early AN and one showed isolated mild adrenergic impairment which could indicate early AN but could also reflect deconditioning. No patient has significant clinical manifestations.

Conclusions

Subclinical AN was present in 67% of patients exposed to bortezomib in this small sample. A further set of autonomic tests is being undertaken to help establish progression. Identifying the presence of autonomic neuropathies may help to appropriately direct future treatment choices. The current change in practice to weekly and subcutaneous administration of bortezomib may impact the incidence and severity of AN in this setting.

Participant	MM isotope	ISS	Induction therapy	Disease response
01	IgGK	I	VcAD	nCR
02	IgGK	I	VcAD	sCR
03	IgAL	III	VcAD	sCR
04	IgGK	I	VcAD	VGPR
05	KLC	III	CyBorD	VGPR
06	IgGK	III	CyBorD	PR
07	LLC	III	CyBorD	CR
08	IgAK	I	CyBorD	PR
09	IgGK	I	CyBorD	CR

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A Program to Develop Improved Supportive Care Approaches for Those Affected by Myeloma

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Background

Delivery of optimal supportive care is challenging on many levels for multiple myeloma (MM) management. To achieve substantive improvements, the prolonged survival associated with MM must be matched with attention to evidenced based effective supportive care measures. This paper outlines a program of supportive care research and practice implantation meeting supportive care needs of patients and family members attending a Haematology Unit in Sydney, Australia.

Supportive Care Research Program

A series of strategic projects on informing and improving the practice and delivery of supportive care for individuals with MM has been implemented under 3 broad areas:

a) *Supportive care research*: Studies series include examination of the impact of MM treatments on day-to-day life of individuals and their families, information needs of individuals and families, managing specific toxicities such as steroids and neuropathy. Findings have been used to guide consumer education programs and printed resources.

b) *Consumer/carer education:* A series of patient and family education seminars are held drawing on information and sup-

portive care needs identified above. Focus is on skill development and self-care strategies. Evaluation of programs identified improved knowledge and decision-making.

c) *Timely implementation:* Drawing on MDT meetings, findings are translated into patient care delivery and education of the health care team. Over the course of this program, clinical practice in relation to information giving, patient education has changed significantly.

Conclusions and future directions

A strategic approach to identifying specific supportive care needs of those affected by myeloma allows for a more targeted approach to meeting those needs. Future research will build upon outcomes to date with current research investigating communication aids, and developing strategies to reduce side effects related to MM treatments.

Section F: Other Plasma Cell Dyscrasias

P-439

Plasma Cell Neoplasm as PTLDs after Renal Transplantation (RT): In 1845 RT Patients during 40 Year in a Single Institute

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Background: Multiple myeloma (MM) developed as post transplantation lymphoproliferative disorder (PTLD) after renal transplantation (RT) is very rare, and there is no standard therapeutic strategy. We report here two cases with plasma cell neoplasm developed as PTLD in 1485 patients who received RT during 40 years. Patients and Method: From January 1972 to December 2011, a total of 1485 patients who received RT in Nagoya Daini Red Cross hospital were retrospectively investigated about plasma cell neoplasm as PTLD. Results: A total of 14 (0.9%) out of 1485 recipients developed PTLDs, and only 2 (0.1%) recipients had plasma cell neoplasm; a 60-yr male patient (pt) with solitary plasmacytoma (SPC) (Pt-1), and a 35-yr male pt with IgG-k MM with del(17p) from recipient origin (Pt-2). Time from RT to onset of SPC and MM were 180 months and 69 months, respectively. EBV and HCV were negative in both pts. Pt1 has been in CR for more than 2 years after several chemotherapies (VAD, MP and VP16) without discontinuation of tacrolimus and prednisolone (PSL) to prevent rejection. After primary refractory to bortezomib, Pt-2 was received CTD therapy, then successfully treated with ASCT followed by RIC allo-BMT in tandem from HLA 7/8 matched unrelated male donor, and achieved CR. The transplanted kidney from his sister remains functional with 5mg PSL to prevent rejection. Thus, triple chimerism from the recipient, BM donor and kidney donor are successfully coexists without any rejection in Pt-2. Conclusion: MM as PTLDs could be manageable with same treatment strategy as ordinary MM

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Bortezomib in Light Chain Deposition Disease Provides Rapid Hematological Response with Delayed Organ Improvement

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Light chain deposition disease <LCDD> is a rare plasma cell dyscrasia characterized by the deposition of immunoglobulin light chains in kidneys and other parenchymal organs, leading to the loss of organ function which accounts for the poor prognosis. Unlike in multiple myeloma the treatment of LCDD with conventional therapeutic regimens is less effective, and with substantial toxicity. High dose chemotherapy with support of autologous stem cell transplant <ASCT> leads to an improvement of the overall response rate, however, with the persistence of renal impairment. Only a few papers reported on the use of novel drugs. We present a series of four patients with LCDD with kidney involvement treated in induction using bortezomib based regimens. All the patients had rapid hematological response reaching at least very good partial remission within three cycles of the treatment, and two patients underwent subsequent ASCT. The levels of serum creatinine as well as other parameters <hemoglobin, proteinuria, proBNP> improved over time even after they quit the treatment. One patient died of an unrelated condition, and the other three are in remission with median follow up of 30 months. Main toxicity was grade 3 peripheral neuropathy, which occured in all patients with standard bortezomib dosing but not in one with weekly administration. We conclude that bortezomib based induction treatment produces a rapid and deep hematological response with delayed organ response and predictable toxicity, and should be together with ASCT a treatment of choice for LCDD patients.

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Progression in Smoldering Myeloma is Independently Determined by High-risk Chromosomal Abnormalities and Tumor-load

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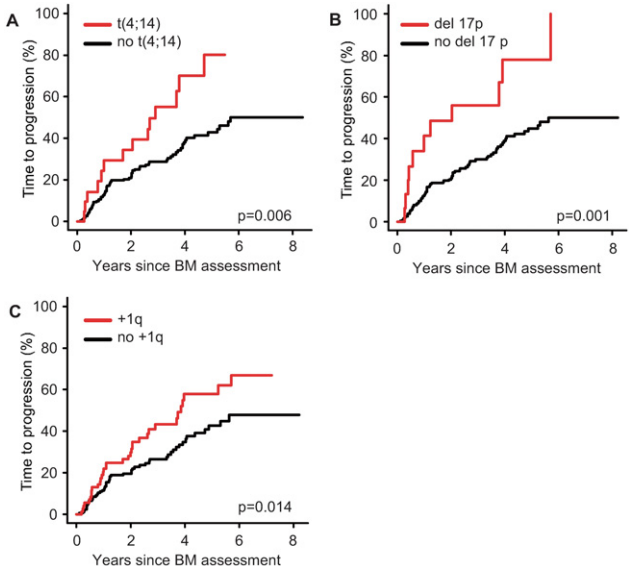
Purpose: Smoldering (asymptomatic) multiple myeloma (SMM) is an asymptomatic plasma-cell proliferative disorder associated with a high risk of progression to symptomatic multiple myeloma or amyloidosis. The aim of the presented study was to analyze chromosomal aberrations in terms of frequency and impact on time to progression (TTP) in patients with SMM on the background of clinical prognostic factors. Patients and Methods: The chromosomal abnormalities 1q21, 5p15/5q35, 9q34, 13q14.3, 15q22, 17p13, t(11;14)(q13;q32), and t(4;14)(p16.3;q32) were assessed in CD138-purified myeloma cells by interphase fluorescence in situ hybridization alongside clinical parameters in a consecutive series of 248 SMM patients. Results: Del(17p13), t(4;14), and +1q21, present in 6.1%, 8.9% and 29.8% of patients, significantly confer adverse prognosis with a 3-year TTP rate of 56% vs. 30%, 55% vs. 28%, and 43% vs. 27%, respectively. Tumor load, surrogated by the percentage of either total or malignant bone marrow plasma cells, or serum monoclonal protein, significantly confer adverse prognosis with a 3-year TTP rate of 41% vs. 24%, 67% vs. 23%, and 47% vs. 16%, respectively. Presence of any of the named aberrations is prognostic independent of tumor load and clinical prognostic factors. Conclusions: Our study for the first time shows that the aberrations del(17p13), t(4;14), and +1q21 are adverse prognostic factors in SMM, as they are in symptomatic myeloma; independent of tumor mass. Their prognostic value is thus not a priori treatment dependent, but an intrinsic property of myeloma cells.



