16TH INTERNATIONAL

Myeloma Workshop

New Delhi, India • March 1-4, 2017

Abstract Book

16th International Myeloma Workshop
New Delhi, India
March 1-4, 2017

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WELCOME MESSAGE

Dear Colleagues and Guests,

It is our distinct pleasure and honor to welcome you to New Delhi for the 16th International Myeloma Workshop! During this prestigious biannual event, myeloma experts from around the world gather to discuss basic, preclinical and clinical aspects in the biology and treatment of multiple myeloma. The scientific program will include oral presentations, consensus panels, debates on controversial and current arguments, and poster abstracts.

We have an exciting social program planned including a wonderful opening and closing reception that will feature the unique culture and cuisine of India. March is also a great time to visit New Delhi and we hope you take some time before or after the meeting to enjoy the many cultural attractions in the "Golden Triangle."

Best Regards,

2017 IMW Organizing Committee

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ABSTRACTS
16th International Myeloma Workshop
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ORAL PRESENTATIONS

OP-001
Non-overlapping promoter and super-enhancer driven processes support myeloma cell growth and survival via distinct regulatory axes

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We have previously reported that E2F1 and its heterodimerization partner DP1 promote MM tumor proliferation both in vitro and in vivo; and observed an inverse correlation between their expression and patient survival suggesting a role in MM pathogenesis. Moreover, E2F functional impairment by a dimerization inhibiting stapled peptide significantly affects myeloma tumor cell growth while sparing effect on normal components of bone marrow as well as normal plasma cells, suggesting an E2F dependency in MM cells. To better understand how E2F1 and DP1 drive proliferation, we mapped the global occupancy of E2F1/DP1 in MM. Integration of E2F1 and DP1 genomic localization to MM reference epigenome revealed specific co-occupancy of the factors at promoters of active genes marked by H3K4me3, with a strong positive correlation between E2F and RNA Polymerase II (RNA Pol II) binding at transcription start sites. In contrast, active enhancers, as defined by promoter distal Mediator (MED1) peaks and marked by H3K27ac and BRD4, showed virtually no E2F binding. The relationship between promoter proximal transcription factor-associated gene expression and super-enhancer-driven transcriptional programs are not well-defined. Prompt by these observations, we explored the transcriptional and functional interrelationship between E2F and BETs to identify their individual contribution to eventual functional effect in MM. Unbiased hierarchical clustering revealed distinct regulatory axes for E2F and BETs, with E2F predominantly localized to active gene promoters of growth/proliferation genes and BETs disproportionately at enhancer-regulated tissue specific genes confirming that these factors establish distinct target gene programs. At the extremes, we found less than 10% of genes were among the top 500 in BRD4 enhancer signal (i.e. SE-regulated) and top 500 E2F promoter signal. We hypothesized that the presence of BETs and E2F in distinct regulatory axes divides active genes in MM into those that can be selectively influenced by BET inhibition or E2F perturbation, but not both. In line with this we have observed that dual E2F and BET inhibition is synergistic for MM cell growth, both in vitro and in vivo. In conclusions, our results highlight the existence of non-overlapping promoter and super-enhancer-associated dependencies in multiple myeloma, suggesting a sequestered molecular control that may be perturbed in cancer with potential for development of a promising therapeutic strategy.

OP-002
Integrating Molecular Genetic and Gene Expression Profiling Allows Stratification of Ultra-High Risk Myeloma

Amy Sherborne[1], Dil Begum[2], Amy Price[2], David Johnson[2], Sidra Ellis[2], Charlotte

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Introduction A significant proportion of myeloma patients relapse early and show short survival. Identifying these high risk patients at diagnosis enable stratified treatment approaches. Using two validated molecular approaches for risk prediction, molecular genetic profiling and gene expression profiling (GEP), we analysed two large multicentric UK National trials to define a category of ultra-high risk patients with significantly worse survival. Methods A representative group of 318 newly diagnosed, transplant eligible patients treated on the UK NCRI Myeloma XI trial were profiled. Molecular genetic profiles included t(4;14), t(14;16), del(17p), gain(1q) and were generated using MLPA (MRC Holland) and a TC-classification based qRT-PCR assay. GEP risk status was defined by a standardised EMC92 risk score, 'SKY92', using a diagnostic Affymetrix platform with the CE-marked MMProfiler array (SkylineDx). Progression-free (PFS) and overall survival (OS) were measured from initial randomization and median follow-up for the analysed group was 36 months. Results were confirmed in an independent dataset, MRC Myeloma IX, for which median follow-up was 82.7 months. Results Of the 318 analysed patients, 161 were found to carry an established genetic high risk lesion [t(4;14), t(14;16), del(17p) or gain(1q)]. By GEP, 78/318 patients (24.5%) were identified as SKY92 high

risk. Genetic and GEP high risk co-occurred in 29 patients (9.1%), 49 patients (15.4%) were high risk only by GEP and 27 patients (8.5%) by genetics only. We and others have recently demonstrated that co-occurrence of ≥2 adverse genetic lesions, termed 'double-hit' high risk, is specifically associated with adverse outcome. 56/318 patients (17.6%) were identified as genetic 'double-hit' high risk. Co-occurring GEP and genetic high risk status was associated with very short PFS (median 13.4 vs. 21.2 vs. 38.9 months; P<0.0001) and OS (median 26.1 vs. not reached vs. not reached; P<0.0001). All patients with molecular Ultra-High Risk relapsed within 3 years, and less than 20% survived beyond 3 years. We confirmed this finding in 116 transplant-eligible patients from the MRC Myeloma IX trial. Patients carrying both SKY92 and genetic high risk status had a median PFS of 7.8 vs. 25.5 months and median OS of 9.5 vs. 62.1 months (both P<0.0001). Moreover, all patients in the Ultra-High Risk group progressed within 2 years with no survivors beyond 4 years. Conclusion We demonstrate and validate that combined genetic and gene expression risk profiling identifies a Ultra-High Risk group of patients with high fidelity. Integrated genetic and gene expression risk profiling could facilitate high risk patient stratification and the development of innovative treatment approaches in myeloma and will be applied in risk stratified clinical trials in the Myeloma UK Clinical Trial Network.

OP-003
Increased mutational burden and alterations to DNA damage repair genes are associated with poor prognosis and sensitivity to PI3K-mTOR inhibitors in multiple myeloma

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Introduction Several novel drugs have recently been approved for multiple myeloma (MM), however, there are few molecular indicators to guide treatment selection. Furthermore, the impact of recurrent myeloma alterations on drug response is often unclear. To address these limitations and identify genotype - phenotype relationships in myeloma, we analyzed 100 MM samples and compared genomic, transcriptomic, and cytogenetic information to ex vivo drug response profiles and clinical outcome of individual patients. Our results reveal insights on i) drug response and resistance mechanisms, ii) molecular indicators for drug response, and iii) novel treatment combinations to overcome drug resistance. Methods Bone marrow aspirates were collected from MM patients (n=100; newly diagnosed n=34; relapsed n=66) and healthy individuals (n=14). CD138+ plasma cells were screened against 142 oncology drugs tested in a 10,000-fold concentration range. Somatic alterations were identified by exome sequencing of DNA from CD138+ cells and matched skin biopsies (n=85). RNA from CD138+ cells was sequenced and the derived read counts of 67 MM samples were used for gene expression analyses. Results A positive correlation was observed between mutational burden and ex vivo sensitivity to targeted therapies. 14% of the samples exhibited a multidrug resistant phenotype and were resistant to proteasome inhibitors, immunomodulatory drugs and glucocorticoids. 30% of the resistant samples were from del(17p) patients. Gene expression analysis revealed elevated expression of integrin signaling molecules plus multidrug resistance gene ABCB1. A combination of protein kinase C inhibitor bryostatin-1 and pan-BCL2 inhibitor navitoclax was highly effective in resistant samples. 26% of the patient samples harbored mutations to genes involved in DNA damage repair signaling, namely TP53, TP73, ATM and BAX, in a mutually exclusive pattern. Patients with these mutations had a high relapse rate and

poor overall survival (HR=7.2,95%CI 3.2-16.08). Interestingly, cells from these patients were highly susceptible to inhibitors targeting PI3K-mTOR signaling axis and HDAC inhibitors. While no strong correlation between RAS pathway mutations and MEK inhibitor sensitivity was observed, samples bearing clonal RAS mutations tended to be more sensitive to MEK inhibitors. Summary Driver alterations in DNA damage signaling pathways were found to contribute to poor prognosis. Samples with these mutations showed enhanced sensitivity to PI3K-mTOR and HDAC inhibitors. While genomic and transcriptomic data highlighted molecular events influencing the drug response, ex vivo drug testing revealed novel combinations to overcome treatment resistance. Our results demonstrate that both molecular information and ex vivo drug profiling may be useful to develop tailored treatment strategies and guide treatment decision, particularly for relapsed/refractory myeloma.

OP-004
Whole-exome sequencing and ultra low pass-whole genome sequencing of cfDNA and CTCs enable a comprehensive mutational landscape of Multiple Myeloma

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Background. Cell-free DNA (cfDNA) and circulating tumor cells (CTCs) sequencing enable serial temporal sampling, which offer the possibility of following the dynamics of clonal evolution in Multiple Myeloma (MM) over time. The use of cfDNA and CTCs in clinical

practice is however dependent on a comprehensive profile of matched cfDNA, CTCs and tumor DNA (tDNA) samples. Here we performed Ultra-Low Pass Whole Genome Sequencing (ULP-WGS) followed by whole-exome sequencing (WES) cfDNA/CTC/tDNA samples from MM patients. Methods. We performed next generation sequencing of 88 cfDNA and 63 CTC samples. Libraries were constructed using the Kappa Hyper kit and sequenced by ULP-WGS (0.1x coverage) to quantify tumor fraction and copy number alterations (CNAs) in cfDNA and CTCs. WES was performed on 40 matched samples cfDNA/CTC DNA/tDNA/germline DNA from 10 patients. Libraries were hybridized to the Nextera Rapid Capture Exome kit and sequenced on HiSeq 4000. Sequencing data were analyzed using MuTect, ABSOLUTE, ReCapSeg, GISTIC and MutSig. Results. We first used a cost-effective approach to establish the tumor content cfDNA and CTCs in a large-scale manner by ULP-WGS. Among 88 tested samples (73 MM, 10 SMM and 5 MGUS), the tumor fraction within cfDNA ranged from 0 to 91% with a mean of 12.4%. Regarding CTCs, among 63 samples tested (66 MM and 6 SMM), tumor fraction ranged from 0 to 80% with a mean of 11.7%. To assess whether cfDNA and CTCs DNA can capture the genetic diversity of MM and inform clinical management, we performed WES of matched cfDNA/CTC/tDNA/germline samples for 10 patients. CNAs assessed by WES were consistent between cfDNA, CTCs and tDNA. We then examined the overlap of single nucleotide variants (SNVs) between WES of cfDNA and matched tDNA. Among driver genes in MM including KRAS, NRAS and TP53, 98% and 93% of the mutations present in tDNA were detected in cfDNA and CTCs, respectively; inversely, 91% of drivers identified in cfDNA and CTCs were detected in tDNA. Regarding clonal heterogeneity, we found, on average, 98% and 100% of the clonal and 64% and 57% of the subclonal SNVs that were detected in the tumor were confirmed to be present in cfDNA and CTCs, respectively. Similarly, for mutations detected in the cfDNA and CTCs, we found, on average, 98% and 99% of the clonal and 63% and 56% of the subclonal

SNVs were confirmed in the tumor, respectively. Clustering analysis of mutations between tDNA, cfDNA and CTCs identified clones and subclones that were either shared in the 3 compartments or present in only one of them, indicating that sequencing cfDNA and CTCs may improve the resolution of clonal heterogeneity in MM. Conclusions. Our study demonstrates that WES and ULP-WGS of cfDNA and CTCs are consistently representative of tumor DNA alterations in terms of CNAs and SNVs. This approach could therefore be used to longitudinally follow clonal evolution and minimal residual disease in MM.

OP-005
Profiling of miRnome in Multiple Myeloma

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Networking of miRNAs and their targets play a crucial regulatory role during disease pathogenesis and response to treatment in a wide variety of diseases including multiple myeloma (MM) and its subgroups. We have evaluated miRNA expression arrays (8x160K) as well as gene expression arrays (8x160K) (Agilent Technologies) among CD138 positive cells from MM patients (n=44) and 4 controls (Pooled from 10 Hodgkin's disease samples). The MM patients were classified as hyperdiploid (n=20) or non-hyperdiploid (n=24) based on aCGH profiles (Agilent technologies). Differentially expressed miRNAs (DEMs) were identified and their targets were predicted with Targetscan, Pictar and Tarbase analytical tools followed by their involvement in pathway network interactions. Extensive analyses revealed ~ 98 significantly deregulated miRNAs including miR193b, miR10, miR15a, miR15b, miR17, miR18a, miR18b, miR29a, miR29b, miR29c, miR181a, miR181c and miR185 (FC $\geq$1.5, p$\leq$0.05). The 284 gene targets of differentially expressed miRNAs as obtained from integration of miRNA and mRNA expression data included genes such as CD48,

oncostatin M, E2F transcription factor 7 and IGF1. Further comparison of miRNA profiles of hyperdiploid Vs. non-hyperdiploid MM subgroups identified 67 miRNAs that were differentially expressed (FC ≥1.5, p≤0.05). The top 10 downregulated miRNAs included miR365a, miR221, miR30d, miR1246, miR29c, miR17, miR138 and miR181b, all of which are reported to be involved either in MM or other malignant conditions. An integrated analysis of miRNA and mRNA expression among hyperdiploid Vs. non-hyperdiploid identified 25 differentially regulated genes as potential targets of differentially expressed miRNAs. These included genes such as CYP1B1 (tumor antigen), MKI67 (proliferation related gene); TAF1 (transcription factor), RBL1 (senescence regulating gene), CTGF (angiogenic factor), and BCL2L10 (antiapototic gene). Identification of miRnome including miRNA and their targets that are deregulated could help understand disease pathology and design of possible therapeutic modalities.

OP-006
Unveiling the biomarker potential of shelterin complex in myeloma and revealing their role as therapeutic targets.

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Background and Objectives: Multiple myeloma (MM) defines as monoclonal antibody producing abnormal plasma cells inhabiting bone marrow (BM). It involves multiple genetic mutations where different signaling pathways get deregulated hence showing malignant features of myeloma. Increased relative telomerase activity (RTA) and altered levels of shelterin complex molecules (TRF1, TRF2, POT1, RAP1, TIN2, TPP1) along with its associated molecules (TANK-1 & PINX1) are underlying principle behind several malignancies. This maiden attempt aims to study expression levels of these molecules in myeloma and revealing therapeutic potential of TanshinoneI (TanI) alone or in combination with lenalidomide by targeting telomerase activity and shelterin molecules.
Methodology:Newly diagnosed 50 MM patients & 20 controls were recruited for BM aspiration with their consent. RTA, mean telomere length, relative mRNA and protein levels were studied in study subjects. Clinical parameters were recorded; correlation was studied between all the studied genes at mRNA levels and between genes and patients' clinical parameters; ROC curves were plotted of all genes. Anti cancer potential of TanI and lenalidomide or their combination were studied with different assays on myeloma cells (RPMI8226 & U266).
Results: Significantly (p<0.05) high relative mRNA expression were found of all molecules except PINX1 which was significantly lowered in patients compared to controls and was correlating with disease severity and progression. Similarly, higher RTA and lowered mean telomere length was observed in patients. Statistically significant correlation was observed between genes, telomerase activity and with clinical parameters. ROC curves analysis showed very high sensitivity and specificity for TRF2 genes and Telomerase activity. Thus, RTA and shelterin complex along with associated factors does play role in causing myeloma and its progression. TanI caused significant toxicity at low doses in myeloma cells while lenalidomide did not have any toxicity. Cell death was enhanced when combination of both (TanI + lenalidomide) drugs were used as observed in Annexin-V/PI and Tunel assay. TanI and its combination with lenalidomide significantly down regulated protein expression of TANK1, TPP1, and RAP1 in myeloma cells compared to untreated cells.
Conclusions: In nutshell, study implies that increased RTA along with altered mRNA and protein expression of shelterin complex molecules with its associated partners might play role in pathogenesis and progression of MM. Stage-wise significant increased expression and correlation of these molecules with each other and with clinical parameters showed their role as potential bio-marker in MM. Significant down-regulation of RTA and

apoptosis by TanI alone or combination with lenalidomide suggests that TanI might have synergizing effect with lenalidomide in causing cytotoxicity in Myeloma.

OOP-007
Quantification of proteins from CD138-purified myeloma cells using the capillary nano-immunoassay technology is a better predictor of survival than the corresponding gene expression value

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Protein analysis in bone marrow samples from patients with multiple myeloma (MM) has been limited by the low protein concentration obtained after CD138+ selection. A novel approach based on capillary nano-immunoelectrophoresis (CNIA) could make it possible to automatically quantify tens of proteins from each myeloma sample. We here present the results of a pilot study in MM using this platform. Our aims were, (i) to simultaneously quantify the protein levels of 13 proteins involved in MM biology and correlate them with the corresponding gene expression (mRNA) levels; (ii) to compare the impact of protein quantification with the value of mRNA assessment on predicting MM survival. Bone marrow aspirates from 63 newly diagnosed MM patients, treated with bortezomib and lenalidomide containing regimens were analyzed. Myeloma cells were purified by anti-CD138 magnetic microbeads (AutoMACs) and stored in RLT+ buffer at -80 C and simultaneous extraction of DNA, RNA and

proteins from the same sample was performed in all cases. Proteins were analyzed using the CNIA methodology (ProteinSimple, WES™) and mRNA expression by q-RT-PCR using TaqMan™ assays. After the analysis of the total protein content, 60 MM samples of 63 (95.2%) fulfilled the quantity and quality requirements for the quantification of the 13 selected proteins in each sample. The highest correlation between protein and mRNA level was observed for Cyclin D1 (ρ= 0.687, p<0.001) and Cyclin D2 (ρ=0.654, p<0.001), whereas no correlation was found for proteins such as PSME1 (Proteasome Activator Subunit 1), cereblon, c-myc, ikaros, HSP90, RIPK1 (Receptor interacting protein kinase 1) and XAF1 (XIAP Associated Factor 1). We observed modest degree of correlation for aiolos, dicer, calnexin (protein of the endoplasmic reticulum) and DDX21 (RNA helicase). High levels of cereblon and PSME1 proteins were associated with longer time to progression (TTP) compared to low levels. Thus, patients with high levels of cereblon and PSME1 had a median TTP of 25.8 and 43.8 months compared to 10.8 and 17.3 months, respectively (p<0.01 and FDR<0.05 for both comparisons). On the other hand, no significant impact on prognosis was observed when TTP was estimated using the mRNA levels. To conclude, the CNIA platform provides the novel opportunity to automatically quantify, for the first time, the expression of more than 10 proteins in CD138+ primary MM samples. We observed a weak correlation between the quantification of proteins and mRNAs encoded by several relevant genes in MM biology. Interestingly, protein measurement of cereblon and PSME1, involved in mechanism of action of IMIDs and proteasome inhibitors respectively, discriminated prognosis of patients with MM better than the corresponding mRNA levels. This work is funded by a grant from the International Myeloma Foundation's Black Swan Research Initiative®, and WES™ by INNOCAMPUS Program (CEI10-1-0010).

OP-008
Post Autologous Transplant (autoHCT)Therapies in High Risk MM. Subgroup analysis of Phase III BMTCTN

0702 STAMINA :autoHCT followed by Lenalidomide Maintenance(Len)(AM) vs auto HCT and Len and Bortezomib (BZ) and Dexamethasone Consolidation Len Maintenance(ACM) vs Tandem autoHCT Len Maintenance;

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The benefit of Len maintenance in patients with high risk cytogenetics remains unclear and a focus has been on increasing post transplant interventions in this group of patients. Options include consolidation, allogeneic transplant, tandem autologous transplant. We have previously reported on BMT CTN 0102 a comparison of tandem autologous versus autologous and reduced intensity allogeneic transplant in upfront therapy of myeloma. This trial did not show a benefit to the auto allogeneic approach in patients with high risk cytogenetics. Herein we report on the use of post autoHCT consolidation therapy or second autologous transplant in patients with poor risk myeloma. Methods: Patients <71years of age,2-12 months from diagnosis without prior progression were randomized 1:1:1 to receive melphalan 200mg/m2 autoHCT and 4 cycles of RVD consolidation (Len 15mg days1-14, bortezomib 1.3mg/m2days 1,4,8,11, dexamethasone 40mg day1,8,15)(ACM), tandem autoHCT (TAM), or single autoHCT(AM). All arms received Len maintenance for three years(amended till progression). High risk disease was defined as del 13 by karyotyping, del 17p, t(4,14),t(14,16),t(14,20), hypodiploid or beta2microglobulin >5.5mg/L. The primary endpoint was PFS at 38 months(m). Events for PFS were disease progression, non protocol directed therapy or death. Results: From June2010 to November 2013, 758 pts (ACM n=254, TAM = 247, AM n-257) were enrolled. 23.9% of the enrolled patients(pts)were high risk (ACM n = 65, TAM n= 57, AM n= 59). Induction for all pts was RVD 57% (TAM), 52.8%(ACM), 55.6%(AM), VCD 13.4%(TAM), 13.8%(ACM),14.2%(AM)(details on high risk subgroup will be presented at meeting)Over 83% of pts received only one line of induction in all arms. 12-13% received 2 lines of therapy prior to SCT in all arms. Median followup is 38 m. Probability of PFS at 38 m for all pts is56.5%(TAM), 56.7% (ACM), 52.2% (AM). In patients with high risk myeloma PFS 42.2%(TAM), 48.3%(ACM), 40.2%(AM). (NS).OS was 79.6%(TAM),77.5%(ACM),79.5%(AM) (NS) Conclusions: Tandem autoHCT did not improve PFS or OS compared to single Auto HCT. Consolidation therapy with RVD had a trend towards improved PFS at 38m but did not achieve statistical significance However, the high 38m survival in all arms is encouraging and is in keeping with the high PFS of the len maintenance arms in the Myeloma XI trial(median PFS60m), CALGB100104 (median PFS53m). Alternate strategies such as combinations with monoclonal antibodies pre and post transplant may lead to further

improvements in PFS and OS in high risk patients.

OP-009

Bortezomib, Lenalidomide and low-dose dexamethasone (VRD) versus Lenalidomide and low-dose dexamethasone (Ld) for newly-diagnosed Multiple myeloma- A Randomized phase III study-Interim Results

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Background: In this prospective study, we compared VRD with Ld as induction therapy for newly-diagnosed Multiple myeloma patients. The primary objective of this study is to compare the progression-free survival in the 2 arms. Methods: Between September 2014 and Oct 2016, 144 patients have been recruited and randomly assigned to receive 4 cycles of either Bortezomib 1.3 mg/m2 SC on days 1, 8, 15 and 22 with Lenalidomide 15mg/day from day 1 to 14 (Arm A) or Lenalidomide 25 mg/day from day 1 to 21 (Arm B). Patients in both arms received oral dexamethasone 40 mg on days 1,8,15 and 22. Both treatment regimens were 28-day cycles. All patients received 75 mg aspirin daily, acyclovir prophylaxis and monthly zoledronic acid. Response assessment was done at the end of the 4th cycle using the International Myeloma Working Group (IMWG) uniform response criteria. The study was approved by the Institute Ethics Committee (Ref IEC/NP-264/01-08-2014, RP-7/2014). Results: These are the results from an interim analysis of 122 patients (arm A-59, arm B-63). Baseline characteristics of patients were similar in both arms with respect to age, gender, ISS and DS stage, immunoglobulin subtype and serum LDH. Patients' median age is 58 years (range 31-70) in arm A and 52.5 years (range 28-69) in arm B. Gender M/F: Arm A 45/18 and 39/20 in arm B. ISS stage III 44 (71%) arm A vs 37 (64%) arm B. Serum LDH raised to >250 u/L was observed in 21 (46.7%) vs 28 (57%) in arms A and B, p=0.4. Revised staging including ISS and serum LDH at baseline: stage III 47 (81%) and 37 (65%) in arms A and B respectively. 10 (16%) and 17 (29%) of patients had light chain myeloma in arms A and B respectively. Overall response rates (sCR+CR+VGPR+PR) is 77.8% vs 72.9% in arms A and B respectively, p=0.7; sCR + CR 18 (29%) and 16 (27%) respectively, p=1.0. Median follow-up 14.7 months (range 1 to 27.5). Median overall survival (OS) is 25.4 months (95% CI 23.9 to 26.9) and 23.6 months (95%CI 21.3 to 25.9) in arms A and B respectively, p=0.17. Median progression-free survival (PFS) was 23.3 months (95%CI 21.3 to 25.3) and 20.9 months (95%CI 18.3 to 23.5) respectively, p=0.16. Estimated one-year OS is 91% vs 83% in arms A and B, p=0.15 and PFS 80% vs 67%, p=0.065 respectively. Grade 3 anemia occurred in one patient in arm B, and grade 3 deep vein thromboses in one patient in arm A. One patient in arm A developed grade 4 myelosuppression leading to therapy change at the end of the first cycle. Conclusion: In this interim analysis - response rates and median progression-free survival are similar in both arms.

OP-010

Lenalidomide (LEN) Maintenance Following High-Dose Melphalan and Autologous Stem Cell Transplant (ASCT) in Patients (Pts) With Newly Diagnosed Multiple Myeloma (MM): A Meta-Analysis of Overall Survival (OS)

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Introduction Several studies have demonstrated that LEN maintenance after ASCT reduces the risk of disease progression or death in pts with MM by ≈ 50% (Attal et al, N Engl J Med, 2012; McCarthy et al, N Engl J Med, 2012; Palumbo et al, N Engl J Med, 2014); however, these studies were not powered for OS. Here, we report the results of a prospectively planned meta-analysis that was conducted to assess the effect on OS of LEN maintenance vs placebo/no maintenance (control) after ASCT. Patients and Methods A search identified 17 randomized controlled trials (RCTs) using LEN following ASCT. Three RCTs (IFM 2005-02, CALGB 100104 [Alliance], GIMEMA RV-209) met prespecified inclusion criteria (had pt-level data and a control arm and achieved database lock for primary efficacy analysis of pts with newly diagnosed MM receiving LEN after ASCT). A March 2015 cutoff for the 3 RCTs was used to obtain the required OS events. Results In the 3 RCTs, from 2005 to 2009, 1208 pts were randomized to receive LEN (n = 605) 10 mg/day on days 1-21 (GIMEMA) or 1-28 (IFM and CALGB) of 28-day cycles or control (n = 603). With a median follow-up of 6.6 yrs, 490 OS events had occurred. Baseline characteristics were generally balanced across the pooled groups. After induction and single (82%) or tandem (18%) ASCT, > 50% of pts achieved a complete response (CR) or very good partial response (VGPR). Median OS in the LEN maintenance group was not reached vs 86 mos for the control group (HR = 0.75; 95% CI, 0.63-0.90; P = .001), and 7-yr OS rate was higher in the LEN maintenance vs the control group (62% vs 50%, respectively). Fisher combination test confirmed the significant OS benefit in the meta-analysis (P = .001). Pts with ≤ PR after

ASCT benefited from LEN maintenance (HR = 0.88; 95% CI, 0.66-1.17), as did pts with CR/VGPR (HR = 0.70; 95% CI, 0.54-0.90). OS benefit was generally consistent across subgroups. Based on a quantitative heterogeneity test (Pignon et al, Lancet Oncol, 2001), the OS results from the efficacy meta-analysis were considered significantly heterogeneous (P = .047) across studies for the intent-to-treat post-ASCT population and for all pts randomized. Potential factors contributing to the heterogeneity between the clinical trials were baseline/disease characteristics (such as International Staging System stage, cytogenetics), study conduct, and second-line therapy. No qualitative heterogeneity in OS was found using the Gail-Simon test (P = .75; Gail, Simon, Biometrics, 1985). Second primary malignancies (SPMs) were higher with LEN maintenance vs control (hematologic SPMs, 6.1% vs 2.8%; solid tumor SPMs, 7.3% vs 4.2%); however, the OS benefit outweighed the risk of SPM. Conclusion This large meta-analysis showed that LEN maintenance following ASCT significantly prolonged OS vs control. A survival benefit was seen in all response categories, with the greatest benefit seen in pts who achieved deep responses.

OP-011
Cardio-vascular toxicity in newly diagnosed, transplant-ineligible multiple myeloma patients treated with Carfilzomib, cyclophosphamide and dexamethasone: results from an integrated analysis of 3 phase I/II trials.

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BACKGROUND Cardio-vascular (CV) adverse events (AEs) in patients (pts) with multiple myeloma (MM) may result from comorbidities, MM itself, and its treatment. Carfilzomib is approved as single agent or in combination with lenalidomide-dexamethasone for relapsed MM. We conducted an integrated, CV safety analysis of newly diagnosed, transplant-ineligible pts treated with Carfilzomib in 3 phase I/II studies (IST-CAR-506, IST-CAR-561, IST-CAR-601). METHODS In all trials pts received nine 28-day induction cycles with carfilzomib, cyclophosphamide (300 mg/m2 on days 1,8,15) and dexamethasone (40 mg weekly), followed by maintenance with Carfilzomib until progression or intolerance. Carfilzomib was administered i.v. at the dose of 36 mg/m2 on days 1, 2, 8, 9, 15, 16 in the IST-CAR-506 trial; at 3 dose levels escalated from 45 to 70 mg/m2 on days 1, 8, 15 in the IST-CAR-561 trial and on days 1, 2, 8, 9, 15, 16 in the IST-CAR-601 trial. AEs were graded based on NCI-CTCAE v4. RESULTS 148 pts were analyzed, median age was 72 years. After a median follow-up of 21 months, any grade CV AEs were reported in 42% of pts (grade 3-5: 15%); hypertension (18%) and dyspnea (9%) were the most common. As compared to younger pts, those aged ≥75 years were at higher risk of any grade (36% vs 58%, p=0.02) and grade 3-5 CV AEs (15% vs 34%, p=0.01). The risk of CV toxicity decreased from induction (34%) to maintenance (22%); the decrease in any grade CV AEs during maintenance was evident only in pts <75 years (15%) and not in those ≥75 years (45%). Pts who developed a CV AE had a higher risk of Carfilzomib dose reduction or discontinuation as compared to those who did not (p<0.0001). The occurrence of any CV AE during induction doubled mortality for any cause, regardless of age: the 2-year overall survival was 74% in pts who experienced CV AE and 83% in those who did not (HR 2.01, p=0.05). As compared to pts without CV toxicity, those who developed at least 1 CV AE were more likely to have baseline hypertension (18% vs 6%), diabetes (15% vs 10%) and chronic pulmonary disease (6% vs 2%). CONCLUSIONS The risk of CV AEs with Carfilzomib is significantly higher in pts older than 75 years and the most important risk factor is hypertension. Developing CV toxicity increases the need for dose reduction or drug discontinuation, with a negative impact on overall survival. Elderly pts should be carefully assessed before starting treatment to derive maximum benefit from Carfilzomib.

OP-012
Carfilzomib Weekly Plus Melphalan and Prednisone in Newly Diagnosed Elderly Multiple Myeloma (IFM 2012-03)

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Background. VMP is the most frequent standard of care used upfront for newly diagnosed elderly myeloma (eNDMM). Carmysap, a phase I/II trial of twice weekly Carfilzomib, a novel generation proteasome inhibitor plus MP in eNDMM, demonstrated Carfilzomib MTD at 36mg/m2. We hypothesized that Carfilzomib can be used on a weekly schedule allowing to increase the dose given its positive safety profile. Methods. IFM2012-03 is a phase 1/2 multicenter symptomatic eNDMM (65 and older) study to determine MTD during the phase 1 part and VGPR+CR rate (IMWG criteria) during the phase 2 part of KMP (Carfilzomib Weekly Plus Melphalan and Prednisone) regimen. Inclusion criteria required absolute neutrophils ≥1G/L, untransfused platelet count ≥75G/L, hemoglobine ≥8.5g/dL and clairance creatinine ≥30ml/min. Induction comprised nine 5 weeks cycles. K is given 36, 45, 56 and 70 mg/m2 on days 1, 8, 15, 22 IV route in combination to oral Melphalan 0.25mg/kg/j and oral prednisone 60mg/m2, both on days 1 to 4. Maintenance. Carfilzomib. 36 mg/m2 weekly, every two weeks IV route for 1 year. Melphalan and Prednisone is not pursued at maintenance. The study was amended following completion of the first cohort at K 70 to add a second cohort of K 70 with clear recommendation in the monitoring of cardiovascular AEs, including HTA.Analysis is done on ITT. Recruitment was 6 patients per cohort, 3 DLTs defined MTD at the lower N-1 dose. Results. 30 treated patients in the study, 6 per cohort. The median age was 76 with 2/3rd older than 75, sex ratio M/F 1.2,

R-ISS 2 and 3 in 80%. There was one DLT at K 36 (grade 4 lymphopenia), one at 45 (lysis syndrome complicated with grade 4 renal insufficiency, two at 56 (cardiac insufficiency grade 3 and febrile neutropenia grade 3) and 2 at 70 (vomiting grade 3 and liver cholestase enzyme grade 3) for the first cohort, and no DLT for the last K 70 cohort. As a whole for the study, the ORR is 87%, with 44% at least in CR. At data cut-off, with a median follow-up at 24 months, one patient had progressed and 2 had died of whom one of cardiac dysfunction considered K related at 56. The safety profile appeared well tolerated particularly after the amendment. Conclusion. IFM2012-03, KMP weekly, Carfilzomib plus Melphalan and Prednisone in elderly NDMM has reached RP2D at 70mg/m2 of K. The recommendation of the DSMB was to launch the phase 2 portion at K 70 upto 75 years old, and 56 from 75 and above. However, the final call from IFM was to conclude the study at this stage, at the end of the phase 1 portion given that Clarion, the phase 3 international multicenter KMP study for registration, compared to VMP, did not show PFS median superiority of KMP, therefore hampering the chance for KMP to be registered upfront for eNDMM in Europe.