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Lenalidomide and Dexamethasone Therapy without Autologous Stem Cell Transplant (ASCT) in a Patient with POEMS Syndrome

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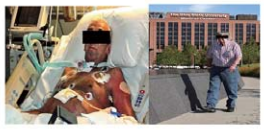
Introduction: POEMS syndrome is a rare plasma cell disorder consisting of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. Here we describe a patient with POEMS syndrome and associated Castleman's disease who had dramatic clinical improvement to lenalidomide and dexamethasone. Case: 55 year old man presented in September 2010 with progressive motor polyneuropathy, hypothyroidism, hypogonadism, nail pitting, dysphagia and respiratory failure requiring intubation. Diagnosis of POEMS syndrome was made after biopsy of the retroperitoneal lymph node showing Castleman's lymphadenopathy, as well as elevated IgG lambda predominant plasma cells (Table 1). He was started on lenalidomide 25 mg days 1-21 every 28 days and dexamethasone 40mg weekly in combination with aggressive physical therapy. His motor and respiratory function improved dramatically and he resumed most ADLS after one year (Figure 1). Laboratory data also revealed resolution of abdominal lymphadenopathy and monoclonal gammopathy. He was evaluated for ASCT but failed mobilization. He is currently on lenalidomide maintenance 5 mg daily after 12 months of combination therapy. Conclusion: The standard treatment for POEMS syndrome is high-dose chemotherapy with ASCT, however, poor performance status often precludes aggressive therapy. This is the first report of long term use of lenalidomide and dexamethasone in a patient with POEMS with remarkable improvement and no sign of progression 24 months after initiating therapy. The patient continues to tolerate therapy.

Table 1.

Date	September 2010	September 2011	December 2012
Nail bed changes	Present	None	None
Hyperpigmentation	Present	None	None
Edema	++++	Trace	None
Performance status (ECOG)	4	2	1
Motor polyneuropathy	Flaccid muscle weakness	Ambulate with assistance	Ambulate without assistance
IgG, (600-1500 mg/dl)	1470	204	468
IgA, (82-453 mg/dl)	186	38.5	36
Kappa, (3.3-19.4 mg/dl)	60.8	<2.7	<2.7
Lambda, (5.7-26.3 mg/dl)	118.00	<2.35	4.33
K/L ratio	0.52	Not calculated	Not calculated
Beta 2 microglobulin, (0.60 - 2.11 mg/L)	4.9	4.5	3.1
Monoclonal protein IgG lambda, (mg/dl)	775	Non detected	36
Bone Marrow	10% plasma cells	-	-
Cytogenetics	Normal	-	-
VEGF, (31-86 pg/mL)	-	74	<31
TSH, (0.55 - 4.78 uIU/mL)	19.257	5.629	2.133
Testosterone, total, (241 - 827 ng/dL)	55	624	457
Free Testosterone, (4.00 - 27.00 pg/mL)	0.1	20.34	-
24 hr Urine protein, (mg/dL)	100	Negative	7
Respiratory Status	Tracheostomy 40% FIO2	2L oxygen	Room air. Tracheostomy closed

Figure 1.

(Left) Patient initially presented with profound motor polyneuropathy and eventual intubation due to neuromuscular respiratory failure. (Right) After 1.5 years of treatment with lenalidomide and initial combination with steroid patient had dramatic improvement in his motor function and resolution of many physical exam findings.



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Treatment Outcomes of 299 Elderly (>75 Years) Patients with Systemic AL Amyloidosis

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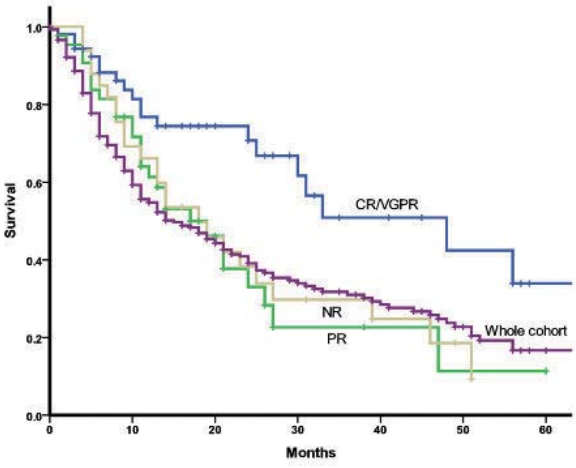
Incidence of AL amyloidosis is thought to increase with age mirroring monoclonal gammopathy but little has been reported on AL amyloidosis in the elderly. We report outcomes on all the patients over the age of 75 years with systemic AL amyloidosis assessed at the UK National Amyloidosis centre between 2005 and 2012. 299 patients (57% male) with median age of 78.5 yrs (range 75-94.3yrs) were reviewed. The median ECOG score was 1 (ECOG >2 in 15%), median involved free light chain (FLC) was 178.5 mg/L and 73% had lambda light chain excess. Median number of organs involved were 2 (range 1-7) with renal and cardiac involvement in 77% and 50% respectively. 68% of the patients were treated with chemotherapy and 32% opted not to receive any chemotherapy. 33% of patients completed full planned course of treatment and 60% had significant toxicity. On an intention to treat basis, 48% had a haematological response (48% of assessable patients) with VGPR or better in 26%. Median overall survival (OS) was 19 months and OS at 1, 2 and 4 years were 58%, 44% and 29% respectively. Cardiac involvement, ECOG >2, NYHA >2 and involvement of >2 organ resulted in a poorer outcome. The OS for untreated group was 6.0 months and in the treated group was 29 months. The median OS for patients achieving a VGPR or better, PR or NR was 56, 21 and 19 months respectively. Achieving an excellent clonal response can translate into improved survival in elderly patients with AL amyloidosis but treatment decision in this vulnerable age group should be individually tailored.