OP-013
A Case Control Study of Syngeneic Transplantation Versus Autologous Transplantation for Multiple Myeloma: Two Decades of Experience at MD Anderson

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INTRODUCTION: High-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-HCT) is the standard of care for eligible patients with newly diagnosed multiple myeloma (MM). For patients with an identical twin, syngeneic-HCT provides a tumor-free graft without the risk of graft vs. host disease. We hypothesized that syngeneic-HCT would result in better disease control than auto-HCT. METHODS: We identified 10 patients with MM who underwent syngeneic-HCT at our institution from 1994-2014. Using a propensity score, we identified 48 controls that received auto-HCT during the same time interval. Matching was done for the year of transplant, age and disease status at auto-HCT (Table 1). Primary endpoint was progression-free survival (PFS). Secondary endpoints were complete remission (CR) rates and overall survival (OS). RESULTS: The two groups were well matched, with no significant statistical differences in age, sex, race, stage at diagnosis, lines of therapy received, or disease status prior to transplant. At the time of transplant, 7 (70%) patients in the syngeneic cohort were in first remission, with 3 (30%) having relapsed disease. Similarly, 28 (58%) patients in the autologous cohort were in first remission, with 20 (41%) having relapsed disease (p value =0.49). All patients engrafted, with a median time to engraftment of 11 and 10 days, for the syngeneic and auto-HCT cohorts respectively (p=0.22). There was no treatment related mortality in the first 100 days post-transplant in either of the cohorts. In the syngeneic group 8 (80%) patients achieved $\geq$ CR, 1 achieved very good partial remission (VGPR), and 1 achieved a partial remission (PR), with an overall response rate (ORR) of 100%. Amongst the control group, 18 (37%) achieved $\geq$ CR, 5 (10%) achieved $\geq$ VGPR, 21 (43%) achieved $\geq$PR, 3 (6%) had stable disease and 1 (2%) had disease progression, with an ORR of 91.6%. There was no significant difference in the ORR between the two groups (p=0.21). At the time of last follow-up, a total of 4 (40%) patients had relapsed in the syngeneic cohort, and 31 (65%) had relapsed in the autologous cohort (p=0.15). The median progression free survival (PFS) for the syngeneic cohort was 98.6 months (95% CI from 76-118 months), while the median PFS for the

auto-HCT cohort was 34.5 months (95% CI from 16-52 months) (p=0.05). Median overall survival (OS) for the syngeneic and auto-HCT cohorts were not reached and 131 months, respectively (p=0.15). The PFS difference was not due to a difference in maintenance therapy after transplant, as 6 (60%) syngeneic patients and 32 (66.7%) auto-HCT (p=0.69) received maintenance therapy respectively.
CONCLUSION: Our study shows that patients with MM who underwent syngeneic-HCT. This benefit may be related to the absence of malignant plasma cells in the syngeneic graft, and a normal donor immune system. The efficacy

OP-014
Impact of treatment intensification according to patient prognosis: a pooled analysis of 3 randomized phase III trials

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Introduction: curable hematologic tumors but not multiple myeloma (MM) benefit from risk-adapted therapy. Intensified treatments such as autologous stem cell transplantation (ASCT) and continuous therapy (CT) improve patients

(pts) outcome. A better evaluation of pts prognosis based on the revised international staging system (R-ISS) is now available. We evaluated the impact of ASCT and CT in pts with different baseline prognosis. Methods: data from 3 phase III randomized trials in newly diagnosed MM (RV-MM-PI-209; RV-MM-EMN-441; GIMEMA-MM-03-05) were pooled together and analyzed. We evaluated: (1) the impact of treatment intensification with ASCT vs no-ASCT and (2) the impact of treatment intensification with CT vs Fixed Duration Therapy (FDT) in pts with R-ISS I vs II/III. All pts in the GIMEMA trial did not receive ASCT and were excluded from the first comparison. All pts in the EMN trial received CT and were excluded from the second comparison. Adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs). Results: Overall, 1302 pts were enrolled in the 3 trials. Median follow-up was 4 years. Comparison ASCT vs no-ASCT: 791 pts were enrolled in the 2 trials, 529 were eligible for the comparison. R-ISS was available for 419 pts. There was an overall advantage for ASCT vs no-ASCT in PFS1 (0.53; p<0.001), PFS2 (HR 0.53; p<0.001) and OS (HR 0.51; p<0.001). The 4-year PFS1 was 53% in pts with R-ISS I randomized to ASCT, 35% in pts with R-ISS II/III randomized to ASCT, 36% in pts with R-ISS I randomized to no-ASCT and 19% in those with R-ISS II/III randomized to no-ASCT (p<0.001); the 4-year PFS2 was 83%, 60%, 71% and 43% (p<0.001), respectively. The 4-year OS was 95%, 75%, 88% and 61% (p<0.001). Comparison CT vs FDT: 913 pts were enrolled in the 2 trials, 550 were eligible for the comparison. R-ISS data were available in 403 pts. CT significantly improved PFS (HR 0.54, p<0.001), PFS2 (HR 0.52, p<0.001) and OS (HR 0.72, p=0.04). The 4-year PFS was 48% for pts with R-ISS Stage-I assigned to CT, 37% for pts with R-ISS Stage II/III assigned to CT, 25% for pts with R-ISS Stage-I assigned to FDT and 18% for pts with R-ISS Stage II/III assigned to FDT (p<0.001); the 4-year PFS2 was respectively 73%, 66%, 59% and 43% (p<0.001); the 4-year OS was 80%, 73%, 77% and 63% (p=0.015). Conclusion: patients with R-ISS I receiving ASCT and/or CT showed the best outcome. Low-risk pts not undergoing intensification with ASCT or CT lost their initial prognostic advantage.

OP-015
Asymptomatic Multiple Myeloma – Molecular Background of Progression and Prognosis

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BACKGROUND. Asymptomatic multiple myeloma (AMM) evolves from monoclonal gammopathy of unknown significance (MGUS) and progresses to symptomatic myeloma characterized by end-organ damage. Aim of our study was to address the determinants of evolution and progression of AMM, their molecular background, and whether they are present upfront or evolve de novo in a multistep process on the background of an ongoing genetic instability. METHODS. CD138-purified plasma cell samples of 2065 patients with asymptomatic and symptomatic myeloma were investigated by fluorescence-in-situ-hybridization (n=432/1633), 889 (n=259/630) by gene expression profiling. Sixty-five paired samples at AMM and disease progression were assessed by iFISH, 28 of these were further assessed by array-comparative-genomic-hybridization, as well as whole exome- (WES), and RNA-sequencing. Serum/urine samples (n=8398) allowed modelling of plasma cell accumulation in AMM and MGUS, respectively

(n=322/196). RESULTS. Up-front tumor mass, plasma cell accumulation rate and molecular characteristics, including alterations in gene expression and presence of progression-associated chromosomal aberrations, i.e. t(4;14), deletions of 13q14, 17p13, 8p21, gains of 1q21, as well as hyperdiploidy, drive and predict progression of AMM. But for hyperdiploidy, the same factors drive progression from symptomatic to relapsed myeloma. This means that the mechanisms driving progression to symptomatic myeloma are (at least in part) the same driving progression under treatment. Molecularly, all chromosomal aberrations, most transcriptomic changes, and most frequent mutations detected in symptomatic myeloma including NRAS, KRAS, DIS3, HIST1H1E are already present in MGUS or AMM. In paired AMM/MM samples, 22/27 (81%) show a stable clonal pattern, 5/27 (19%) the de novo appearance of expressed clones, including KRAS or FAM46C. No significant transcriptomic differences are found by RNA-sequencing. (Sub-)Clonal complexity with 4-5 discernable clusters of 103-363 single nucleotide variants with an allele frequency of ≥10% remains fairly constant during disease progression with most being detectable in both AMM and MM, incompatible with clonal outgrowth to any reason in these patients. In CONCLUSION, progression of AMM is driven and can be well predicted by factors being present upfront, i.e. tumor mass, plasma cell accumulation rate, and the set of molecular alterations. Progression is in the vast majority of patients not driven by de novo acquired expressed clonal alterations. This is proven in our set of paired samples on the level of chromosomal numeric or structural alterations (as per iFISH and aCGH), expressed clonal single nucleotide variants (as per whole exome- and RNA-sequencing), and remaining subclonal complexity. This in turn disproves other de novo alterations (e.g. methylation), as the subclone harboring these would then need to become clonal.

OP-016
Neutral tumor evolution in myeloma is associated with poor response to therapy

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BACKGROUND Understanding the evolutionary history of a tumor is an important determinant of patient outcome. To gain insight into clonal dynamics of newly diagnosed multiple myeloma (MM), we studied whole exome sequencing data of 436 patients from the Myeloma XI trial. METHODS Tumor mutant allele frequency distributions were analysed using a novel approach (Williams, MJ, Nat Gen 2016) that discriminates whether clonal competition with changing dominance or neutral evolution with a stable sub-clonal structure characterised the clonal development up to diagnosis. RESULTS We demonstrate that a high proportion (19%) of MM tumors at diagnosis is under neutral evolutionary dynamics. We further characterised these tumors and their patient characteristics. Neutral evolution tumors were more likely to carry IGH translocations and gain of 1q21. Overall, 26.7% of t(4;14) and 29.4% of t(14;16) versus 16.7% of HRD cases were characterised by neutral evolution. Gain of 1q21 occurred in 34.2% of HRD cases and 24.6% of this group showed neutral evolution, compared to 12.9% in the HRD group without gain(1q). While overall, recurrent mutations occurred at a similar frequency in tumors with neutral and non-neutral architecture (58% vs. 55%), a number of key mutations were more frequently mutated in tumors with non-neutral clonal dynamics, including TP53 (10/10) and TRAF3 (13/14). Clincally, a significantly inferior response to

IMiD induction therapy was seen in patients with neutral MM (P<0.001). None of the patients whose tumors displayed neutral clonal dynamics reached a complete response (CR) as compared to 8.8% of patients with non-neutral tumors. Moreover, 11% of patients with neutral tumors had progressive disease or no response after induction treatment as compared to 5% for those with non-neutral tumors. High-dose melphalan and autologous transplant had a somewhat balancing effect with CR rates of 10% and 17% after transplant, respectively. In the non-intensive treatment arm of the trial, median survival for patients with neutroal evolution tumors was signficiantly shorter, with median PFS 13.4 (95% CI: 11.5-20.9) and 19.0 (95% CI: 15.9-23.7) months (P=0.020) and median OS of 36.1 (95% CI: 22.5-NA) and 49.6 (95% CI: 45.6-NA) months (P=0.021), respectively. In contrast, patients in receipt of intensive therapy had similar PFS and OS between neutral and non-neutral groups (P-values 0.98 and 0.8 respectively). CONCLUSION We demonstrate a high frequency of MM tumors with neutral clonal evolution dynamics. Neutral evolution is associated with reduced responsiveness to micro-environment-modulating IMiD therapy, which might indicate superior tumor cell 'fitness' with relative independence from microenvironment survival factors. Assaying for neutral evolution might improve our understanding of therapy resistance and help with improving therapy outcomes.

OP-017
The Presence of MDS-like Phenotypic Abnormalities (MDS-PA) Identifies Newly Diagnosed Multiple Myeloma (MM) Patients With MDS/AML-Related Somatic Mutations And Inferior Survival

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Long-term complications including SPMs such as MDS and AML are becoming new challenges in designing optimal patient care. Thus, there is need to investigate for biomarkers that uncover cellular alterations predisposing for higher risk of MDS/AML in MM. Here, we started by investigating in 312 newly diagnosed MM patients the presence of MDS-PA in BM neutrophil, monocytic, and erythroid lineages, using multidimensional flow cytometry. Up to 33/312 (11%) patients showed MDS-PA at diagnosis, which were observed in the neutrophil lineage (6%), followed by monocytic (4%) and erythroid (4%) lineages. Afterwards, we investigated if the presence of MDS-PA was associated with underlying somatic mutations (sSNV) by performing targeted sequencing of 54 MDS/AML related genes (depth ≥500x) in 44 patients from the previous series (10 with MDS-PA and 34 without). NGS was performed in FACS sorted CD34+ HSCs and dysplastic cell lineages from patients with MDS-PA, as well as in HSC from cases without MDS-PA. CD138+ BM PCs from both cohorts were also sequenced using the same panel. Six out of the 10 cases with MDS-PA showed sSNV. Namely, HSCs from one patient had two sSNV in TET2 one in CALR and another in ASXL1. A second patient had NPM1 mutated in HSCs. A third case had TET2 mutated in HSCs as well as in dysplastic monocytes and neutrophils. In the fourth case, a sSNV in BCORL1 was noted in dysplastic erythroid cells. The fifth patient had TET2 mutated in both HSCs and dysplastic monocytes. The sixth case had PHF6 mutated in HSCs. In none of the patients were the sSNV found in HSCs and/or dysplastic lineages, present in PCs. Within the control cohort of the 34 patients without MDS-PA, only two of them displayed sSNV in HSCs; one case had DNMT3A mutated and the other TET2. After

demonstrating a correlation between MDS-PA and MDS/AML-related sSNV, we sought to analyze its prognostic significance. Thus, we focused on a large series of 965 patients with longer follow up (median of 6.5 years) enrolled in GEM clinical trials, and for which the presence of CD56+ aberrant monocytes could be investigated. As compared to the overall MM population, patients with MDS-PA (n=63; 6.5%) showed significantly higher age, lower hemoglobin values and higher BMPC infiltration at diagnosis. Furthermore, they experienced more frequently hematological toxicity including anemia and neutropenia during treatment. Most interestingly, as compared to the overall MM population, patients with MDS-PA had significantly inferior PFS and OS. We showed for the first time that a fraction of MM patients harbors MDS/AML-related sSNV, and that such patients could be predicted through flow-based screening for MDS-PA. The presence of MDS-PA identifies a subset of patients that experience more frequently hematological toxicity and display inferior survival; accordingly, screening for MDS-PA could become an important biomarker to tailor treatment in MM.

OP-018

A more mature immunophenotypic make-up of Multiple Myeloma clone(s) at diagnosis correlates with a higher genomic instability

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The sequence of events underlying the Multiple Myeloma (MM) plasma cells (PC) differentiation have not yet fully elucidated, even if recent findings suggest that different cell subpopulations, with distinct phenotype, compose the MM clone(s), whose plasticity has emerged as a typical feature. Aim of the study was to evaluate the phenotypic plasticity and genomic background of MM clone(s) at diagnosis in order to stratify patients (pts) according to the PC differentiation stages and to evaluate the impact of this stratification on the disease outcome. Phenotypic characterization of both CD138+/CD38+ and CD19+ populations was carried out on 44 newly diagnosed MM. Fresh BM samples was analysed by 6-color multiparametric flow citometry analysis, combining CD138-PE, CD38-PE-Cy7, CD20-APC, CD19-APC-Cy7, CD27-FITC, CD45-FITC, CD28-APC, CD44-FITC, CD54-APC, CD81-PerCP-Cy5.5, CD56-APC and SHH-PE, as a functional marker of Hedgehog pathway activation. Cytoscan HD array were carried out in order to detect genomic copy number alterations (CNAs). According to the CD19 and CD81 markers co-expression, pts were stratified in 3 different subgroups, recapitulating a progressive PC maturation process: the most immature one, including pts with CD19+/CD81+ PC (11/44 = 25%); the intermediate CD19-/CD81+ phenotype one (19/44 = 43%), and the CD19-/CD81- PC one, whose clone was mainly composed by most mature PCs. The two extreme subgroups were characterized by a differential expression of maturation markers: the more mature PCs displayed a higher expression of CD28 and CD44, which usually characterized advanced disease stages, as well as a reduced expression of CD20, CD27 and CD45, commonly associated to preceding PC differentiation stages ($p<.05$). Any differential expression of SHH pathway's ligand was observed. On the contrary, a higher Hedgehog pathway activation was detected in the immature CD19+ compartment of pts with immature plasma cells (median SHH expression CD19+/CD81+ vs. CD19-/CD81-: 98,1% vs. 11,3%; $p<.05$), which probably highlighted a less quiescent immature reservoir pool. The CNAs analysis showed that mature PCs were characterized by a higher genomic instability, as compared to the more immature ones (total CNA: 306.9 vs. 171.5, p 0.08; genome changed: 36.96 vs. 13.55, p 0.01), including several alterations commonly

associated to worse prognosis (e.g. del17p). Finally, a higher frequency of baseline clinical characteristics associated to bad prognosis was observed in the more mature, as compared to the more immature subgroups of pts (e.g. n. PET lesions, k/l ratio; p<.05). In conclusion, MM clone(s) is a mixture of different cell populations endowed with an inner phenotypic plasticity. Various PC differentiation stages were appreciable already at diagnosis and genomic features associated to bad prognosis characterize pts carrying more mature clones. Acknowledgements: AIRC, Berlucchi, Fond.Veronesi.