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Clinical Significance of CD56 in Multiple Myeloma and AL Amyloidosis

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Aim: CD56 is frequently expressed by malignant plasma cells of patients with multiple myeloma (MM) or AL amyloidosis (ALA). The aim of this study was to examine CD56 expression in patients with MM or ALA and the clinical characteristics of CD56 expression. Methods: This study included 215 MM patients and 101 ALA patients who underwent bone marrow examination during the period from May 2006 to December 2012. The bone marrow samples were analyzed using a flow cytometer. Various clinical data were evaluated by comparison with regard to the expression or non-expression of CD56. Results: Among the 316 patients CD56 expression rate is significantly higher in MM patients than ALA patients ($p < 0.0001$). Among 215 MM patients, 152 patients (70.7%) showed CD19-/CD56+ clonal plasma cells and 44 patients (20.5%) showed CD19-/CD56- clonal plasma cells. Among the 101 ALA patients, 38 patients (37.6%) showed CD19-/CD56+ clonal plasma cells and 37 patients (36.6%) showed CD19-/CD56- clonal plasma cells. CD19-/CD56+ MM patients presented higher serum total protein ($p = 0.00045$) and serum calcium levels ($p = 0.053$), lower CD20 expression rates ($p = 0.0044$) than CD19-/CD56- multiple myeloma patients. CD19-/CD56+ ALA patients did not present these significances. Conclusion: CD56 expression rate seems to be different in monoclonal plasma cells obtained from MM and ALA patients. This study suggests that M protein secretions are promoted in CD56+ MM patients. No clinical significance was suggested for CD56+ ALA patients.

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Laryngo-tracheobronchial Amyloidosis. A 30 Year Institutional Experience

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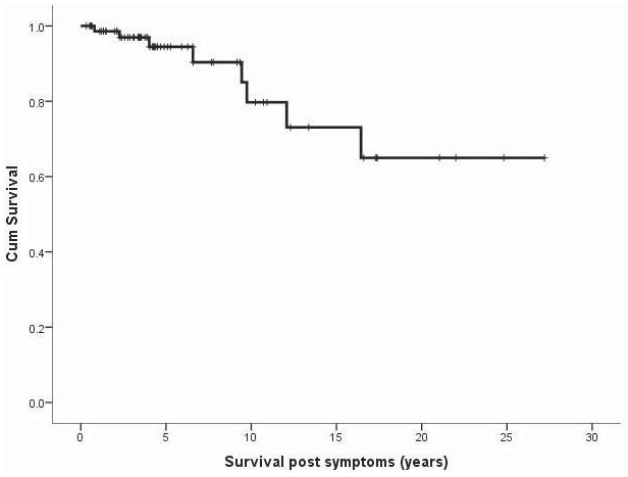
Localised AL amyloidosis is rare. Laryngo-tracheobronchial Amyloidosis(LTBA) occurs due progressive local formation and deposition of AL amyloid fibrils within the endoluminal region of this tract. We report clinical outcomes of 97 patients with LBTA seen at the UK National Amyloidosis Centre over the last 32 years, accounting for 15% of 634 patients with localised AL(63 laryngeal and 34 lower airway involvement) between 1980-2011. The median age was 55.3 years(range 13-80), 58% female, median symptom duration was 9 months(range 0.25-96). The main presenting symptoms were dysphonia (51%), haemoptysis(16%) and dyspnoea(12%). 8% patients had disabling or progressive symptoms affecting quality of life. One hypothesis is based upon an immune dysregulation following a recurrent or prolonged antigen challenge. Smoking history was present in 75% of the tracheobronchial group and only 29% of the laryngeal group. In this cohort, the 2 and 5 year OS was 96% and 94% respectively(Figure1). Therapeutic options are not well defined and primarily directed locally to the lesion, in our cohort involving surgical resection(20%), laser therapy(37%), inhaled steroids or nebulisers(4%). 25% needed repeated treatments. Local radiotherapy was used in (6%) in refractory cases with improvement in symptoms. The overall survival of LBTA is excellent and markedly different from systemic AL amyloidosis but is often a late diagnosis. Treatment strategies are challenging due to the recurrence of the lesions. Radiotherapy appears to be associated with improvement in symptoms in refractory cases.



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Ten Years Favorable Effect of Autologous Transplantation with POEMS Syndrome Developed from Solitary Plasmacytoma

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A 44-year-old male was admitted for left-arm numbness. CT showed a spinal cord with an adjacent thoracic vertebral osteosclerotic lesion. The histopathology of the tumor showed diffuse proliferation of atypical plasma cells with expressed vascular endothelial growth factor (VEGF). Though serum VEGF (sVEGF) level was elevated, a diagnosis of solitary plasmacytoma with an osteosclerotic lesion was made as the patient presented no polyneuropathy, organomegaly, endocrinopathy, or skin changes The patients experienced muscle weakness of the lower limbs and skin pigmentation/hemangioma one year after irradiation of the osteosclerotic lesion. Laboratory tests revealed hypothyroidism, hyperglycemia, serum monoclonal gammopathy, further elevation of sVEGF, and increased atypical bone marrow plasma cells. CT imaging showed splenomegaly, and a nerve conduction test revealed demyelinating motor peripheral neuropathy. The patient was therefore diagnosed with POEMS syndrome. Plasmacytoma is very rare as an initial manifestation of POEMS syndromes. He received tandem high-dose melphalan followed by autologous stem-cell transplantation. Although he continued to show demyelinating sensory peripheral neuropathy and endocrinopathy (hypothyroidism) ten years after transplantation, the serum IgG remains normal level and M protein was not detected by immunofixation, and he has since been able return to normal life. Patients presenting with plasmacytoma with an osteosclerotic lesion should be carefully observed and evaluated for the expression of sVEGF and development of POEMS syndrome.

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High Dose Melphalan and Autologous Stem Cell Transplantation for Systemic AL Amyloidosis

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We report 36 patients who received high dose melphalan and autologous stem cell transplantation for systemic AL amyloidosis. Between Sep. 2006 and Nov. 2012, 36 patients with AL amyloidosis were transplanted at Japanese Red Cross Medical Center. Characteristics of patients were shown as follows: median age; 54 (range 39-70), M/F=15/21, major organ involvement; heart 13, kidney 20, others 3 (liver 1, trachea 1, peripheral nerve 1), median melphalan dose 129 (range 50-200) mg/m^2, median infused CD34+ cells; 2.69 (range 1.17-11.26) x 10^6/kg. Out of 36 patients, 29 are alive after median follow up of 20.6 (range 2-71) months and two and four years estimated overall survival were 84.6% and 66.6%, respectively. Four patients died of heart failure and other three patients died of either gastrointestinal bleeding, bacteremia, or malignancy. Four year estimated survival of patients with cardiac involvement is 46.2% and is significantly lower as compared with that with others (92.9%). Serum albumin increased (average 21%) in patients survived more than 12 months after ASCT. Serum free light chain (FLC) was measured before and after ASCT in 7 patients, and of those, FLC rapidly decreased after ASCT in 5 patients. Patients without cardiac involvement showed satisfactory survival with improvement of clinical symptom and serum albumin. Careful patient selection and experienced management are important especially for patients with cardiac involvement. Serum FLC may be useful for evaluating effectiveness of ASCT and also for early detection of relapse.

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Validity and Completeness of the Monoclonal Gammopathy of Undetermined Significance (MGUS) Registration

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Objective: To estimate validity and completeness of the monoclonal gammopathy of undetermined significance (MGUS) diagnosis coding in the Danish National Patient Registry (DNPR). Patients and Methods. We reviewed the medical records of 327 patients registered with MGUS in the North and Central Jutland Regions in Denmark. The positive predictive value (PPV) of the MGUS diagnosis was computed based on this sample. We also estimated the completeness of DNPR by linking data from a previously validated MGUS cohort of 791 patients in the North Jutland Region. Results. The diagnosis of MGUS was confirmed in 231 patients and assessed as probable in additional 38 patients corresponding to a PPV of 82.3% (95% confidence interval (CI): 78.1% - 86.4%). By contrast 58 (17.7%) of the patients did definitively not meet the diagnostic criteria for MGUS. When we excluded patients with a diagnosis of malignant monoclonal gammopathy recorded prior to or within the first year after registration of MGUS in the DNPR the PPV increased to 88.3% (95% CI: 84.5% - 92.1%). DNPR only registered a diagnosis of MGUS in 133 of the 791 MGUS patients previously diagnosed corresponding to a completeness of 16.8% (95% CI: 14.1% -19.6%). Conclusion. The PPV of the diagnosis coding for MGUS in the DNPR is high. It can be further improved by a simple data restriction which makes it a suitable tool for epidemiological studies of hospitalized MGUS patients. However, the completeness of the registry is very low which suggests that MGUS patients registered in the hospital system are likely to be highly selected.

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Autologous Stem Cell Transplantation in POEMS Syndrome: the Spanish Experience

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POEMS syndrome results from a clonal plasma cell proliferation producing a small monoclonal protein usually of λ type. Progressive peripheral neuropathy is its major clinical feature. Therapy may consist in radiation for single osteosclerotic lesions or autologous transplant (ASCT) in patients with disseminated disease. Between 1999 and 2009, 19 patients with POEMS syndrome received an ASCT (melphalan-200 in 16 and mel-140 in 3) at 9 Spanish institutions. All patients presented an M protein (16 IgA- λ ; 3 IgG- λ) and 18 peripheral neuropathy. Other clinical features included osteosclerotic lesions (12 patients), organomegaly (16), endocrinopathy (7), skin lesions (18), extravascular volume overload (14), papilledema (6), pulmonary hypertension (4), portal hypertension (2), Castleman´s disease (3), thrombocytosis (12) and polycythemia (2). Median number of prior therapies was 2 and median time from diagnosis to ASCT was 8 months. Morbidity consisted in a delayed hematopoietic recovery in 2 patients (one needing a back-up infusion) and engraftment syndrome in 5. No transplant-related-mortality was observed. After a median follow-up of 45 months, one patient has died of progression 90 months post-ASCT. Among 16 evaluable patients for response: 8 obtained a complete hematologic response (CR), 7 a near-CR and one disease progression. All patients experienced a significant organic improvement (including pulmonary and portal hypertension) arount 4-6 months post-ASCT. In conclusion, ASCT proved to be highly effective for patients with disseminated POEMS syndrome in our series.

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Long Term Follow up of Primary Therapy with Bortezomib and Dexamethasone for Patients with AL Amyloidosis

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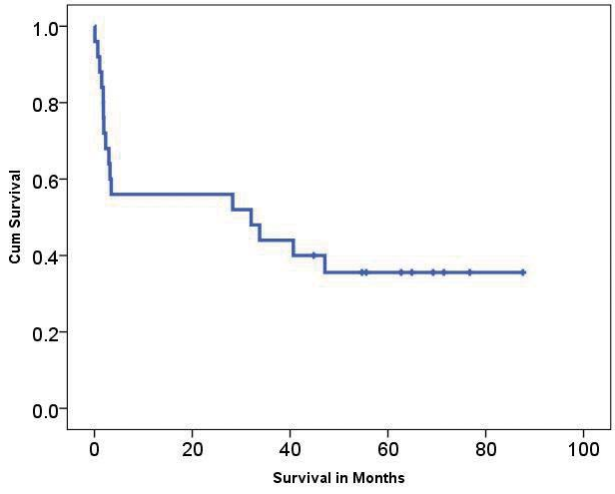
Bortezomib has significant activity in AL amyloidosis and is increasingly used even as first line therapy. However, there are no data from phase III studies for the use of this agent as a frontline therapy. We analyzed 25 consecutive patients who received first line therapy with bortezomib plus dexamethasone (BD) for AL amyloidosis and who started therapy at least 2 years before current analysis. Median age was 70 years, 52%

were males, 60% had renal and 84% cardiac involvement, while per cardiac biomarkers 20%, 52% and 28% were stage 1, 2 and 3 respectively. On intent to treat, 80% achieved a hematologic response and 36% a hemCR while 48% achieved a response in at least one affected organ. Median follow up for patients still alive is 5.5 years. Median time to any progression (hematologic or organ progression or death) was 9 months, while 8 (32%) remain progression free after a median of 58 months (range 40-81), including 3 (12.5%) who received consolidation with high dose melphalan. Among patients who survived at least 12 months, hematologic progression occurred in 29%. Median survival is 32 months while 1,2, 3 and 5-year survival is 56%, 56%, 52% and 44% respectively indicating a two-phase survival curve, the initial steep part of which is affected by the fatal complications of cardiac amyloid. In conclusion, first line therapy with BD induces high rates of hematologic response, including hemCRs in a significant proportion of patients; importantly, responses may be long lasting, even without consolidation with alkylators.



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Reappraisal of Multicentric Castleman's Disease: Proposal of a Novel Japanese Variant of TAFRO Syndrome.

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Background: Multicentric Castleman's disease (MCD) is a polyclonal lymphoproliferative disorder that manifests as marked hypergammaglobulinemia and severe inflammation. Recently, Kojima and Takai shed the light on a unique clinicopathologic aspect of Japanese patients with MCD, characterised by thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction, and organomegaly, leading to the proposal of TAFRO syndrome (Castleman-Kojima disease). Design: To better define this novel syndrome, hematologists and pathologists analyzed clinicopathologic data on 15 patients. Results: The patients enrolled in this study were significantly accompanied by a combination of thrombocytopenia, ascites, pleural effusions, anemia, fever, myelofibrosis, renal dysfunction, and organomegaly. Multiple lymphadenopathy was generally of mild degree, less than 1.5 cm in a diameter, and consistently featured by the histopathology of mixed or less hyaline vascular type Castleman's disease. Autoantibodies were often detected, however, this disease did not fulfill the diagnostic criteria for the well-known autoimmune diseases including SLE. Furthermore, glucocorticoid, immunosuppressive therapy, or tocilizumab may be effective as treatment for patients with this condition, but some had a deteriorated clinical course despite the treatment. Conclusion: Cases of TAFRO syndrome are still rare. Therefore, it is necessary to conduct multicenter clinical surveys to reach a consensus regarding diagnostic criteria, therapeutic strategy, and pathophysiological etiology for this syndrome.

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Autologous Stem Cell Transplantation in Six Newly Diagnosed Patients with POEMS Syndrome.