OP-019
Evolutionary fitness of relapsed Multiple Myeloma patients who responded to upfront combination therapy including new drugs

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The early establishment of Multiple myeloma (MM) intra-tumor heterogeneity is probably leaded by the "Big Bang" model dynamics, followed by a Darwinian type evolution. In this context, therapy might represent a significant population bottleneck, in which different clones compete to relentlessly survive. Aim: to explore the existence of different evolutionary fitness of MM clone(s), eventually driven by therapeutic selective pressure. The study included 33 pts with symptomatic MM, up-front treated either with combination regimens including a proteasome inhibitor (28), or with cyclophosphamide. For each pts, paired BM samples were collected both at diagnosis and at relapse. SNPs array analyses were performed on the CD138+ enriched cell fractions and data were analyzed in order to obtain CNAs results. The genomic landscape's modulations were evaluated in details both by monitoring the variations of macro CNAs types and by focusing on changes of CNAs frequencies. Both approaches were consistent in highlighting three major evolution patterns: in 7/33 (21%) pts, the genomic background at relapse was almost identical to that of diagnosis. In 13/33 (39%) pts, an overall increase in the frequencies of the same CNAs as observed at diagnosis was detected at relapse. Finally, in 13/33 (39%) pts, either increased or decreased frequencies of several CNAs, as well as several differences in the CNAs type's prevalence were observed at relapse, as compared to diagnosis. Of interest, even if an overall CNAs median number increase was observed from diagnosis to relapse (226 vs 507, respectively) - supported by acquisition of CNAs either commonly described as secondary genomic events (i.e. del17p13, amp1q21, del1p23), or associated to the resistance to bortezomib (i.e. del8p21) - any peculiar CNAs resulted significantly prevalent in the 3 identified subgroups of pts. A high rate (92%) of achievement of VGPR or better quality of response to upfront therapy characterized the third subgroup of pts, whereas the rate of VGPR in the remaining pts was only 20% and PR or SD were observed in 9 and 7 pts, respectively. Finally, the median time to first progression of this subgroup of pts was significantly shorter as compared to that of pts with branching evolution (24 vs 35 months, range 4-41 and 7-123 months, respectively, p=0,01). The genomic architecture of a subgroup of relapsed MM pts, up-front responsive to new drugs-based combination therapies, resulted overall different from that of diagnosis, suggesting a branching evolution of the disease, sustained by the shrinking of the most prevalent clone (therapy-sensitive), as well as by the expansion of subclones (therapy-resistant) not already evident at diagnosis. This observation raises the question whether re-treatment of relapsed pts should be appropriate in the case of branching evolution. Acknowledgements: AIRC (MC), Fondazione Berlucchi (CT), FUV (EB).

OP-020
Glutamine deprivation-elicited sensitization of multiple myeloma to venetoclax is associated with electron transport chain inhibition.

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Cancer cells exhibit altered glucose and glutamine metabolism to sustain survival and proliferation. Altered nutrient utilization also contributes to the development of resistance to apoptosis via regulation of pro and anti-apoptotic BCL-2 family members. We previously reported that glutamine deprivation enhanced binding of BIM to BCL-2 thereby sensitizing myeloma cell lines and patient samples to Venetoclax (ABT-199). In this study we investigated the metabolites regulated by glutamine withdrawal that contribute to enhanced BIM-BCL-2 association and ABT-199 sensitivity. Metabolite profiling and isotope tracing flux analyses of glutamine deprived myeloma cell lines revealed specific reduction of TCA cycle metabolites including succinate, that were not maintained by glucose present in the medium. Cellular bioenergetics end points i.e. OCR and ATP were also suppressed upon glutamine withdrawal correlating with a suppression of the TCA cycle and oxidative phosphorylation. Supplementation of cell permeant dimethyl-α-ketoglutarate (DMK), a TCA cycle metabolite derived from glutaminolysis, to glutamine deprived cells reversed sensitivity to ABT-199. This ability of DMK to reverse ABT-199 sensitization in glutamine deprived cells was associated with a replenishment of TCA cycle intermediates without restoration of ATP levels. Therefore, we sought to further interrogate the TCA cycle and electron transport chain (ETC) in facilitating glutamine withdrawal-associated ABT-199 sensitization. TCA cycle metabolites are linked to mitochondrial respiration through ETC complexes. Inhibition of ETC complexes I, II, III or V in myeloma cell lines enforced similar effects as glutamine deprivation and sensitized cells to ABT-199. Among all five complexes, complex II is more explicitly linked with the TCA cycle through succinate dehydrogenase (SDH). SDH facilitates the oxidation of succinate to fumarate in the TCA cycle through its subunit SDHA, and transfers the released electrons to ubiquinone via its SDHB, C and D subunits supporting the ETC activity of complex II. Competitive inhibition of succinate dehydrogenase by 3-nitro propionic acid (3NPA) induced BIM expression and sensitized myeloma cells to ABT-199, similar to that detected upon glutamine deprivation. Our observations thus narrow down a role for ETC inhibition in facilitating ABT-199 sensitivity and underscore the importance of further interrogation of ways to metabolically perturb and sensitize cancer cells to the highly potent BH3 mimetic ABT-199.

OP-021
Integrative Network Analysis Identifies Novel Drivers of Pathogenesis and Progression in Newly Diagnosed Multiple Myeloma

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Multiple Myeloma (MM) is an incurable malignancy of plasma cells characterized by wide clinical and molecular heterogeneity. In this study we applied an integrative network biology approach to molecular and clinical data measured from 450 patients with newly diagnosed MM. A novel network model of myeloma (MMNet) was constructed, revealing complex molecular disease patterns and novel associations between clinical traits and genomic markers. Patterns of genomic alterations and gene co-expression correlating with disease stage, tumor clonality, and early progression were elucidated, and novel candidate drivers identified by prioritizing somatic mutations and copy number alterations based on their impact on gene expression. We validated CDC42BPA and CLEC11A as novel drivers of MMSET-related myeloma, and used MMNet to define a high-risk gene co-expression signature and identify new patient classes defined by network

features and genetic events. Our findings demonstrate the utility of integrative network approaches to improve disease understanding and patient stratification in myeloma.

OP-022

Oral selinexor shows single agent activity enhanced with PI or IMID combinations in refractory multiple myeloma (MM)

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Introduction: Selinexor (S) is an oral, first-in-class Selective Inhibitor of Nuclear Export compound that binds and inactivates Exportin 1 (XPO1). XPO1 inhibition forces the nuclear retention and reactivation of tumor suppressor proteins (p53, p21, I-κB, FOXO), and causes the reduction of many proto-oncogenes (MDM2, MYC, cyclin). S has shown broad single-agent anti-tumor activity and synergy with many existing therapies. S with low-dose dexamethasone (Sd) demonstrated a 27% ORR in phase (Ph) 1 studies in MM. Based on this, the STORM trial was initiated with Sd in patients (pts) with QUAD (2 PIs and 2 IMiDs) and PENTA (QUAD + anti-CD38 mAb) refractory MM. Methods: We summarize the results of three Ph 1b/2 studies that provide the rationale for the Ph 2 STORM trial and the randomized Ph 3 BOSTON trial. Results: Part one of the Ph 2 STORM trial, MM Pts were treated twice weekly (BIW) with oral S 80 mg per 28 day cycle and dex 20 mg BIW. The primary objective was overall response rate (ORR) and duration of response (DOR), both by an independent review committee (IRC). 79 pts were enrolled with a median of 7 prior treatment regimens (PTR). 48 pts with QUAD and 31 with PENTA refractory MM. Common G 1/2 adverse events (AEs) were: nausea, anorexia, fatigue, and vomiting. G 3/4 AEs were:

thrombocytopenia and anemia. The IRC-determined ORR (≥PR) was 21%. Median OS was 9.3 mos for all pts, median not reached (>11 mos) for pts with ≥MR. Median DOR was 5 mos. The STOMP phase 1b/2 study was used to determine the recommended phase 2 dose (RP2D) for Sd + bortezomib (SVd), Sd + lenalidomide and Sd + pomalidomide. In the SVd escalation arms, 22 pts were enrolled, with a median of 4 PTR (73% refractory to prior PI). G 3/4 AEs include: thrombocytopenia, anemia, and neutropenia. The ORR was 77%. Based on tolerability and anti-MM activity, RP2D of SVd is S 100 mg QW, bort 1.3 mg/m2 QW for 4 of every 5 weeks, and dex 40 mg QW and this will be used in the BOSTON study. In the SPd cohorts, with 5 PTR and 15 evaluable pts, the ORR was 60%. Tolerability was similar to single agents. Another Ph 1b/2 trial has established the MTD and activity of a Sd + carfil in pts with MM refractory to prior carfil regimens. 21 pts were enrolled with a median of 4 PTR.. G 3/4 AEs were: thrombocytopenia lymphopenia, and neutropenia. The ORR was 63% Conclusions: Oral Sd is active in heavily pretreated pts with refractory MM, including those with MM refractory to anti-CD38 Ab. Based on the activity observed, an expansion of the STORM trial has been initiated at sites across the US and EU to enroll an additional 122 pts with PENTA refractory MM. Sd in combination with other anti-MM agents is generally well tolerated and highly active in refractory MM, and toxicities are manageable and typically less than the individual monotherapies. The Ph 3 BOSTON trial comparing SVd vs Vd will enroll 360 pts with MM following 1-3 PTR.

OP-023

A Multicenter, Open-Label, Phase 1b Study of Carfilzomib, Cyclophosphamide, and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients (CHAMPION-2)

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Introduction: Carfilzomib is a selective and irreversible second-generation proteasome inhibitor. The CHAMPION-2 study evaluated different dose levels of carfilzomib in combination with fixed-dose cyclophosphamide and dexamethasone (KCyd) for the treatment of newly diagnosed multiple myeloma (MM). Patients and Methods: This was a multicenter, single-arm, open-label, phase 1b study that enrolled patients with newly diagnosed symptomatic MM. Patients were allowed regardless of transplant eligibility status, but autologous hematopoietic stem cell transplantation while on the study was not permitted. Treatment was given in 28-day cycles and continued for eight cycles or until unacceptable toxicity, withdrawal of consent, or progressive disease. A traditional 3 + 3 design was used, with carfilzomib evaluated at 36, 45, and 56 mg/m2, followed by a dose-expansion cohort. Carfilzomib (30-minute infusion) was administered on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (beginning with 20 mg/m2 on days 1 and 2 of cycle 1). In each cycle, cyclophosphamide (oral, 300 mg/m2) was administered on days 1, 8, and 15, and dexamethasone (oral or intravenous, 40 mg) was administered on days 1, 8, 15, and 22. Results: No dose-limiting toxicities were observed at any of the dose levels evaluated, and the maximum planned dose of 56 mg/m2 was brought forward into dose expansion. A combined total of 16 patients (median age, 65 years; range, 49–81 years) received carfilzomib at 56 mg/m2. At 56 mg/m2, the overall response rate was 87.5% (95% confidence interval [CI], 61.7%–98.4%). Best overall responses at 56 mg/m2 were complete response (n = 1), very good partial response (n = 7), and partial response (n = 6). The median time to response for patients who received the 56 mg/m2 dose was 1 month. At 56 mg/m2, grade 3 or higher adverse events included anemia (25.0%), neutropenia (18.8%), acute kidney injury (12.5%), and decreased white blood cell count (12.5%). Peripheral neuropathy (grade 1) was reported for 1 patient treated with the 56 mg/m2 dose. In total, 10 of the 16 patients who received carfilzomib at 56 mg/m2 completed all eight cycles of the study treatment; 5 patients withdrew or discontinued treatment due to adverse events; and 1 patient discontinued due to progressive disease. No deaths occurred during the study in the 36 or 56 mg/m2 cohorts, and 1 patient died in the 45 mg/m2 cohort due to sudden cardiac arrest. Conclusions: Carfilzomib (56 mg/m2) twice weekly combined with cyclophosphamide and dexamethasone had manageable toxicity and was effective for treating patients with newly diagnosed MM.

OP-024
Phase 1b Study of Daratumumab plus Pomalidomide and Dexamethasone in Relapsed and/or Refractory Multiple Myeloma (RRMM) with ≥2 Prior Lines of Therapy

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Introduction: Daratumumab (DARA), a CD38-targeting human monoclonal antibody, is approved as monotherapy and in combination with lenalidomide (LEN) + dexamethasone (D) or bortezomib (BORT)+D in relapsed patients (pts) with RR MM. A multi-arm, phase 1b study (NCT01998971) evaluated DARA + backbone therapies; data from the DARA + pomalidomide and D (DARA+POM-D) arm are presented. Methods: Pts in the DARA+POM-D arm had RRMM, an absolute neutrophil count of ≥1×109/L, ≥2 prior lines of therapy including ≥2 consecutive cycles of LEN and BORT, and were refractory to their last therapy. 28-day cycles comprised DARA 16 mg/kg at the recommended dosing schedule until progression; POM 4 mg daily for 21 days; and D 40 mg weekly. Safety was the primary endpoint. Overall response rate (ORR) and minimal residual disease (MRD) by next generation sequencing were secondary endpoints. An independent data safety monitoring board evaluated response. Results: 103 pts received ≥1 dose of DARA+POM-D. Median (range) age was 64.0 (35-86) years. Median number of prior therapies was 4 (1-13) and 52% of pts had received >3 prior therapies; 89%, 71%, 30%, and 71% of pts were refractory to LEN, BORT, carfilzomib, and a proteasome inhibitor + immunomodulatory drug, respectively. Of the 87 pts with cytogenetic data, 25% were high risk (del17p, t[4;14], or t[14;16]). At a median follow-up of 9.8 (0.2-22.3) months, 57% of pts discontinued treatment: progressive disease (33%), adverse events (AEs; 14%), pt withdrawal or physician's decision (4% each), and death (2%). Median number of DARA infusions was 14 (1-28). Other than DARA-specific infusion related reactions (IRRs), which occurred in 50% of pts (largely during the first infusion), and a higher incidence of neutropenia, the safety profile of DARA+POM-D was similar to that of POM-D. Common grade ≥3 AEs were neutropenia (77%; febrile neutropenia [7%]), anemia (27%), and leukopenia (24%). Among pts with grade ≥3 neutropenia, 63% received growth factors. Five (5%) pts died due to treatment-emergent AEs. ORR was 59% (8% stringent complete responses, 6% complete responses [CR], 28% very good partial responses, and 18% partial

responses) and was generally consistent across subgroups. Median time to best response was 2.1 (0.9-9.9) months. Among pts with ≥CR, 29% were MRD–ve at a threshold of 10–5. Among responders (n=61), median duration of response was 13.6 (10.0-not estimable [NE]) months. Median PFS was 10.4 (4.6-NE) months; 12-month PFS rate was 45% (95%CI, 32.5-55.9). Median overall survival was not reached. The estimated 12-month survival rate was 72% (95%CI, 60.8-80.9). Updated data will be presented. Conclusions: With the exception of a higher incidence of neutropenia, adding DARA to POM-D resulted in a safety profile consistent with that of the individual therapies. Deep, durable responses were observed overall and across subgroups.

OP-025
ANALYSIS OF THE AVAILABILITY OF ANTI-MYELOMA DRUGS AND IMPACT ON THE CURRENT MANAGEMENT OF MYELOMA IN LATIN AMERICAN COUNTRIES

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Latin American countries (LATAMC) represents a large fraction of Multiple Myeloma (MM) treated patients worldwide. However, there is scanty data regarding the use of the main MM drugs and clinical practices in these nations. We aimed to investigate in each country: I- The influence of different health system models (public and private) in drug access and treatment in MM eligible and frail setting. We collected data by a web questionnaires sent for MM treating physicians from 17 countries during 2014 until 2015. In spite of heterogeneity among nations and regions of the same country, clearly, most LATAMC (92%) had mixed public and private practices, and the majority of MM pts were cared in public institutions (88%,n=14). At 2015 the scenario of new agents approval by local regulatory boards were: total for Thalidomide (Thal) and Bortezomib (Btz) but only partially for Lenalidomide (Len) and rarely or not yet authorized for market to Carfilzomib (Cfz) and Pomalidomide (Pom). Moreover, taking as a baseline the FDA approval of Btz in 2003 and Len in 2005 the mean time of these drugs to be authorized were 3.6(1-7) years for the former and 4.4(3-7) years for the latter. Even though, Btz and Len were legal in 100% and 73% in LATAMC, this figures did not translated for most of MM patients and great disparities were observed between public (governments health care) and private (health insurance companies). For instance, a comparison in drug access between the systems showed that less than 50% of the countries had the same drugs in both public and private systems (ej.Thal, Btz and Len). Conversely, oral Alkilating agents (Alk) represented by melphalan (Mel) and cyclophosphamide were not available commercially in 25%, n=4 in both health systems. In turn, venous Mel, an essential and

unique drug for MM auto-transplant program, was absent in 44%, n=7 in public but with some replenishment in private services 27%, n=4. The presence of generic drugs among LATAMC was: Thal 81%; BTZ 75%, Len 40% , none for Cfz and Pom. Interestingly, each drug insertion had distinct profile such as: Thal freely supplied by the governments (ej. leprosy programs), BTZ was marketed and rarely generic in 50%, whereas Len was marketed but was used frequently as a generic in 34%. Thus, the best approach as first line treatment for old and young pts in public hematology was Thal and Alk as backbone (ej. MPT, 54% and CTD, 42%). In contrast in private, were Btz-based triplets (ej. BtzMP, 74% and Btz-CD, 90%). Additionally we estimated that 26% of old pts and 34% of young ones were receiving suboptimal regimens (ej. VAD and TD) or have not been transplanted in public services. Our data indicates that to achieve the standard of care in MM, LATAMC will need to: adjust disparities between health systems, accelerate incorporation of essential new drugs, (balancing cost and effectiveness) and finally reestablish the commerce of old drugs.

OP-026
A Phase 1b Study of Venetoclax Combined with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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Background: Venetoclax (VEN) is a potent, selective, orally bioavailable small-molecular inhibitor of BCL-2. When combined, VEN can enhance the activity of bortezomib in multiple myeloma (MM) cell lines and xenograft models. Methods: Phase 1b study of patients (pts) with relapsed/refractory (R/R) MM who received daily VEN (50–1200 mg for dose escalation cohorts; 800 mg in safety expansion) with standard bortezomib (1.3 mg/m2 SC) and dexamethasone (20 mg PO). Results: As of 19Aug2016, 66 pts were enrolled. Median age was 64 years; 9 (14%) pts had t(11;14), 5 (8%) had t(4;14), 15 (23%) had del(17p), and 30 (45%) had del(13q) abnormalities. Median number of prior therapies was 3 (range: 1–13), with 39% of pts refractory to prior bortezomib, 14% to carfilzomib, 53% to lenalidomide, and 21% to pomalidomide. Median time on study was 5.9 months (range: 0.3–29.8). Forty-six (70%) pts discontinued, with 36 due to disease progression (PD). Common AEs in ≥30% of pts were diarrhea (46%), constipation (41%), thrombocytopenia (39%), nausea (38%), peripheral neuropathy (33%), and insomnia (32%). Common grade 3/4 AEs in ≥10% of pts were thrombocytopenia (29%), anemia (15%) and neutropenia (14%). Serious AEs in ≥2 pts were febrile neutropenia, thrombocytopenia, cardiac failure, pyrexia, influenza, lower respiratory tract infection, pneumonia, sepsis, acute kidney injury, respiratory failure, embolism, and hypotension. Dose-limiting toxicities were grade 3 cardiac failure in the 300mg cohort (possibly related to dexamethasone) and grade 3 thrombocytopenia during the first cycle in the safety expansion. No events of laboratory or clinical TLS were reported. Four deaths were due to PD and 1 due to respiratory syncytial virus infection. Overall response rate (ORR) for all pts was 67% (44/66); 28 (42%) pts achieved very good partial response (VGPR) or better (3 stringent complete response [sCR], 10 CR, 15 VGPR). Pts non-refractory to prior proteasome inhibitors (PI) or immunomodulatory drugs (IMiDs) had higher ORR than refractory pts (PI, 92% vs 32%; IMiDs, 82% vs 57%). Among pts refractory to any 2 or more (n=15), 3 or more (n=7), or all 4 (n=4) prior therapies (bortezomib, carfilzomib,

lenalidomide, pomalidomide), ORR was 40%, 43%, and 25%, respectively. Median time to progression (~10 vs 3 months) and duration of response (~10 vs 7 months) were longer for pts not refractory to any of these therapies versus refractory pts. ORR for pts with or without cytogenetic abnormalities, respectively, was as follows: 78% vs 65% for t(11;14), 60% vs 67% for t(4;14), 47% vs 73% for del(17p), and 63% vs 69% for del(13q). Conclusions: VEN combined with bortezomib and dexamethasone has an acceptable safety profile with promising anti-myeloma activity, and the highest response rates were observed in R/R MM pts who were not refractory to PI or IMiDs. These data support the ongoing phase 3 trial with this regimen in R/R MM.

OP-027
Preliminary Results From a Phase Ib Study of Isatuximab in Combination with Pomalidomide (Pom) and Dexamethasone (Dex) in Relapsed and Refractory Multiple Myeloma (RRMM)

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Background: Isatuximab (ISA) is an anti-CD38 monoclonal antibody with multiple modes of action for killing tumor cells. In preclinical studies, Pom enhanced both the direct and indirect anti-tumor activity of ISA to a greater degree than lenalidomide (Len) (Jiang et al. Leukemia 2016). Here, we report preliminary

results of an ongoing Phase Ib dose-escalation study of ISA plus Pom and Dex in patients (pts) with RRMM (NCT02283775). Methods: Pts with RRMM (≥2 prior MM therapies, including Len & a proteasome inhibitor) with adequate bone marrow reserve/organ function were sequentially enrolled to ISA 5, 10, or 20 mg/kg (QW × 4 doses, then Q2W until disease progression or intolerable toxicity) plus Pom 4 mg (days [D] 1–21) and Dex 40 mg (D1, 8, 15, & 22; 20 mg if ≥75 yrs old), in 28-day cycles. Primary objective: determine MTD or recommended dose, based on occurrence of treatment-related DLTs. Secondary objectives included evaluation of efficacy (IMWG criteria), safety, & pharmacokinetics (PK). Results: At data cutoff (Aug 15, 2016) 20 pts had been treated: 5 mg/kg (n=8); 10 mg/kg (n=6); 20 mg/kg (n=6). Overall median age was 65.5 (42–77) yrs. Median number of prior regimens was 4.5 (3–11); prior carfilzomib in 50% of pts. 15 (75%) pts had received ≥1 prior stem cell transplant. Median duration of dosing was 33.6 (3–50), 19.1 (17–23), and 9.1 (3–12) wks in the 5, 10, and 20 mg/kg cohorts, respectively, with the latter cohort also having the shortest follow-up. 8 pts discontinued treatment, with 5 cases due to progressive disease. 1 pt discontinued treatment due to a TEAE (perforated bowel, leading to death [10 mg/kg]; not related to treatment, attributed to intestinal plasmacytoma). Three DLTs were reported: prolonged Grade (Gr) 4 neutropenia (5 mg/kg); Gr 4 neutropenic infection (10 mg/kg); and Gr 3 confusional state (20 mg/kg); DLTs resolved with Pom dose delay/reduction. MTD has not been reached. Gr 3/4 TEAEs were reported in 17 (85%) pts. The most frequent TEAEs, excluding infusion associated reactions (IARs) and laboratory abnormalities, were fatigue (70%), dyspnea (35%), & URTI (30%). IARs occurred in 9/20 pts; all Gr 1/2 and 8/11 IAR events occurred during the 1st infusion. The most common Gr 3/4 hematologic abnormality was neutropenia (90%). Gr 3/4 thrombocytopenia reported in 8 (40%) pts. Pts in the 5 and 10 mg/kg cohorts were evaluable for confirmed response: 9/14 (64%) achieved at least partial response (PR) and 10/14 (71%) at least minimal response (MR) (1 complete response, 4 very good PR, 4 PR, 1 MR). 7 pts

continued to respond without confirmed disease progression at data cutoff. PK parameters of ISA were unaffected by co-administration with Pom/Dex. Conclusions: These preliminary data suggest ISA plus Pom/Dex is generally well tolerated and clinically active in pts with heavily pretreated RRMM. A Phase III trial to evaluate this combination has been initiated. Funding: Sanofi Genzyme

OP-028
Depth of Response and MRD with Daratumumab Plus Lenalidomide and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in RRMM: POLLUX

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Introduction: Daratumumab is a human CD38 IgGκ monoclonal antibody that significantly improves clinical benefit associated with established standard of care regimens. The aim of this study was to further evaluate the depth of responses observed among treated patients in POLLUX. Methods: All patients received ≥1 prior line of therapy and received Rd (lenalidomide 25 mg PO on Days 1-21; dexamethasone 40 mg PO weekly) with or without daratumumab (16 mg/kg IV once weekly for 8 weeks, every 2 weeks for 16 weeks, then every 4 weeks until progression). Patients refractory to lenalidomide were ineligible. High cytogenetic risk (determined using next generation sequencing) was defined as having any of t(4;14), t(14;16), or del17p abnormalities. Minimal residual disease (MRD) status was determined with bone marrow aspirates that were ficolled using next generation sequencing (ClonoSEQ™) at 3 sensitivity thresholds (10^{-4} to 10^{-6}), and were assessed in patients with suspected complete response (CR) and at 3- and 6-months after achieving CR. Progression-free survival (PFS) was the primary endpoint. Results: Median (range) number of prior lines of therapy was 1 (1-11). After median 17.3 months of follow-up, DRd demonstrated significantly prolonged PFS vs Rd (median not reached [NR] vs 17.5 mo; HR, 0.37; 95% CI, 0.28-0.50; P<0.0001). Overall response rates (ORR) were higher with DRd vs Rd (93% vs 76%), with significantly higher rates of very good partial response or better (78% vs 45%) and CR or better (46% vs 20%), respectively (all P<0.0001). Likewise, more patients achieved deeper responses with DRd vs Rd (MRD-negative rates: 32% vs 9% at 10^{-4}; 25% vs 6% at 10^{-5}; 12% vs 3% at 10^{-6}; all P<0.0001). Among MRD-negative patients, patients receiving DRd reached MRD negativity earlier vs those receiving Rd, and most patients maintained MRD negativity over time. Compared with MRD-positive patients, MRD-negative patients showed longer PFS across all sensitivity thresholds. In patients with high-risk cytogenetic status, ORR (85% vs 67%; P=0.14) and MRD-negative rates (18% vs 0% at 10^{-5}; P=0.0027) were higher with DRd vs Rd; no MRD-negative, high-risk patients progressed. In standard-risk patients, patients receiving DRd demonstrated significantly higher ORR (95% vs 82%; P=0.0020) and MRD-negative rates (30% vs 10% at 10^{-5}; P<0.0001) vs Rd. Individual case studies of patients who achieved MRD negativity will be presented at the meeting. Conclusions: MRD negativity was observed in ≥3 times as many patients receiving DRd vs Rd, and these deeper responses were both rapid and durable. No MRD-negative, high-risk patients progressed during the study. MRD-negative patients achieved prolonged PFS compared with MRD-positive patients. Deeper responses associated with DRd may provide long-term clinical benefit.

OP-029
Next Generation Sequencing Based Revised International Staging System (R-ISS) for Multiple Myeloma

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Background: The Revised International Staging system (R-ISS) combines ISS stage with serum lactate dehydrogenase (LDH) and chromosomal abnormalities (CAs) to assess prognosis. We hypothesized that utilizing sequencing-based FISH (Seq-FISH) rather than clinical FISH assays for detection of CAs (R-ISS-NGS) would improve prognostic value as Seq-FISH has similar specificity and greater sensitivity (Miller, et al, Abstract 374, ASH 2016). Methods: Data was extracted from the open-access MMRF Researcher Gateway corresponding with interim analysis 9 from the CoMMpass study. All sequencing was performed by the Translational Genomics Research Institute (TGEN). CAs were identified using custom Seq-FISH software on long-insert whole genome sequencing data. R-ISS stage was calculated as: stage I (ISS stage I, no high-risk CA, and normal LDH); stage III (ISS stage III with high-risk CAs and/or high LDH levels);

stage II others. High risk CA were defined as the presence of Del(17p), t(4;14) or (4;16). High LDH was defined as LDH >300units/L. Multivariate Cox regression analysis was used to compare event-free survival (EFS), defined as the interval from diagnosis to disease progression or death, controlling for age (>65 vs <65 years) and sex. Results: 995 patients were present in the dataset of which 657 had data to calculate R-ISS, and 534 to calculate R-ISS-NGS. The median age was 64 years old at MM diagnosis (range 27-93) and 54% were male. 24% (196/806) of patients had high-risk CAs by clinical FISH, 26% (172/654) by Seq-FISH. 12% (85/738) of patients had high-LDH.. R-ISS-NGS staging was more predictive than R-ISS with clinical FISH. R-ISS-NGS Stage II and III patients had a 134% and 482% increase in hazard ratio for progression or death (aHR 2.34 [95% CI 1.31-4.18], p = 0.004; aHR 5.82 [95% CI 3.12-10.86], p < 0.001), respectively, compared to Stage I. R-ISS Stage II and III patients as determined by clinical FISH had a 80% and 343% increase in hazard ratio for progression or death (aHR 1.80 [95% CI 1.16-2.80], p = 0.009; aHR 4.43 [95% CI 2.66-7.38], p < 0.0001), respectively, compared to Stage I. Conclusion: Seq-FISH was more sensitive in detecting CAs than clinical FISH which led to a more accurate prognosis. A single Seq-FISH assay is sufficient to investigate all translocations; with clinical FISH, each translocation requires a separate analysis and inconsistent probe selection results in lower CA detection rates. Also, the false-negative rate of clinical FISH is higher as many clinical FISH labs do not perform plasma cell selection prior to testing. Seq-FISH is a promising new method for CA detection and should be evaluated further.

OP-030
Going off the "Gold-Standard": Replacing Electrophoretic Methods with Mass Spectrometry for Plasma Cell Disorders

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Background: At our institution, protein electrophoretic (PEL) methods have been the mainstay for detecting and monitoring plasma cells disorders (PCD) since 1967. Although widely accepted by hematologist, these electrophoretic methods remain labor intensive and recent developments in treatments for PCDs are pushing electrophoresis to its analytical limits. Our group has recently published a series of articles describing clinically viable methods for M-protein detection and characterization based on mass spectrometry. Two variations of this technology have emerged: a MALDI-TOF MS method (MASS-FIX) and a LC-ESI-Triple TOF MS method (miRAMM) and are currently starting validation in our laboratory. The two methods share the same pre-analytical immunoglobulin purification but differ in their turnaround time, instrument cost, sensitivity and resolution. Proposal: MASS-FIX in combination with appropriate reflex testing to miRAMM can replace and extend our current capabilities for detecting and monitoring patients with PCD. Results: As a PCD screening tool, a serum MASS-FIX applied to 182 samples submitted for routine M-protein detection revealed that serum MASS-FIX had an analytical sensitivity equivalent to a panel of serum PEL, serum imunofixation and the Hevylite assay. In a clinical sensitivity study, MASS-FIX in combination with serum FLC or urine MASS-FIX had equal sensitivity to current IMWG recommended panels. These features, along with the rapid analysis speed (<1 minute per patient) with fully automatable workflows, urine testing without pre-concentration, allow MASS-FIX to be cost competitive to current technologies. Unlike electrophoretic methods, the use of MS allows for the detection of post translation modifications which also may provide useful information. Repetitive M-protein mass measurements using miRAMM have demonstrated that M-protein light chains can be resolved to +/- 2 Da. Therefore, t-mAbs can easily be resolved from M-Proteins as long as their masses differ by 2 Da. In spiking experiments miRAMM was demonstrated to be

10 to 100 times more sensitive than IFE. In a study of 22 MM patients who were in determined to be in complete remission, miRAMM was able to detect residual M-protein (MRD) in 63% of these patients. Since miRAMM can be run from serum in lieu of bone marrow, serial monitoring of CR patients can be easily performed detecting possible early relapse or continued response. Using data from our lab on current IFE test results and patient history, MASS-FIX will be able to provide informative data on greater than > 95% of samples submitted for testing. The remaining samples for questions on MRD or t-mAB interference could be reflexed directly to miRAMM for further testing.

OP-31
SLAM family member "CD229": a novel gating marker for plasma cells in flow cytometric immunophenotyping (FCI) of multiple myeloma (MM)

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Introduction: Flow-cytometric Immunophenotypic (FCI) characterization of plasma cells (PCs) in multiple myeloma (MM) is solely based on gating of PCs using CD138 and CD38. However, variable loss of CD138 and decreased-expression of CD38 is well-known in clonal-PCs, especially in relapsed or resistant cases. Additionally, CD138 is known for lower stability at low temperature. Hence, there is a need of a reliable and stable marker in FCI-panel of MM. CD229 is shown to have strong expression in myeloma cell-lines. Hence, we investigated the expression-pattern of CD229 in normal and clonal PCs and its role as gating marker in FCI of MM. Methods: We analyzed expression-pattern of CD229 in clonal-PCs in bone marrow (BM) from 227 newly-diagnosed MM and in normal-PCs from 64

control samples (uninvolved staging BM). FCI characterization was performed on Navios instrument and data was analyzed using Kaluza-v1.3-software. We further compared the expression-pattern of CD229 with CD138 and CD38. Results: Mean, median, standard deviation (SD) of mean fluorescent intensity (MFI) of CD229 on normal and clonal PCs was 15.0, 17.1, 11.1 and 19.7, 15.4, 12.9 respectively. CD229 showed over-expression in clonal-PCs (p=0.04) of MM. Expression-patterns and mean, median, SD of MFI of CD229, CD138 and CD38 is given in Table 1. Ratio of SD-MFI to mean MFI in clonal-PCs (an indicator of the level of heterogeneity in antibody expression) was very high for CD138 (1.34) as compared to CD229 (0.74) and CD38 (0.66). Thus, CD138 was found to be highly variable marker and CD229 and CD38 revealed stable markers with homogenous expression. Conclusion: CD229 is stable immunophenotypic marker with strong and homogenous expression in PCs. However, CD138 is highly variable markers with almost one-third of cases with weak expression. Hence, CD229 is a better gating marker in flow-cytometric diagnosis and MRD analysis in MM, especially for anti-CD38-based clinical-trials. Table -1 Characteristics of markers in clonal PCs of MM CD229 CD138 CD38 Geometric Mean fluorochrome Intensity (MFI) Mean 15.10 43.34 52.5 Median 17.13 23.59 46.7 SD 11.13 55.96 34.89 CV% 74 134 66 Expression-pattern of the markers in % of MM cases Weak 12.2 30.3 23.5 Intermediate 80.5 54.5 29.8 Strong 7.3 15.2 46.7

OP-032
Changes in Serum B-Cell Maturation Antigen Levels are a Rapid and Reliable Indicator of Treatment Efficacy for Patients with Multiple Myeloma

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Introduction: B-cell maturation antigen (BCMA) is found on the surface of plasma cells. Compared with healthy subjects (HS), multiple myeloma (MM) patients (pts) show higher serum (s) BCMA levels, and these can be used as a prognostic indicator and monitoring tool. We compared changes in levels of sBCMA to sM-protein (M-Pro) and sfree light chain (FLC) among all MM pts receiving new treatments (Txs). Methods: sBCMA, sM-Pro and sFLC levels were collected from all MM pts starting new therapy at a single clinic from March 2015 to November 2016. Blood samples were obtained at least weekly during their first cycle of new therapy (C1) and once monthly during subsequent Tx cycles. Percentage changes in sBCMA, sFLC and sM Pro levels during treatment were determined relative to the level obtained at baseline (C1D1). Results: Thirty-seven MM pts receiving a total of 42 new Tx regimens (IgG [n=27], IgA [n=6], light chain only [n=4]), were studied. Sixty-six percent (25/38) of eligible pts showed evaluable levels of sM-Pro, and 55% (23/42) had evaluable levels of sFLC using IMWG criteria. Evaluation of sBCMA was determined using an optimized threshold set at 65.9 ng/mL from a ROC curve. Levels above the cutoff could be differentiated from age-matched HS (sensitivity 88%, specificity 95%, AUC: 0.91) for 88% (37/42) of pts. For 19 pts, sFLC data was collected along with sM Pro and sBCMA during C1. In 10/19 (53%) of these cases, the sFLC levels showed large, discordant variability (changes >25%) differing from the results of both the sBCMA and sM-Pro levels drawn simultaneously. sBCMA levels changed more quickly during the remainder of C1 than sM protein for all response groups (Best response PD [n=2]: +60% [range 55%-65%] vs sM-Pro: +19% [range 3%-36%; MR [n=4]: -45% [range 38%-56%] vs sM-pro: -17% [range 3%-29%]; Best response ≥PR [n=14]: -69% [range 18%-91%] vs sM-pro: -33% [range, -58%-3%]) and showed a median change of -27% (range, 4%-58%) vs sM-Pro -6% (range -57%-15%) in the first week for all pts who responded to therapy (n=18) and -3% (range -69%-64%) vs sM-Pro +3% (range -

24%-34%) for non-responders (n=24). Among pts who achieved SD during C1, mid cycle changes in the levels of sBCMA resulting in >30% increases relative to the sample obtained one week prior (n=5) correctly predicted disease progression during subsequent cycles. Conclusions: We have shown that sBCMA levels change more quickly than conventional sM Pro levels and more reliably than sFLC levels among MM pts receiving any new treatment. Specifically, changes in sBCMA levels >30% predict disease progression. Thus, frequent assessment of serum BCMA levels during the first cycle of any new treatment may be helpful to make more rapid decisions determining the efficacy of a new MM therapy.