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POEMS syndrome is a rare clonal plasma cell disease. Autologous stem cell transplantation (ASCT) has become a favored therapy, but relapses have been reported. We retrospectively analyzed six patients with POEMS who had undergone ASCT between 2004 and 2012. The study included 4 males and 2 females, the median age at transplantation was 50 years (range 33-60 years). High-dose therapy was the first-line treatment in 5 patients (high dose dexamethasone (DEX) in 3, lenalidomide/DEX in 1, bortezomib/DEX in 1), while one patient did not have prior therapy before ASCT. The median time to ASCT from the time of first symptoms and diagnosis of POEMS were 10 and 4 months (range, 3-24 and 6-27 months). All patients were treated with melphalan 200mg/m2 as the conditioning chemotherapy. A periengraftment syndrome was recognized in 1 patient. All 6 patients got improvement of clinical feature and VEGF level, 3 patients had normalized VEGF after ASCT. There was one patient with negative immunofixation on the serum. The median duration of follow-up from the time of the ASCT was 44 months (range, 2-102 months). Two patients had progressed in 25 and 38 months after their ASCT with clinical symptoms. VEGF level were increased associated with clinical symptoms in one relapsed patient, but not in the other patient. These two relapsed patients could be salvaged with immunomodulatory drugs (IMiDs). Though peripheral neuropathy is an important dose-limiting toxicity, IMiDs were effective for POEMS relapsed after ASCT.

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Sensitive Assay Using Monoclonal Antibodies for the Simultaneous Measurement of Kappa and Lambda Serum Free Light Chains

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Monoclonal κ and λ immunoglobulin free light chains (FLC) in blood and urine are important biomarkers in the diagnosis and monitoring of B cell dyscrasias. Current laboratory methods to quantify serum FLC have a number of well-observed limitations. We describe a new method using specific mouse anti-human FLC monoclonal antibodies (mAbs). Anti-κ and anti-λ FLC mAbs were separately coupled to polystyrene beads and assayed, simultaneously, by Luminex (mAb assay). The mAbs displayed no cross-reactivity to bound LC, the alternate LC type, or other human proteins. The mAb assay gave good linearity and sensitivity (<1 mg/L). The competitive inhibition format gave a broad calibration curve (1 to 437mg/L) and prevented anomalous results for samples in antigen excess i.e. high FLC levels. The mAbs displayed good concordance with Freelite for the quantitation of normal polyclonal FLC in plasma from healthy donors (n=249). By abnormal κ: λ ratio the mAb assay identified all monoclonal FLC in serum from 1000 consecutive patient samples (50.1% with monoclonal paraprotein by serum IFE). In 13,090 sequential urine samples the mAb assays detected all of the 22.8% with monoclonal κ FLC , the 9.0% with monoclonal λ FLC, and the 0.8% with polyclonal FLC identified by urine IFE. Identification of FLC by the mAb assays in all of large cohorts of samples shows that the mAbs are at least close to the ideal of accurately quantitating levels of FLC in blood and urine from all patients and neoplastic plasma cell clones.

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Rapid Test to Identity Myeloma Kidney by Measurement of Serum Free Light Chains

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Monoclonal κ and λ immunoglobulin free light chains (FLC) in blood and urine are important biomarkers to determine if acute kidney injury (AKI) may be attributable to a plasma cell dyscrasia. Laboratory FLC tests offer the only means of detecting FLC and commonly have a slow turnaround time that delays early diagnosis of myeloma kidney and thus increases risk of kidney damage. We have developed a point-of-care (POC) lateral flow test that can rapidly measure FLC levels in blood or urine in 10 minutes. The POC test simultaneously quantitates κ and λ FLC levels using highly specific anti-κ and anti-λ FLC monoclonal antibodies (abstract also submitted). POC capture antibodies displayed no cross-reactivity to bound LC on whole immunoglobulin, the alternate LC type, or other human proteins, and had excellent sensitivity <1 mg/L. The competitive inhibition format prevented anomalous results for samples in antigen excess i.e. from high FLC levels. POC results had good concordance with Freelite for the quantitation of FLC in both AKI serum from healthy donors (n=150). POC test validation for detecting myeloma kidney was conducted by analysis of stored urine and serum from AKI patients with GFR <15mls/min and found that AKI patients with myeloma had a very abnormal κ; λ FLC ratio in sera (n=78/78) and urine (n=58/58),

indicative of myeloma kidney, whereas, AKI patients without myeloma (n=133) had moderately raised serum FLC levels with a normal κ; λ FLC ratio. FLC POC tests to diagnose myeloma kidney should be investigated in clinical practice.

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Cardiac AL Amyloid; a Single Centre Experience in Incidence and Outcome

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A study of incidence and outcome of cardiac AL Amyloid at our centre (population 550,000) from 2005 to 2012. Results: 13 cases. Presentation: Median age 61 years (43-82 years). Multi-organ involvement: 7 cases (53%) renal, 1 case required renal dialysis. 3 cases (23%) peripheral neuropathy, 1 case autonomic neuropathy. Diagnosis: Clonal serum free light chain detected in all cases (23% kappa and 77% lambda). 6 cases (46%) associated with Myeloma. Imaging: 8 cases had cardiac magnetic resonance imaging (MRI), 7 of these were in study period 2009-12. 8 cases were confirmed by serum amyloid protein (SAP) scan at the National Amyloid Centre. An additional 12 cases of transthyretin (TTR) senile cardiac amyloid were diagnosed 2009-2011 by MRI. These cases had an underlying plasma cell dyscrasia excluded. Treatment: Disease modifying treatment was limited due to performance status and therapy intolerance. 10 of 13 patients received Thalidomide or Bortezomib. 2 patients (median age 50 years) with Myeloma had high dose therapy and Autologous Stem Cell Transplant (ASCT). Survival: 9 of 13 patients alive (overall survival (OS) 9.8 months). 9 deceased patients OS: 6.6 months. 2 ASCT patients alive: OS 25 months. 12 TTR cardiac amyloid cases OS: 19 months. Conclusions: Poor OS of Cardiac AL Amyloid. Prolonged remissions achieved if adequate disease modifying treatment tolerated. MRI provides a non-invasive diagnostic tool but cannot distinguish between AL and senile TTR amyloid. Diagnosis of AL and TTR cardiac amyloid is increasing due to use of cardiac MRI in an elderly population.

P-456

Plasma Cell Phenotype and B-cell Status are Independent Predictors of Progression-free and Overall Survival in MGUS.

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MGUS progresses to myeloma in 1% of cases per year and is associated with immune suppression and 2% per year excess infectious mortality. Depletion of normal plasma cells (PC) and abnormal sFLC ratio predict an increased risk of progression. Abnormalities in B-cell subsets are also reported. The aim of this study was to identify B-cell related factors which affect outcome in 1206 MGUS cases diagnosed since 2004.

During follow-up (median 3.5, range 0.5-8yrs), 48 developed myeloma and 9 a B-cell malignancy; 281 died, of which 151 were potentially MGUS-related (i.e. myeloma, infectious or renal condition).

Normal PC were depleted in 18% of cases and this was strongly associated with disease progression (P<0.001). There was 63% concordance between PC phenotype and sFLC ratio; either factor alone was equally predictive of disease progression (P=0.026). B-cell abnormalities (i.e. depleted normal subsets, perturbed K:L ratio, or MBL) were detected in 26% of cases. There was no clonal relationship with the neoplastic PC but B-cell abnormalities were strongly associated with progression and disease-related mortality (univariate P=0.001, multivariate P=0.021).

MGUS is characterised by perturbed B-cell/humoral immunity and neoplastic PC proliferation which each predict disease progression while B-cell abnormalities are strongly associated with excess infectious mortality. Current treatment for myeloma can reverse B-cell/humoral abnormalities with low toxicity. This study identifies MGUS patients eligible for an early intervention trial aimed at reducing infectious mortality.