OP-033
Natural history of t(11;14) multiple myeloma

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Introduction: Presence of t(11;14) in interphase fluorescent in-situ hybridization (iFISH) on bone marrow plasma cells is seen in about 15% patients of multiple myeloma (MM) at diagnosis. t(11;14) is regarded as a standard risk cytogenetic marker for prognosis in MM. We examined the long term outcomes of MM with t(11;14) seen at our institution between 2004 and 2014. Methods: We retrospectively identified 366 patients with MM who had t(11;14) demonstrable in bone marrow samples by iFISH done before or within one year of starting treatment for MM. Their clinical records were reviewed and outcomes analyzed with respect to time to first progression or death (PFS1), time to second progression or death in

patients receiving second line therapy (PFS2) and overall survival (OS). The study was approved by institutional review board. Results: The median age at diagnosis was 63.7 years (range, 22.1-95.4) with 64.5% of patients being male. Eighty nine (24.3%) patients were above 70 years of age at diagnosis. Bone disease at diagnosis was present in 70.5% patients. 33.8%, 40.3% and 25.9% patients belonged to ISS 1, II and III stages respectively. 13% patients had elevated LDH. mSMART high risk cytogenetic abnormalities (del 17p or monosomy 17) were identified in 10.6% patients. The median follow up period was 3.8 years (95% CI, 0.5-9.8and 209 (57.1%) patients were alive at last follow-up. Among patients receiving proteasome inhibitor (PI)-based, immunomodulator (IMiD)-based, PI+IMiD based or other agent based induction therapy, 71.2%, 70.3%, 90.4% and 37.5% patients respectively attained ≥PR as best response to induction (p<0.0001). During their course, 223 (60.9%) patients underwent stem cell transplant. Median PFS1, PFS2 and OS were 2.0 (95% CI, 1.8-2.3,), 4.0 (95% CI, 3.3-4.4,) and 6.5 (95% CI, 5.5-8.8,) years respectively. At 5 and 10 years from diagnosis, estimated 59.5% and 32.3% patients were surviving respectively. In a Cox-proportional hazards model with age >70 years, male gender, induction therapy type (novel agent-based vs others), presence of high risk cytogenetics, and ISS stage as baseline predictor variables, age>70 years [HR-2.27 (95%CI=1.55-3.29) and p<0.0001], high risk cytogenetics [HR-2.38 (95% CI=1.43-2.95) and p=0.0012], ISS III vs ISS II [HR-1.80 (95%CI=1.11-2.95) and p=0.0168]and ISS II vs ISS I [HR-1.71 (95%CI=1.10-2.71) and p=0.0162] were associated with reduced survival. There was no difference in OS between those patients who started treatment before, or in 2010 and later. Conclusion: Our study characterizes the outcomes of a large cohort of MM patients with t(11;14) at diagnosis. Advanced age, high risk cytogenetic abnormalities and advanced stage at diagnosis were associated with worse OS.

OP-034
Treatment Patterns from 2009-2015 in

Patients With Newly Diagnosed Multiple Myeloma in the United States: A Report From the Connect® MM Registry

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Introduction: From 2009-2015, use of novel therapies (immunomodulators and proteasome inhibitors) in multiple myeloma (MM) increased. Regimens initiated during this time may help project near-term future treatment patterns. Connect® MM is the first and largest prospective, observational, US-based, multicenter disease registry designed to characterize treatment patterns and outcomes for patients (pts) with newly diagnosed (ND) MM. Study sites represented all census regions, allowing a reasonable generalizability to patterns for the US. Methods: Enrollment was initiated in Sep 2009 at 250 community and academic sites. Pts were enrolled within 2 months of diagnosis. Cohort 1 enrolled 1493 NDMM pts from Sep 2009 to Dec 2011; Cohort 2 enrolled 1518 NDMM pts from Dec 2012 to Apr 2016. Data were collected at baseline and quarterly visits until death or discontinuation. This analysis was conducted for all treated pts (N=2848) as of May 2016. Choice of first-line, maintenance, and second-line treatment was analyzed in 6-month intervals. Trends will be visually represented in a novel way ("Tepee" plots). Results: Median (range) follow-up for all pts was 39.3 mo (0.03-78.4 mo) in Cohort 1 and

15.4 mo (0.2-40.1 mo) in Cohort 2. For treated pts, the median age was 67 y (range, 24-94 y), 58% were male, 83% were white, and 38% of those reporting ISS stage had stage III MM. By US region, 329 (11.6%) pts were from the Northeast, 1036 (36.4%) from the Midwest, 1117 (39.2%) from the South, 360 (12.6%) from the West, 4 (0.1%) from Puerto Rico, and 2 missing (0.05%). Most pts (2285; 84%) were from community sites; 397 (13.9%) were from academic sites, and the rest from government sites. A total of 1805 (63.4%) were aged ≤70 y and 1043 (36.6%) were aged >70 y; 666 (23.4%) have progressed and entered second-line treatment. The 4 most common induction regimens for pts aged ≤70 y, in decreasing frequency, were lenalidomide (R), bortezomib (V), and dexamethasone (D) combined (RVD); VD; cyclophosphamide plus VD (CyBorD); and RD. The 4 most common induction regimens for pts aged >70 y were VD, RD, RVD, and CyBorD. Triplet therapy in first-line induction increased in use from 2009 to 2014. The 4 most frequent maintenance regimens for stem cell transplant (SCT) recipients (n=553) were R monotherapy, V monotherapy, RD, and RVD. The 4 most common maintenance regimens for non-SCT pts (n=547) were R monotherapy, RD, V monotherapy, and VD. The most prevalent regimens in the second line were VD, RD, V, and RVD. Conclusions: Our work characterized induction and maintenance treatment patterns over time, for both SCT and non-SCT intent pts, using the largest, prospective, noninterventional, registry study in the US. Use of triplet therapy increased in the time period; RVD was the most frequently used triplet for all pts. The most common maintenance regimens included R as monotherapy or in combination.

OP-035
Incidence of secondary primary malignancies (SPM) in patients with multiple myeloma (CALM study)

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Introduction: As the outcome of multiple myeloma (MM) patients (pts) continues to improve, development of late complications particularly SPM are of concerns. We examined the incidence of SPM in MM pts who were enrolled in the prospective EBMT CALM study (Collaboration to Collect Autologous Transplant outcome in Lymphoma and Myeloma). Marterial and methods: A total of 3757 pts with MM were enrolled and underwent first autologous hematopoietic stem cell transplant (HSCT). Pts characteristics are as follows: median age 59 y/o (19-77), gender M/F 2180/1577, subtype IgG 2028 (54%), IgA 714 (19%), IgM 21 (0.6%), lines of induction regimens prior to HSCT one in 2003 pts (53%), two in 724 pts (19.3%), > 2 in 348 pts (9.3%), and missing in 682 pts (18%). Induction regimens included IMIDs and proteasome inhibitor (PI)s with alkylating agents in 1266 pts (33.7%), IMIDs and PIs with no alkylating agents in 1328 (35.5%), and alkylating agents with no IMIDs or PIs in 478 (12.7%) and missing data in 685 (18%). Radiotherapy was used pre HSCT in 614 pts (16.3%), no radiation in 2461 pts (66%) and missing data in 682 (18.2%). Plerixafor (P) was administered mostly for poor HSC mobilization as defined by the centers in 285 pts (7.6%), 3373 pts (90%) did not get plerixafor, and data are missing in 99 pts (2.6%). Disease status at HSCT; CR/VGPR in 1664 pts (44.3%), PR in 1721 (46%), 12 mo 799 pts (21%). Conditioning regimen was mainly melphalan in 3659 pts (97.4%), and melphalan with other drugs in 75 pts (2.0%). KARNOFSKY PERFORMANCE STATUS >90% was documented in 2326 pts (62%) and <90 % in 1086 pts(29%). Number of HSC collected <3x 10 6 in 239 pts (6.4%), 3-5 in 397 pts (10.6%), > 5x 10 6 in 1394 pts (37%), and data missing in 1727 (46%). The number of CD 34+ HSC infused <3x 106 in 760 pts (20%), 3-5x 10 6 in 1055 pts (28%0, >5 x 10 6in 799 pts (21%), and missing in 1143 (30%). Results: A total of 141 pts developed SPM with cumulative incidence of 5.4% (95%CI 4.4,6.3) at 72 mo. Data are missing in 414 pts (11%). Median time to development of SPM is 33 mo. (2.1-86.5) with 75% occurring in the first 50 mo. Ninety nine pts developed solid tumors and 31 hematologic malignancies and unknown type in

11. Overall survival for the whole group is 65.4% (63-67) at 5 yr post auto transplant, and 38% (25-52%) at 5 yr post-SPM in pts who developed SPM. Use of radiotherapy, type of induction, HSC cell dose did not influence the cumulative incidence of SPM. Conclusion: The incidence of SPM in this large prospective study is 5.4% at 72 months and is comparable to the reported incidence of SPM in the literature. Disclosure of Interest: F. Sahebi, none declared, S. Iacobelli, none declared, L. Koster none declared L. Gardaret none declared, N. Kroger received research fund from Sanofi , Curly Morris, none declared.

OP-036
Clinical profiles and outcomes in 1203 newly diagnosed patients with Systemic AL amyloidosis – first analysis of the ALChemy study.

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Background Systemic AL amyloidosis is associated with an underlying plasma cell dyscrasia and caused by deposition of abnormally folded monoclonal immunoglobulin light chains. Catastrophic visceral dysfunction and early death can result. We report data on baseline clinical presentations and outcomes of patients in the ALChemy study, the largest prospectively studied cohort with systemic AL amyloidosis. Methods This study reports patients with newly diagnosed systemic AL amyloidosis from January 2009-March 2016. All patients underwent serial organ function assessment, imaging and biomarkers. Treatment, toxicity and clonal response were recorded. Organ involvement was defined with international amyloidosis consensus criteria. Survival was calculated by Kaplan-Meier analysis. All outcomes are reported on an intention-to-treat basis. Results 1203 patients were recruited (M:F 1.4:1). Median age was 66 yrs (range 29.5-89.5 yrs). ECOG performance status was: ECOG 0-1 – 61%; ECOG 2 – 31%, ECOG 3 - 7%; ECOG 4 - 1%. The median number of organs involved was 2 (>2 organs– 18%); renal - 68% and cardiac - 81%. Other organ involvement included: liver 13.8%; GI 3%; peripheral nerve 9%; autonomic neuropathy 8%; soft tissue 13%. Median creatinine was 96 umol/L, median albumin 33g/L (35-50g/L), albumin <25g/L - 21% and 24 hour proteinuria >3g - 51%. Median LV wall thickness was 13.7 mm. Median NT pro-BNP was 5262ng/L (range 16-147940ng/L). Median presenting dFLC was 181 mg/L. 84% had an abnormal sFLC ratio and the involved abnormal light chain was lambda in 75%. A serum paraprotein was detected in 78% (IgG type in 45%), with a median paraprotein of 7g/L. Cardiac Mayo Stage was 1, 2, 3A and 3B in 14%, 27%, 42% and 17% respectively. Median time from diagnosis to treatment was 2.3 months. Responses were assessed in 849 patients at 6 months post treatment. 15.4% had non-evaluable data. Of the remaining 718 patients, haematological responses on an intention-to-treat basis were: dFLC VGPR or better 30.1%; dFLC PR 14.5%; non-response 6.5%, death 32.5%, non-assessable (presenting dFLC<50mg/L) 16.4%. Evaluable response: dFLC VGPR or better 58.9%; dFLC PR 28.3%; non-response 12.8%. Median survival was 38.8 months. 5 year overall survival (OS) in Cardiac Mayo Stage 1, 2, 3A and 3B was 81%, 62%, 44% and 25%. Median survival in patients with NYHA 1-2 and NYHA 3-4 symptoms was 57 months and 5.6 months respectively. 2 year OS in patients with an initial 6 Minute Walk Test of 40-353, 354-377 and 378-697 metres was 33%, 61% and 81% respectively. Discussion Haematological responses in this large real world cohort are extremely disappointing, contrary to previous retrospective and prospective data. Patients with early stage disease continue to have excellent outcomes. Advanced NYHA symptoms and a poor 6 Minute Walk Test both independently confer an

adverse prognosis, and the latter finding has not been previously reported.

OP-037
NEOD001 Demonstrates Organ Biomarker Responses in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction: Results From a Phase 1/2 Study

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Introduction: In light chain (AL) amyloidosis, misfolded light chain (LC) soluble aggregates and insoluble amyloid accumulate and cause dysfunction of vital organs. Current AL amyloidosis therapies limit LC production but do not directly target residual misfolded LC underlying multiorgan failure. NEOD001, an investigational monoclonal antibody, targets misfolded LC and is thought to neutralize circulating LC aggregates and to clear insoluble deposits. We report updated phase 1/2 trial results. Patients and Methods: Inclusion criteria for this trial were that patients complete ≥1 plasma cell–directed (PCD) treatment before enrollment, attain partial hematologic response or better to any previous therapy, and have persistent organ dysfunction. NEOD001 was administered intravenously every 28 days. During the dose-escalation phase, 27 patients received NEOD001 at 0.5, 1, 2, 4, 8, 16, or 24 mg/kg in a 3+3 study design. An additional 42 patients with renal, cardiac, or peripheral nerve involvement were enrolled and treated (24 mg/kg) in the expansion phase. We assessed safety/tolerability, pharmacokinetics, immunogenicity, and cardiac and renal responses based on consensus criteria and neuropathy responses using the Neuropathy Impairment Score–Lower Limb (NIS-LL). Results: In the overall population (N = 69), the median age was 61 years (61% male). Median (range) time since diagnosis was 2.9 (0.4-16.0) years, and 45% of patients underwent ≥3 previous PCD regimens. Infusions were administered over a mean of 12.8 (range, 2-35) months. NEOD001 treatment was not associated with dose-limiting toxicities, discontinuations, antidrug antibody development, or treatment-related serious adverse events. The most frequent treatment-emergent adverse events were fatigue, nausea, upper respiratory tract infection, and peripheral edema. In a best response analysis, 53% of cardiac-evaluable patients (n = 36) and 64% of renal-evaluable patients (n = 36) met respective criteria for organ response; remaining patients met criteria for stable disease. The median time to initial response was 2 months (cardiac) and 4 months (renal). After 9 months of treatment, 82% of patients with measurable peripheral neuropathy at baseline (N = 11) achieved a peripheral neuropathy response based on the NIS-LL score. Conclusions: These results demonstrate that monthly NEOD001 infusions were safe, well tolerated, and associated with responses across 3 different organ systems, and they support the design of ongoing late-stage clinical studies.

OP-038
Comparison of Haematopoietic Stem Cell Transplantation Approaches in Primary Plasma Cell Leukaemia
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Autologous stem cell transplantation has been shown to improve outcome in patients with primary Plasma Cell Leukaemia (PCL). However response durations are short and further strategies are needed. Data is needed to help guide clinicians on the best approach to manage this disease. Therefore in an era of novel agents and improved transplantation strategies this study compared different transplantation approaches in the treatment of PCL. Methods A retrospective analysis was undertaken of the European Group for Bone Marrow Transplantation (EBMT) experience of patients with primary PCL undergoing haematopoietic stem cell transplantation between 1998 and 2012. Only patients who had achieved complete response, partial response or stable disease prior to transplantation were included. Patients with progressive or relapsed disease were excluded. The primary end point was overall survival and data was analysed according to the information on the planned transplant strategy reported at the time of first transplant (intent-to-treat principle). Results 460 patients were identified and categorised into 4 transplant groups; single auto (333), double auto (49), auto-allo (20) and allo upfront (58). The follow up period ranged from 1 to 208 months with a median follow up of 48.9 months. Patients undergoing allo upfront were found to have the worst overall survival. Compared to single auto this was statistically significant with a Hazard Ratio (HR) 1.85 (p=0.007). Compared to auto-allo the allo up front group had an even

higher risk HR 3.18 (p=0.018). The double auto versus single auto had a HR 1.39 which was not statistically significant (p=0.28). The auto-allo compared to single auto has a time varying effect with a higher mortality at the beginning and better risk afterwards. The effect on average is not significant HR 0.58 (p=0.24). When we consider time varying effects three periods were examined, 0-12, 12-36 and 36-60 months. Allo upfront is still confirmed to be inferior to single auto and also to auto-allo in the first year. Auto-allo has a trend to superiority versus single or double auto in the mid-term. However due to lack of follow up data in the auto-allo group it is difficult to assess possible benefits of auto-allo in the long term as there are few patients still at risk. Our initial analysis does suggest an advantage. Preliminary analysis suggests that the auto-allo group enjoy the best progression free survival. The superiority of auto-allo versus allo upfront may be attributed to the higher rates of non-relapse related mortality observed in allo upfront. Conclusion Preliminary work has demonstrated that allo upfront is associated with the worst overall survival. Further data is needed to reliably assess the outcome of auto-allo group which appears to be superior. We have requested additional information from involved centres to strengthen the power of our results.

OP-039
IMPACT OF EVOLVING PATTERN IN EARLY PROGRESSION OF PATIENTS WITH SMOLDERING MULTIPLE MYELOMA

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Introduction: Smoldering multiple myeloma (SMM) is a plasma cell dyscrasia defined by the

presence of a monoclonal protein (MP) ($\geq$ 30 g/L in serum or >1g/24-hours in urine) and/or plasma cell bone marrow involvement (BMPC) $\geq$ 10%, in the absence of symptoms due to the gammopathy. Several biomarkers and prognostic index associated with risk of early progression, crucial when considering therapeutic intervention. The aim of this study was to analyze the factors associated with early progression to multiple myeloma (MM) in patients diagnosed with SMM and long follow-up in a single institution. Methods: 206 patients (75M/131F; median age 64 years) diagnosed with SMM at our institution between January 1973 and December 2012 were systematically reviewed. The median follow-up for the cohort was 6.8 years from diagnosis of SMM. Progressive increase in the value of MP was defined as "evolving" when at least 10% increase in each of the consecutive measurements up to a period of 3 years in (Rosiñol et al, Br J Haematol. 2003 & Mayo Clin Proc. 2007). Immunoparesis was defined as any value below normal in not involved immunoglobulins. BMPCs were were reviewed independently by 2 observers. The main endpoint was progression to symptomatic MM. The evolving type was analyzed as a time-dependent covariate. Results: One hundred and seven patients (52%) progressed to symptomatic disease (106 to MM and 1 to AL amyloidosis) after a median of 2.8 years since SMM diagnosis. Considering death as a competing event, the cumulative incidence of progression at 2 and 5 years was 19% (95% CI: 15%-25%) and 45% (95% CI: 39%-50%) respectively. Factors at diagnosis associated with increased risk of progression to symptomatic MM included the size of the MP, the percentage of BMPC, presence of immunoparesis, and the Mayo Clinic risk group. At the time of progression, clinical manifestations were mainly anemia (52%) and skeletal lytic lesions (40%), without differences between evolving and non-evolving patients. IgA isotype was more frequent in patients with an evolving pattern than in those with non-evolving SMM (p=0.02). Median time from recognition of evolving type to progression into symptomatic MM was 1.1 years (95% CI: 0.5-2.0) and 71% patients had progressed by the 3rd year. Development of the evolving type drastically worsened the prognostic estimation made at diagnosis for every covariate predictive of progression (serum MP, BMPC, immunoparesis and Mayo Clinic risk). On average, the hazard ratio for progression to symptomatic MM increased to 5.1 (95% CI: 3.4-7.6) after recognition of the evolving type. Conclusion: In patients with SMM the evolving pattern accurately predicts the risk of early progression to symptomatic disease, thereby allowing the identification of ultra-high risk patients who are candidates for immediate therapy. Evolving type should be routinely monitored during the follow up of these patients.

OP-040
Persistence of Minimal Residual Disease by multiparameter flow cytometry can hinder recovery of organ damage in patients with AL amyloidosis

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Introduction. In multiple myeloma, Minimal Residual Disease (MRD) demonstrated by multiparameter flow cytometry (MFC) identifies subjects with significantly shorter survival among those who attain complete response (CR). The role of MRD in AL amyloidosis has not been assessed so far. In the present study, we assessed the MRD by MFC in patients with AL amyloidosis who attained CR. Methods. CR was defined as per current criteria (negative serum and urine immunofixation and normal free light chain ratio). For flow cytometry studies bone marrow samples were processed following the Euro Flow Bulk Lysis Standard Operating Protocol and stained with the EuroFlowIMF MM MRD panel. At least 5x106 events were measured using a FACSCanto II (USA) instrument. Data were analyzed using the

Infinicyt software (Spain). Patients were identified as having residual disease if a discreet population of clonal plasma cells comprising ≥50 events was identified (10-5 limit of detection). Results. Twenty-two patients were tested (6 were found to have relapsed at the time of MRD assessment with monoclonal components detectable and MRD+) and 16 satisfied current criteria for CR. All of them had renal and 7 (44%) had cardiac involvement at diagnosis. More than 2 lines of therapy were required to achieve CR in 6 subjects. Median time to CR was 10 months (range: 3-50). Three patients (50%) had achieved cardiac response and 8 (45%) renal response at the time of CR. The median time from CR to MRD was 25 months (IQR: 11-67). Flow cytometry identified MRD in 7 patients (44%). A median of 1256 (range 600-2500) corresponding to 0.04% (range 0.02-0.3%) plasma cells with abnormal phenotype were detected in patients MRD+. No differences in organ involvement, cardiac and renal stage, type of therapy, number of treatments, and organ response at the time of CR was found between the two groups. However, a further improvement of cardiac function compared to the time of CR was observed in all 4 evaluable MRD-patients and in none of the 2 MRD+ patients (P=0.067). Compared to the time of CR, renal response was obtained in 5 MRD- subjects (83%) and in 1 (20%) MRD+ (P=0.069). Overall, further improvement of cardiac or renal function after CR was significantly associated with absence of MRD (P=0.022). Interestingly, 1 patient MRD+ had otherwise unexplained increase in proteinuria and anti-clone therapy was started. After 2 cycles of bortezomib and dexamethasone, MRD was no longer detectable and proteinuria decreased from 3.4 to 1.9 g/24h without change in eGFR. Conclusion. This proof-of-concept study indicates that almost 44% of patients with AL satisfying current criteria for CR have detectable MRD. MRD makes further organ improvement less likely and can explain organ progression. A validation study in a larger sample is ongoing. The possible impact of MRD should be considered in trials aiming at increasing organ response rate in patients in CR.

OP-041
Long term Outcomes in Monoclonal Gammopathy of Renal Significance (MGRS)

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Background: Outcomes in patients with diagnosis of cast nephropathy and renal amyloidosis have been previously reported. But long-term outcomes of MGRS patients with other renal histologies remain unclear. Data on whether the level of clonal cells in the marrow and treatment for MGRS influence long-term outcomes is lacking. This analysis was conducted to study long term outcomes in renal biopsy proven (non cast nephropathy & AL Amyloid) MGRS patients. Aims: This multi-centre retrospective study was set up to analyse clinical outcomes in renal biopsy proven MGRS patients. Long-term haematological and renal outcomes were analysed. Correlation between clone size, type of therapy applied and level of response obtained was also analysed. Methods: Forty MGRS patients were retrospectively audited across 4 centres in the UK and 1 centre in the Ireland between 2004-2016. Patients were eligible for inclusion if they had a renal biopsy confirmed MGRS. Patients with cast nephropathy and renal AL Amyloidosis were excluded. Renal survival was defined as the time until renal replacement therapy was required or failure to come off the renal replacement therapy commenced at diagnosis. Overall survival (OS) was calculated from the

time of MGRS diagnosis until death from any cause. Results: Median age at diagnosis was 68 years and median follow-up was 33.5 months (range, 0.7-146) months). Majority of patients were kappa light chain (LC) restricted 80% vs 20% lambda LC restricted. 65% of patients had Light Chain Deposition Disease on renal histology. Renal survival for the whole cohort was 76% and overall survival was 85%. At the time of renal biopsy, 44% of patients had >10% plasma cells versus 46% of patients with <10% plasma cells. Renal survival was comparable with 76% renal survival in patients with >10% plasma cells versus 73 % in <10% plasma cells (P = 0.86). Chemotherapy treatment for the PC clone was administered in 25/40 (63%) patients. 20 patients had Bortezomib-based therapy (VEL) and these patients had a renal survival of 84 % versus 68% in patients who did not have VEL treatment (P = 0.69). Good haematological response (≥VGPR) was achieved in 12/40 patients and renal survival in these patients was significantly better at 91 % versus 63 % in patients who had<="" div="">

OP-042
Role of multicolor flow cytometry in assessing bone marrow involvement by solitary plasmacytoma

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Introduction: Solitary plasmacytoma (SP) are a rare type of plasma cell neoplasm (PCN) characterized by local plasma cell infiltration that renders high-risk of progression to multiple myeloma (MM). M-protein is typically absent or present in a low amount and bone marrow (BM) is normal with less than 10% of plasma cells. Persistence of M-protein after a year of radiotherapy and abnormal free light chain ratio (FLCR) are commonly used risk-factors in SP. Recently, BM involvement using multicolor flow cytometry has been shown to be a new valuable risk factor; however, a very limited data is available on the MFC-based bone marrow involvement in SP. We present a study of the BM involvement in cases of SP using MFC in morphologically uninvolved BM. Since percentages of abnormal plasma cells (aPC) on MFC is shown as a prognostic marker in MM and precursor gammopathies, we further studied the association between aPC and levels of M-proteins and FLCR. Patients & Methods: We evaluated 95 cases of PCN presenting with SP in last 3-years. After a complete evaluation, 60 were diagnosed as MM and 35 cases were categorized as SP as per updated IMWG criteria. Complete clinical, laboratory and radiological evaluation was performed. MFC was performed in BM samples using 9-10 color comprehensive antibody panel on Navios instrument. A minimum of 500000 cell events was acquired and MFC data was analyzed with Kaluza-software. Results: Of 35 SP patients, 26 (74%) were osseous and 9 (26%) were extraosseous type (age- median 53 years & range 32 to 80 years and M:F ratio- 2.2). Osseous SP most frequently involved the vertebral column (50%). M-protein was identified in 24/35 (66%) cases with majority (74%) below 1500 mg/dl (median 700 mg/dl, range 100-4000 mg/dl). FLCR was available in 26/35 patients with a median ratio of 3.98 (range 0.82-86.5) and 5/26 had normal FLCR. BM plasma cell percentage was <5% in 28/35 patients. MFC analysis showed presence of aPC in 13/35 (37%) patients. In these 13 patients, MFC levels of total plasma cells were 0.12-1.9% (median 0.47%) and percentages of aPC out of total plasma cells were 15-98% (median 88%). 6/13 patients had aPC percentage above 90% of total PC. Percentages of aPC were correlated with M-protein levels and FLCR using Pearson correlation test, but there was no statistical correlation between % aPC & M-protein (r= 0.07, p=0.8) and FLCR (r= 0.19, p=0.3). Of 11 M-protein-negative patients, 6 (55%) had the presence of aPC by MFC highlighting the importance of MFC in identifying high-risk patients. Conclusion: MFC

is a sensitive technique and can detect clonal aPC in more than one-third patients of SP. MFC-based BM involvement is independent of M-protein burden & FLCR. Hence, BM-MFC is a valuable investigation in initial workup of solitary plasmacytoma.

OP-043
The Multiple Myeloma Genome Project: Development of a Molecular Segmentation Strategy for Risk Stratification of Multiple Myeloma (MM)

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*First 5 share co-first; last 3 share co-senior. Segmenting MM into subgroups with distinct pathogenesis and clinical behavior is important to implement a targeted therapy approach. Current technologies have elucidated 5 major translocation groups and recurrent copy number changes with varying effects on prognosis. However, minor translocation and mutational groups are poorly described due to limited sample numbers and small datasets. The availability of multiple sets of high quality genomic data associated with clinical outcomes provides an opportunity to create an integrative genomic predictor using mutational, chromosomal, and gene expression alterations to develop a classification system to segment MM into therapeutically meaningful subgroups. The Multiple Myeloma Genome Project (MGP) is a global collaborative initiative that aims to develop a molecular segmentation strategy for MM to inform development and deployment of clinically relevant tests that could improve diagnosis, prognosis, and treatment of patients with MM. We have established a set of 2161 patients for which whole exome sequencing (WES; n=1436), Whole Genome Sequencing (WGS; n=708), targeted panel sequencing (n=993) and expression data from RNA-Seq and Expression arrays (n=1497) were available. Data were derived from the Myeloma XI trial, Intergroupe Francophone du Myelome/Dana-Faber Cancer Institute, The UAMS Myeloma Institute and the Multiple Myeloma Research Foundation (IA1–IA9). Data were investigated for genetic abnormalities following preprocessing with state of the art methods and algorithms. We have begun to integrate these large genomic datasets with various correlates. WES data identified the main cytogenetic groups, somatic variants, and significantly mutated genes. 28 significantly mutated genes were present in newly diagnosed samples (17 genes in >2% of samples). The main recurrent mutations included KRAS and NRAS, and negative regulators of the NF-κB pathway; however, novel genes were also identified. Distinct mutational patterns, proportions, and sites between translocation subgroups were identified and will be presented. In addition we identified recurrent copy number abnormalities and examined the interaction with mutations and fusion gene expression from RNASeq. Early integrative model developed with random forest using CN, SNV and structural variants predicted a subset of high-risk patients. We will present risk groups based upon an integrative genomic model. We have established the largest repository of molecular profiling data in MM associated with clinical outcomes. Integrated analyses are enabling generation of clinically meaningful disease segments associated with differing risk that will inform development of clinical tests. The MGP intends to build a global network by expanding collaboration with global MM centers to incorporate additional datasets through current and new collaborations.

OP-044
Phase 3 Study (CLARION) of Carfilzomib, Melphalan, Prednisone

(KMP) v Bortezomib, Melphalan, Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: VMP is approved for use in transplant-ineligible NDMM patients (pts). Carfilzomib is an irreversible proteasome inhibitor approved for use in relapsed or refractory MM. CLARION compared KMP with VMP in transplant-ineligible NDMM pts. Patients and Methods: In this randomized, open-label, multicenter study, transplant-ineligible NDMM pts received 1:1 KMP or VMP in 42-day cycles (C) until disease progression, unacceptable toxicity, or completion of C9 (54 weeks). Carfilzomib was administered (30-min IV infusion) on days (D) 1, 2, 8, 9, 22, 23, 29, and 30 (20 mg/m2: C1D1 and C1D2; 36 mg/m2 thereafter). Bortezomib (1.3 mg/m2; IV or SC) was administered on D1, 4, 8, 11, 22, 25, 29, and 32 (D4, 11, 25, 32 omitted for C5–9). Melphalan (9 mg/m2) and prednisone (60 mg/m2) were given on D1–4. Primary endpoint was progression-free survival (PFS) in the intent-to-treat (ITT) population. Secondary endpoints included overall survival (OS), overall response rate (ORR), complete response rate (CRR), grade ≥2 peripheral neuropathy (PN; SMQN) rate, health-related quality of life, and safety. Pts who received ≥1 study drug dose were included in safety analyses. Results: 955 pts were randomized and included in the ITT population (KMP, n=478; VMP, n=477). There were no major imbalances in baseline characteristics between treatment arms. Median age was 72 years in both arms. A total of 59% (KMP) and 61% (VMP) of pts received the entire 54 weeks of treatment as planned. Median PFS was 22.3 months (95% confidence interval [CI], 20.9–26.7) in the KMP arm and 22.1 months (95% CI, 20.8–24.4) in the VMP arm (hazard ratio [HR], 0.906; 95% CI, 0.746–1.101; 1-sided p=0.159). Time to progression HR was 0.841 (95% CI, 0.679–1.041) for KMP v VMP. OS data were immature with 99 (20.7%) and 78 (16.4%) events in the KMP and VMP arms, respectively (HR, 1.211; 95% CI, 0.896–1.637). ORR was 84.3% for KMP and 78.8% for VMP (odds ratio [OR], 1.412; 95% CI, 1.010–1.973). CRR was 25.9% for KMP and 23.1% for VMP (OR, 1.179; 95% CI, 0.875–1.589). Treatment discontinuation due to an adverse event (AE) occurred in 16.7% (KMP) and 14.7% (VMP) of pts. Rate of fatal treatment-emergent AEs was 6.5% (KMP) and 4.3% (VMP). Rate of grade ≥3 AEs was 74.7% (KMP) and 76.2% (VMP). AEs of interest included acute renal failure (grouped term; all grade: 13.9% [KMP] v 6.2% [VMP]; grade ≥3: 7.4% v 2.1%), cardiac failure (grouped term; all grade: 10.8% v 4.3%; grade ≥3: 8.2% v 2.8%), dyspnea (high-level term; all grade: 18.1% v 8.5%; grade ≥3: 3.6% v 0.6%), and hypertension (grouped term; all grade: 24.7% v 8.1%; grade ≥3: 10.1% v 3.6%). Grade ≥2 PN rate was lower in KMP arm than in VMP arm (2.5% v 35.1%). Conclusion: With a maximum of 9 cycles of therapy received, KMP did not improve PFS compared with VMP in transplant-ineligible NDMM pts. These results suggest that melphalan may not be an ideal drug to combine with carfilzomib in this setting.