P-457

IgM Hevylite Assay as a Biomarker of Clinical Outcome in Patients with Anti-MAG Neuropathy

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Background: Monoclonal IgM (MIgM) with auto-antibody activity against myelin-associated glycoprotein (MAG) leads to symptomatic peripheral neuropathy (PN). 30-50% of clinical responses are observed after rituximab based treatment. Responses are not well correlated with the MIgM or anti-MAG antibody (MaAb) levels. Methods: To investigate the interest of the IgM Hevylite assay, we retrospectively analysed 55 sera taken at diagnosis and during the follow up of 15 patients (median age 67 years) with anti-MAG PN and MIgM. 5 patients were treated with rituximab alone or combined with alkylating agents and/or fludarabine. Samples were subjected to immunofixation and serum protein electrophoresis (SPE). MaAb were quantified by Elisa. Results: IgM κ / IgM λ ratio ((IgM κ (6.39-35.07); IgM λ (0.26-0.75)) was abnormal in all samples: In 8/15 patients, including 4/5 treated, the spike <2g/l was not accurately measurable by SPE. Those 4 clinically improved pts and their IgM hevylite ratio decreased by 25 to 66%, while the MaAb level was reduced only in 2 patients. The non responder's MIgM measured by SPE decreased (50%), while the hevylite ratio and MaAb level remained stable. In the 10 untreated patients, no correlation was found between the SPE quantified MIgM and MaAb level (.R2:0.3-0.6) or between the hevylite ratio and MaAb level (R2: 0.15-0.61). Conclusion: IgM hevylite ratio allowed the follow up of MIgM level when <2g/l and was better correlated to the clinical outcome than MaAb level. It may be useful to follow patients with anti-MAG PN and should be evaluated in larger series.

P-458

Electron Microscopy and Functional Studies Reveal Cellular Stress in Amyloidogenic Plasma Cells

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Systemic light chain amyloidosis (AL) is a lethal plasma cell (PC) dyscrasia caused by the deposition of clonal PC-produced Ig light chain fibrils in vital organs. The clinical approach to AL imitates multiple myeloma (MM) therapy. Recently, the proteasome inhibitor (PI) bortezomib demonstrated unprecedented response rates in AL patients, nearing 90% complete remission when associated with alkylators. The established unique sensitivity of normal and malignant PCs to PIs encourages to investigate the biology of AL PCs in search for potential therapeutic targets. We thus characterized, for the first time, primary AL cells biochemically, functionally, and morphologically by electron microscopy (EM) and EM cytochemistry. EM studies revealed higher cellular stress in AL PCs as compared to MM cells, hallmarked by expanded and less discontinuous endoplasmic reticulum (ER) and perinuclear mitochondria. In line with higher stress, AL PCs proved significantly more sensitive than primary MM cells to PI-induced apoptosis, despite comparable proteasome stress, as assessed by ubiquitinated proteins accumulation, and similar proteasome activity. Our data reveal that primary AL PCs are intrinsically extremely sensitive to PIs. Moreover, altered ER homeostasis in AL PCs, together with our recent discovery of a critical autophagic control of ER homeostasis in PCs in vivo, suggests that autophagic exhaustion in AL PCs may underlie increased proteasome sensitivity, possibly contributing to high clinical responses. Hence, autophagy merits investigation as a potential therapeutic target in AL.

P-459

Melphalan and Dexamethasone vs. Bortezomib, Melphalan and Dexamethasone in AL Amyloidosis: a Matched Comparison

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Based on promising results of small retrospective series, combinations of bortezomib (B), dexamethasone and alkylators are being used to treat patients with AL amyloidosis. However, no controlled study exists comparing such combinations with current standards of care. We compared 33 unselected newly-diagnosed subjects treated with B, melphalan and dexamethasone (BMDex) with 66 controls treated with MDex. Cases and controls were matched for organ involvement (heart 82%), cardiac stage (III 42%), renal function, blood pressure, heart failure and free light chain concentration. The addition of B did not result in increased toxicity, with 21% of patients experiencing severe adverse events in the BMDex group and 29% in the MDex group (P=0.682).

By intent-to-treat the hematologic response rate was identical in the two groups (54%). However, BMDex induced a more pronounced decrease in free light chains in responders (95% vs. 82%, P=0.048), and patients receiving BMDex were more likely to obtain complete and very good partial responses at 6 months (54% vs. 30%, P=0.047). Thirty-three percent of patients died in the first 6 months in the BMDex group vs. 24% in the MDex group (P=0.470). Median follow-up of living patients was 38 months; 17 patients (51%) died in the BMDex group and 47 (71%) in the MDex group. Overall survival was no different (estimated 3-year survival 46% with BMDex vs. 35% with MDex, P=0.496). These data support the need to perform randomized controlled trials in order to better define the role of bortezomib combinations in the upfront treatment of AL amyloidosis.

P-460

Prognostic Value of IgM Heavy Immunoglobulins Chain Analysis in IgM MGUS and Waldenstrom Macroglobulinemia

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Background: New determinations of heavy immunoglobulins chains have been developed as biomarkers to apply at clinical practice. We present our experience in use of IgM κ /IgM λ ratios (HLCR) at diagnostic to discriminate between MGUS and WM, and to evaluate their potential prognostic value. Patients and Methods: 50 patients were examined following clinical protocol; serum samples were collected and kept frozen at -70ºC in the Biobank. Analysis of IgM was performed with HLCR, (Hevylite immunoassay the Binding Site). For ease of comparison IgM hevylite ratios were expressed as the involved monoclonal immunoglobulin/uninvolved polyclonal immunoglobulin (iHLC/uHLC). Results: 29 WM, 21 IgM-MGUS, median age 67 years; M/F ratio 1.38. Median IgM HLCR was 381.8 in WM symptomatic, 75.84 in WM asymptomatic and 15.65 in IgM MGUS (p=0.001). Median IgM HLCR was higher in WM patients requiring treatment at diagnosis (370.7 v 43.897 p=0.026) and it was higher at relapse/refractory (478.5 v 44.24 p=0.012). Median uHLC was higher in IgM-MGUS than WM patients to IgM κ and IgM λ: 0.39 g/L v 0.21 g/L, p=0.036; and 1.2 g/L v 0.32 g/L, p=0.019. Relapse/refractory patients had a mean uHLC lower than the patients who did not relapse (0.29 g/L v 0.52 g/L, p=0.04). Conclusion: At diagnostic IgM HLCR seems identifies patients WM / IgM MGUS and it discriminates WM symptomatic, asymptomatic and progressing patients. Uninvolved polyclonal immunoglobulin was significantly lower in Relapse/refractory patients, showing that these patients have a less robust immune system.

P-461

A Case of Multiple Extramedullary Plasmacytoma Surviving for a Long Term without Systemic Therapy

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【background】 Extramedullary plasmacytoma (EMP) is a rare plasma cell tumor of soft tissue. Good prognosis is achieved with radiotherapy (RT) for solitary EMP. Nevertheless, multiple EMP cases are rare and standard management is not established. The strategies range from watchful waiting to autologous hematopoietic stem cell transplantation. We present a case with multiple EMP surviving for a long term without systemic treatment. 【case report】 59-year-old Japanese man complained progressive subcutaneous mass in his right lower leg in 2005. He was diagnosed as EMP with tumor biopsy, with a tumor in parotid gland and mediastinal lymphoadenopathy. No bone marrow involvement was observed. After a 3 years observation, he was treated with RT to tumor in his right lower leg. After RT, he was observed without systemic therapy for 4 years. Thereafter swelling of soft palate emerged and slowly progressed. In 2012 he consulted to our hospital. Screening examination detected tumors in the left orbit, right parotid grand, soft palate and left lower leg. Neither bone lesion nor bone marrow involvement was detected. Pathological analysis detected abnormal plasma cells with the phenotype of CD20(-),CD56(-),CD138(+),IgG(+),kappa chain(+). Progression to multiple myeloma was not confirmed. Because he suffered from disconfortness due to soft palate tumor, HD-DEX and subsequent lenalidomide+DEX(Ld) was started and partial response was achieved so far. 【discussion】 This case suggests that watchful waiting could be an initial treatment option for some cases with EMP.

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Molecular Characterization of *IgH* Rearrangements in Waldenstrom's Macroglobulinemia. Correlation with Clinical Features

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Background and aim: Waldenstrom's Macroglobulinemia (WM) cells express a unique clonotypic rearrangement of heavy chain immunoglobulin gene (*IgH*) in each individual patient. We characterized *IgH* rearrangements in a cohort of WM patients and investigated any eventual correlation with clinical features. Patients and methods: 39 patients were studied (median age 65y, 46% male) symptomatic 72% asymptomatic 28%, of whom 47%, 38% and 15% were staged IPSSWM 1, 2 and 3 respectively. Median time to treatment was 13 months and median overall survival 61 months. DNA was extracted from patient's blood/bone marrow cells, IgH VDJ locus was amplified, monolclonal VDJ rearranged fragments were sequenced and analyzed through the international immunogenetics information system. Results: The most frequent family used was IGVH3 (69%). IGVH3-23 and IGVH3-74 segments were used in 23% and 18% respectively. Somatic hypermutation was seen in all but three cases (92%). Median percentage of mutations in all cases, IGVH3 family, IGVH3-23 and IGVH3-74 segments was 7,6%, 8%, 9,4% and 7,5% respectively. Features of selection pressure were found in most cases. CDR3 length was short in 81% of cases. The abovementioned findings were compared with patients' physical and routine laboratory workup results, time to treatment and survival; no correlations were found. Conclusions: WM repertoire is associated with IGVH3-23 and IGVH3-74 overexpression, and differs from those in normal B-cells, MZL and B-CLL. In addition high *IGVH* mutation rate with features of selection pressure and short CDR3 segments was found.

P-463

Uninvolved Heavy-light-chain Pair Suppression (UHLCPs) in Smoldering Myeloma: New Insights

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Uninvolved heavy-chain Ig isotype immunoparesis (e.g., IgA or IgM levels in IgG) is a risk factor for transformation from smoldering multiple myeloma patients (SMM) to multiple myeloma (MM). Recently, uninvolved heavy-light-chain Pair Suppression (UHLCPs) (e.g. decreased polyclonal IgG lambda with paired monoclonal IgG kappa) was found to be a risk factor in MGUS for progression to MM. Using HevyliteTM on SPAplus (Specialty Protein Analyzer) platform, we assessed serum from 44 SMM patients enrolled in our prospective natural history study (NCT01109407). Also performed was SPEP, IFE, serum free light chains (sFLC), quantitative Ig levels (IgG, IgA, and IgM), bone marrow aspiration / core biopsy, and flow cytometry for abnormal plasma cells (aPC%). We found 26/44 (59%) of SMM patients had demonstrated uninvolved heavy-chain Ig isotype immunoparesis; 25/26 (96%) of these patients also had UHLCPs. Among SMM patients without uninvolved heavy-chain Ig immunoparesis, 8/18 (44%) had UHLCPs. Patients with uninvolved heavy-chain Ig isotype immunoparesis and uninvolved UHLCPs had similar adverse biological features when compared with the SMM group without uninvolved heavy-chain Ig immunoparesis and UHLCPs reflected in aPC%, FLC-ratio skewing, M-spike, and percentage of PCs in the BM. Using the HevyliteTM assay, among SMM patients without uninvolved heavy-chain Ig isotype, we found UHLCPs associated with adverse biological features. Our ongoing prospective study will evaluate the contribution of both UHLCPs and immunoparesis in SMM to the risk of progression to MM.

SMM	Immunoparetic + No UHLCPs (n=1)	Immunoparetic + UHLCPs (n=25)	Non-Immunoparetic + No UHLCPs (n=10)	Non-Immunoparetic + UHLCPs (n=8)
	Mean %	***Mean %***	***Mean %***	***Mean %***
Abnormal PC ≥95%	70	97	80	89
M-Protein ≥3 g/dL	1.3	2.0	1.0	1.4
FLC Ratio (<0.125, >8)	0.16	17.4	2.5	14.1
%PC in BM Biopsy	10	26	12	15.1

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Value of ECG and Echocardiographic Criteria for Diagnosis of Cardiac Amyloid in the Cardiac Magnetic Resonance Era

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Background: Cardiac amyloidosis is often diagnosed by the combination of low electrocardiographic (ECG) voltage

and typical transthoracic echocardiography (TTE) appearance. Aim: To determine the diagnostic accuracy of classical ECG and TTE criteria in patients referred for cardiac amyloid evaluation with late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR). Methods: We retrospectively reviewed consecutive patients referred for CMR for clinically suspected cardiac amyloidosis. Cardiac amyloidosis was defined as positive cardiac biopsy or typical LGE pattern. Low voltage was defined as the sum of precordial voltage < 15 mm. Left ventricular (LV) hypertrophy (LVH) was defined as increased LV mass according to gender-based reference values, and considered concentric if relative wall thickness was > 0.42. A typical TTE pattern was defined as the combination of concentric LVH, severe left atrial enlargement (indexed volume > 40 mL/m2) and significant (pseudonormal or restrictive) diastolic dysfunction. Results: We analyzed 125 patients (85 males [68%], age 63 ±13 years), 51 [40.8%] had cardiac amyloidosis. The diagnostic accuracies of the different criteria are shown in the Table below. Analysis of this cohort for presence of systemic amyloidosis (with subtype) and multiple myeloma will be completed shortly. Conclusion: Classical ECG and TTE diagnostic criteria of cardiac amyloidosis have high specificity but low sensitivity; therefore, other techniques, such as CMR, are needed for early detection.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Low voltage	56.8%	82.1%	71.4%	70.8%	56.8%
Concentric LVH	60.8%	78.4%	66%	74.4%	71.3%
Typical TTE pattern	33.3%	94.6%	81%	67.5%	69.6%
Low voltage + Concentric LVH	25.5%	95.9%	81.3%	65.1%	67.2%
Low voltage + Typical TTE pattern	11.8%	100%	100%	62.2%	64%

PPV: positive predictive value, NPV: negative predictive value, LVH: left ventricular hypertrophy, TTE: transthoracic echocardiography

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Systemic Amyloidosis and Multiple Myeloma in Patients Diagnosed with Cardiac Amyloid by Cardiac Magnetic Resonance

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Background: Evaluation for cardiac amyloid with late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) cardiac has shown usefulness in the diagnosis of cardiac amyloid. However, few data exist on the presence (and subtypes) of systemic amyloidosis and/or multiple myeloma (MM) in these patients. Aim: To determine the incidences of systemic amyloidosis and multiple myeloma in patients diagnosed with cardiac amyloidosis by cardiac magnetic resonance (CMR). Methods: We retrospectively evaluated consecutive patients referred for 3.0 Tesla CMR with a final diagnosis of cardiac amyloidosis (defined as typical diffuse, predominantly subendocardial pattern of delayed contrast enhancement) and for whom data exist to determine the presence of systemic amyloidosis and MM. Results: We included 32 patients (15 males [47%], age 66 ± 22 years) with cardiac amyloid. Of these, 15 (47%) were diagnosed with light-chain (AL) amyloidosis (4 had confirmed MM), 9 (28%) with TTR amyloidosis (1 had concurrent MM), and 7 (22%) had no evidence of systemic amyloidosis. Conclusion: Patients diagnosed with cardiac amyloidosis require further evaluation for systemic amyloidosis (of distinct subtypes) and for MM. Of note, the presence of systemic amyloidosis and concurrent MM does not ensure the amyloidosis is of AL subtype.

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Risk Adapted Treatment Strategy without Autologous Stem Cell Transplant (ASCT) in AL Amyloidosis: the French Experience since 2007.

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The recommendation among the French network for amyloidosis is to use melphalan and dexamethasone (MDex) as first-line treatmentand to addbortezomib, for refractory patients (pts)after one cycle in those with cardiac involvement and after 3 cycles for those without. Pts with severe cardiac disease (Mayo clinic stage III) are given a combination of bortezomib, cyclophosphamide and dex (VCD).

We collected 242 ptstreatedin 28 French centers since January 2007. Median age was 66 years (29-86), 101 pts were 70 or older, 60% were male. Baseline organ involvement was car-

diac 67%, renal 65%, peripheral nerve 23%, liver 19%. The Mayo clinic staging was stage I for 44 pts, II for 92 pts and III for 106 pts. Median NT-proBNP was 1767 ng/l. First line treatment was ASCT in only 2 pts, M-Dex in 105, a combination with bortezomib in 94, with IMID in 11.Bortezomib was secondarily added for no response in 50 pts. Median dFLC was 193 mg/l (1.4-13398) at diagnosis and 43 mg/l (0.2-4585) after 3 cycles of treatment. Overall hematological response rate was 63%, including VGPR or better in 36% and PR in 27%.With a mean follow-up for living pts of 1.3 year, estimated median survival was 4.11 years, not reached for pts younger than 70, versus 2.9 years for older pts (p=0.009). Mayo clinic staging was highly predictive of survival. One-year survival was 88% for stage I, 83% for stage II and 51% for stage III(p< O.001).

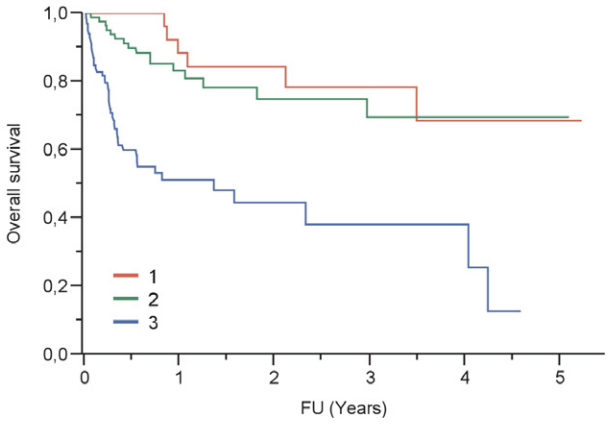
In AL amyloidosis, a risk-adapted and response-tailored conventional strategy can give a high response rate and a relatively good survival in a multicenter setting.

Disclosures:

Survival according to Mayo Clinic staging:

AJ: Research support: Celgene, honoraria Celgene and Janssen.

MR: Research support and honoraria Janssen.



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Clinical Comparison of the Freelite and N-Latex Serum Free Light Chain (FLC) Assays in the Diagnosis and Monitoring of AL Amyloidosis

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Aims: We compared a novel assay for FLC quantitation based on monoclonal antibodies (N-Latex, Siemens, Germany) to the established polyclonal antibody-based assay (Freelite, The Binding Site, UK) in AL amyloidosis.

Methods: 61 diagnostic samples were analysed on a BNII nephelometer, 31 of which also had a post-treatment sample.

Results: In the diagnostic samples: for AL of kappa type, the median involved FLC (iFLC) was significantly lower by the N-Latex assay (354 vs 808mg/L, p=0.0003) whereas for lambda AL the values were similar (148 vs 161mg/L, p=0.84). Measurable disease, defined as a difference between involved and uninvolved FLC (dFLC) >50mg/L was present in 82% by the N-Latex assay compared to 89% by the Freelite assay. For diagnostic sensitivity, the FLC ratio was normal in 21% and 15% of patients by the N-Latex and Freelite assays, respectively. The combination of serum and urine IFE with either FLC assay, however, allowed identification of the amyloidogenic clone in 98% producing comparable sensitivity.

For the monitoring samples the median reduction in dFLC was 48% for the N-Latex assay and 79% for the Freelite assay (p=0.03). This led to some differences in assigning response categories. Response as assigned by both assays predicted overall survival (N-Latex p=0.0027, Freelite p=0.0275).

Conclusions: There are significant differences between iFLC as measured by the N-Latex and Freelite assays, but overall the two assays have similar diagnostic sensitivity. Disease response calculated by both assays predicts survival but more clinical validation is required.

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Changes in IgAκ / IgAλ Heavy / Light Chain (HLC) Ratios Offer an Alternative Method of Monitoring IgA Multiple Myeloma Patients

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Background: Quantification of monoclonal immunoglobulins (M-Ig) by SPEP is recommended for monitoring intact Ig MM patients. However, M-Ig co-migration can make SPEP quantification inaccurate; in such instances international guidelines recommend total immunoglobulin measurement. Here we assess the utility of assays quantifying IgA κ and IgA λ and the production of the IgA κ /IgA λ ratio (HLCr) as methods to monitor IgA MM patients.

Methods: Sera from 10 IgA (6 IgA κ, 4 IgA λ) MM patients with co-migrating IgA (by SPEP) were analysed using IgA κ, IgA λ HLC and HLCr (normal range = 0.80-2.04). Results were compared to tIgA and IFE.

Results: There was good correlation between tIgA and sum-

mated IgA κ and IgA λ HLC (R^2=0.98 median tIgA=11.7g/L (range: 0.48-47.1g/L), median summated HLC = 11.9g/L (range: 0.45-46.1g/L). 6/10 patients achieved <VGPR, all 6 showed similar responses by both HLC and tIgA. 4/10 patients could be monitored using HLCr when the tIgA value had normalised, including an IgA κ oligosecretory MM patient (tIgA 7g/L, <10% plasma cells, HLCr 18.7) whose tIgA concentrations normalised after 28 days of CTD therapy, at this time HLCr remained abnormal in concordance with clinical symptoms. A second IgA κ MM patient (tIgA 23g/L, 40% plasma cells, HLCr 48.3) similarly responded to CTD treatment after 155 days, whileboth IFE and HLCr identified the presence of disease.

Conclusion: Accurate monitoring of IgA MM patients with co-migrating M-Ig requires SPEP, tIgA and IFE measurements. IgA HLC obviates a number of these tests and is a sensitive alternative for monitoring MM patients and measuring response to treatment, including transplantation.

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