OP-045
Venetoclax as Targeted Therapy for Relapsed/Refractory Multiple Myeloma

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Background: Venetoclax (VEN), an orally available selective small-molecule BCL-2 inhibitor, induces cell death in multiple myeloma (MM) cells, particularly those with the t(11;14) translocation. Methods: Patients (pts) with relapsed/refractory (R/R) MM received VEN monotherapy in this phase 1 study. Daily VEN was given at 300–1200 mg in dose escalation cohorts and 1200 mg in the safety expansion. Pts with disease progression (PD) on VEN monotherapy could receive VEN plus dexamethasone and remain on study. Results: As of 19Aug2016, 66 pts were enrolled. Median age was 63 years and 30 (46%) pts had t(11;14). Median number of prior therapies was 5 (range: 1–15); 46 (70%) pts were refractory to bortezomib, 20 (30%) to carfilzomib, 51 (77%) to lenalidomide, 35 (53%) to pomalidomide, and 52 (79%) were refractory to the last prior therapy. Median time on VEN monotherapy was 2.5 months (range: 0.2–23); 17 pts received VEN plus dexamethasone after PD for a median of 1.4 months (range: 0.1–13). Fifty-five (83%) pts discontinued, with 41 due to PD. Common adverse events (AEs) were nausea (47%), diarrhea (36%), vomiting (21%) and grade 3/4 hematologic toxicities [thrombocytopenia (32%), neutropenia (27%), anemia (23%), leukopenia (23%)]. Common serious AEs were pneumonia (8%), sepsis (5%), cough, hypotension, pain, and pyrexia (3% each). There were no events of TLS. Six deaths were reported due to PD, and 1 each due to lung disorder and brain hemorrhage following trauma. Overall response rate (ORR) for all pts on VEN monotherapy was 21% (14/66); 10 (15%) achieved very good partial response (VGPR) or better [2 stringent complete response (sCR), 3 CR, 5 VGPR]. For all pts, median time to progression (TTP) and duration of response (DoR) were 2.6 and 9.7 months, respectively. A clear difference in responses was seen among pts with t(11;14) vs without [ORR, 40% vs 6%; ≥VGPR, 27% vs 6%]. For pts with t(11;14), median TTP was 6.6 months [vs 1.9 months for pts without t(11;14)] and median DoR was 9.7 months. A high BCL2:BCL2L1 (BCL-XL) gene expression ratio was observed in 10/44 (23%) baseline tumor samples, enriched in pts with t(11;14) compared with non-t(11;14) (38% vs 5%) and associated with clinical response; 80% (8/10) of pts [all t(11;14)] with a high BCL2:BCL2L1 ratio achieved ≥PR with a median TTP of 11.5 months. Among pts with t(11;14) who were refractory to the last therapy, ORR was 42% (11/26); for t(11;14) pts refractory to both bortezomib and lenalidomide, or who were refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide, ORR was 40% (8/20) and 50% (3/6), respectively. No difference was seen in ORR for t(11;14) pts with high-risk del(17p) versus those without the deletion [40% (2/5) vs 40% (10/25)]. Conclusions: VEN has an acceptable safety profile with promising single-agent anti-myeloma activity in pts with R/R MM positive for t(11;14) who failed multiple prior lines of therapy.

OP-046

An International, Randomized, Double Blind Trial Comparing Denosumab With Zoledronic Acid (ZA) for the Treatment of Bone Disease in Patients (Pts) With Newly Diagnosed Multiple Myeloma

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Multiple myeloma is characterized by osteolytic bone disease, with approximately 80% of pts presenting with detectable lesions. Myeloma bone disease is mediated by factors such as RANKL, increasing the risk of skeletal related events (SREs) leading to morbidity and mortality. Denosumab, a human monoclonal antibody that targets RANKL, can be administered SC to pts regardless of renal function. This international, phase 3, randomized, double blind study evaluates the efficacy and safety of denosumab compared with ZA in newly diagnosed symptomatic myeloma pts. Adult pts were randomized 1:1 to denosumab 120mg SC Q4W or ZA 4mg (adjusted) IV Q4W along with anti-myeloma therapy. Key stratification factors included type of first-line therapy (novel or non-novel) and previous SRE. Pts with renal insufficiency were excluded if baseline CrCl<30mL/min. The primary endpoint was non-inferiority of denosumab with ZA with respect to time to first on-study SRE. Secondary endpoints included superiority of denosumab for time to first on-study SRE and first-and-subsequent on-study SRE, and overall survival (OS). Progression-free survival (PFS) was an exploratory endpoint. Safety was also assessed. A total of 1718 pts were randomized, 859 to each arm. Baseline demographics and disease characteristics were balanced, with CrCl≤60mL/min reported in 26.7% of pts. During the primary blinded treatment period (median follow-up 17.4 months [m]), 43.8% pts on denosumab and 44.6% on ZA had a first on-study SRE. The median time to first on-study SRE was similar between denosumab (22.83m) and ZA (23.98m). Denosumab was non-inferior to ZA (P=0.01) in delaying time to first on-study SRE (HR[95%CI]=0.98[0.85,1.14]). Superiority was not demonstrated for time to first on-study SRE (P=0.82) and time to first-and-subsequent on-study SRE (rate ratio[95%CI]=1.01[0.89,1.15]; P=0.84). OS was similar between denosumab and ZA (HR[95%CI]=0.90[0.70,1.16]; P=0.41),

with fewer deaths in denosumab (121 [14.1%]) than in ZA (129 [15.0%]). PFS yielded a HR(95%CI)=0.82(0.68, 0.99); descriptive P=0.036. The most common (>25%) TEAEs for denosumab (%) and ZA (%) were diarrhea (33.5, 32.4) and nausea (31.5, 30.4). The rates of serious AEs (46.0, 47.3), hypocalcemia (16.9,12.4; serious:0.9,0.2), and positively adjudicated ONJ (4.1, 2.8) were comparable to known safety profiles. Fewer AEs potentially related to renal toxicity occurred with denosumab (10.0, 17.1). TEAEs led to IP discontinuation in 12.2% of all pts (12.9, 11.5). Denosumab demonstrated non-inferiority to ZA in delaying time to first on-study SRE in pts with newly diagnosed myeloma, meeting the primary endpoint of the study. The rates of AEs, including hypocalcemia and ONJ, are generally consistent with the known safety profile of denosumab 120mg Q4W. The lack of OS difference is reassuring and will need further follow-up. The PFS data is provocative and warrants further investigation.

POSTER DISPLAY – THURSDAY

(d) *denotes a poster discussion abstract.*

1. Disease Biology and Related Disorders

PS-047
Prevalence and prognostic impact of cytogenetic abnormalities in 220 patients with multiple myeloma

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Background: Prognostic studies of patients with multiple myeloma (MM) are attracting more and more attention. Among them, detecting cytogenetic abnormalities is powerfully implicated in risk stratification. Method: Using

our MM database, we retrospectively reviewed all cases of MM seen at the Department of Hematology/Oncology of Kameda Medical Center, Kamogawa, Japan, from May 1994 to April 2016. We retrospectively surveyed the prevalence of cytogenetic abnormalities including t(4;14), t(14;16), del(17p), del(13q), t(11;14) and 1q gain by FISH and analyzed their prognostic impact in 220 patients at our hospital. Results: Median age of the patients was 72.2 years (43.8-92.3 y), and median follow-up period was 30.3 months (0.1-263.8 m). Patients harboring t(4;14), t(14;16), del(17p), del(13q), t(11;14) and 1q gain were 28/213 (13.1%)、5/213 (2.3%)、9/183 (4.9%)、91/182 (50.0%)、48/190 (25.3%) and 38/88 (43.2%), respectively. Patients harboring any of high-risk cytogenetic abnormalities including t(4;14), t(14;16), and del(17p) was significantly younger (positive vs negative：67.5y vs 72.0y, p=0.010). According to the analysis of 213 patients of new agents' era, patients with t(4;14) had shorter PFS (positive vs negative：21.2 m vs 37.2 m, p=0.012) and patients with del(17p) had shorter OS than those without (positive vs negative：39.5 m vs 138.6 m, p=0.004). Patients with 1q gain had significantly shorter PFS (positive vs negative：21.2 m vs 45.6 m, p=0.033). Patients without any of high-risk cytogenetics had significantly longer PFS than those with (median; 39 m vs 23.9 m, P=0.03), but it was not translated to longer OS (median; not reached vs 60 m, P=0.57). Among patients who received ASCT, high-risk patients had significantly shorter PFS than non-high risk patients (positive vs. negative：24.0 m vs. not reached, p=0.011). Patients without high-risk cytogenetics who received ASCT showed the longest OS. On the contrary, patients who had high-risk cytogenetics and did not receive ASCT showed the shortest OS. Patients with high-risk cytogenetics who received ASCT showed close survival curve to that of patients who did not have high-risk cytogenetics and did not receive ASCT. By multivariate analysis, harboring 1q gain was detected as an independent factor related to shorter PFS. Conclusion: We report a cytogenetic analysis of relatively large number of MM patients as a

single-center study in Japan. Patients carrying 1q gain had shorter PFS. High-risk cytogenetic abnormalities were more frequently detected in younger patients, and they were related to shorter PFS and PFS after ASCT, but patients harboring these abnormalities may receive benefit of longer OS by ASCT. Searching cytogenetic abnormalities in MM patients is valuable for prognosis prediction and determining therapeutic strategy.

PS-048 (d)
Acute lymphoblastic leukemia (ALL) as a second primary malignancy (SPM) after multiple myeloma (MM): Secondary clonally related neoplasm or therapy-related leukemia?

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Introduction: SPMs, including rarely ALL, are a known complication of MM, with data conflicting if this is a therapy related phenomenon or if this could represent a clonally related but phenotypically different progression of myeloma as a B-cell neoplasm. Methods: Retrospective chart and tissue review of all consecutive cases of ALL diagnosed at our institution between 2000 and 2016, with an antecedent MM diagnosis. Paired MM and ALL samples were obtained when available, and exome sequencing was performed to assess the association clonality between the two malignancies. Results: Eleven cases of ALL with prior MM diagnosis, all had a B-cell phenotype. The median age at ALL diagnosis was 60 years (range;43-67), and 55% were male. The median interval from MM to ALL

was 6.6 years (range;2.1-18.1). The median WBC at the time of ALL diagnosis was 2 (range;1.2-29). Prior MM treatment included; immunomodulatory agents in all patients (100%) [lenalidomide = 4, thalidomide = 8], bortezomib in 6 (55%), chemotherapy in 10 (91%), and radiotherapy in 3 (27%). Eight (73%) patients underwent previous autologous hematopoietic cell transplantation (HCT). Cytogenetic abnormalities at the time of ALL diagnosis showed diploidy (N=5), complex (N=3), hyperdiploidy (N=1), hypodiploidy (N=1) and combination of trisomy 8 and 7p deletion (N=1), with no cases of 11q23 abnormalities. Treatment of ALL was with HyperCVAD regimen in the majority of cases, and 9 out of 10 evaluable patients achieved complete remission (CR). Seven patients subsequently underwent allogeneic HCT. Transplant conditioning regimen was reduced-intensity in 5, and source of stem cells were related (N=3), unrelated (N= 3), and haplo (N=1). The median follow up for all patients was 14.7 months (1.8-19.7), and for living patients was 6.8 months (1.8-118). 2-year EFS and OS from the time of ALL diagnosis was 58% for both. Two patients had their MM active during the course of ALL. In one case, comparison of the fragments sizes from IGH/IGK gene rearrangement studies indicate that ALL and previously diagnosed MM were derived from different clones. Conclusion: Secondary or therapy-related ALL may occur many years after MM diagnosis and treatment and has no defining cytogenetics. Outcomes of ALL after MM appear comparable with de novo ALL, especially when allogeneic HCT is utilized. Exome sequencing data for paired samples will be available and presented at the time of the meeting, and data will help in distinguishing whether the ALL is represents evolution of a myeloma clone or if this is a new leukemia triggered by the exposure to genotoxic myeloma therapy parallel to t-MN.

PS-049
Infections in Multiple Myeloma: An Understimate Risk Factor of Comorbidity

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Background Multiple myeloma (MM) represents the second most common haematological malignancy characterized by the proliferation of monoclonal plasma cells (PC) in the bone marrow. The natural history of the disease may be complicated by the occurrence of infections that can be related to the development of therapy induced neutropenia but other factors (mainly hypogammaglobulinemia) can be involved. The aim of this study was to analyse the frequency, the type and the major risks factors for severe infections in our cohort of patients affected by MM. Material and Methods A cohort of 341 patients affected by MM (104 with smouldering MM and 237 with symptomatic MM) followed from 1996 to 2016 was retrospectively studied for the presence of severe infections (as defined by the need of hospitalization) during the natural history of the disease. Only not neutropenia related infections, according to Absolute Neutrophil Count>1,000/μl, were considered. International Staging System (ISS) and Durie-Salmon (DS) were used for MM patients staging. Results In our cohort of patients, severe infections were significantly associated to symptomatic MM (28,69% of symptomatic patients vs 3,85% of asymptomatic patients; p=0.0001, χ2=25,318). Among the 68 of 237 symptomatic patients who developed severe infections during the natural history of the disease (for a total amount of 99

events), 36 patients (52,94%) presented the infectious event at the time of the diagnosis or during induction therapy (40 total events) while remnant 59 events occurred during second lines therapies. Considering the site of infection, 58 out of 99 events (58,6%) were pulmonary infections whereas 25 out of 99 (25,3%) bloodstream infections; in 10 cases (9,9%) they were both concomitant. At least in half of the cases (53,5%), no specific pathogenetic microorganism was identified whereas in the other patients bacterial infections were predominant (83%) with no differences between Gram+ and Gram- infections. Major factor presented at the time of diagnosis significantly associated to severe infections were DS stage III (p=0.0004, $\chi 2$=12,14), ISS stage III (p=0.0001, $\chi 2$=21,11), age >70 years (p=0.0195, $\chi 2$=5,455), bone marrow plasma cells >60% (p=0.034, $\chi 2$=4,50), acute renal failure (p=0.0003, $\chi 2$=13,010) or MM presenting with at least three of CRAB criteria (p=0.0123, $\chi 2$=6,26). Discussion Severe infections represent a significant comorbidity in MM, characterizing all phases of the disease and not only refractory/relapsed patients receiving multiple lines of therapy. Considering that most of these events involved pulmonary and bloodstream bacterial infections, immunoglobulin replacement therapy or antibiotic prophylaxis may possibly have a protective role in high risk old patients characterized by ISS and DS stage III, bone marrow PC>60% and aggressive disease at the time of diagnosis.

PS-050
Rates of Upfront Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (NDMM): A report from the MRDR

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Aim: Despite clear evidence for the use of front-line ASCT, utilisation rates are lower than expected. We reviewed the utilisation of ASCT and maintenance therapy in age-eligible patients registered on the Myeloma and Related Diseases Registry (MRDR) and its impact on outcome. Method We conducted a retrospective review of adult patients registered on the MRDR, a prospectively maintained database from 25 sites across Australia (22) and New Zealand (3). Patients aged 70 with NDMM from June, 2012 to Oct, 2015 with review data available at least 12 months post diagnosis were eligible for analysis. Baseline characteristics, therapies and outcomes were compared between recipients and non-recipient using chi square tests for categorical variables and rank sum tests for continuous variables. Cox regression survival analysis was used to estimate time to disease progression. Result: 218 patients met eligibility criteria and by Oct, 2016 163 (75%) had received an ASCT. Patients who did not receive an ASCT were older (median age at diagnosis 66.1 vs 58.0 years p<0.001) and had lower estimated glomerular filtration rates (eGFR)

(71.5 vs 86.5, p=0.004). Neither higher ECOG (ECOG≥2 19.4% vs 9.7%, p=0.12) or ISS stage 3 (32.5% vs 22.9%, p=0.22) were statistically significant in predicting for patients receiving an ASCT. Patients not receiving an ASCT were less likely to have been treated with bortezomib-based induction (88.0% vs 93.9%, p=0.046) and more likely to be treated with melphalan or thalidomide-based induction (8.0% vs 0%, p<0.001 and 8.0% vs 3.7%, p=0.21 respectively). Patients who did not receive an ASCT had a shorter progression free survival (PFS) (median 19.4 vs 31.7 months, p<0.001). ASCT was utilised less frequently in older patients (50% of patients aged >65 to 70 years at diagnosis vs 85% of patients aged ≤65 years at diagnosis, p<0.001). The predictive value of lower eGFR (75 vs 87, p=0.02 in the non-ASCT and ASCT group respectively) remained statistically significant in the ≤65 age group but not those aged >65 to 70 years (eGFR 69 vs 79, p=0.3 in the non-ASCT and ASCT group respectively). Maintenance therapy was used in 105 (64.4%) of patients post ASCT with thalidomide containing therapy most frequent (73%). Conclusion ASCT is a highly effective therapy in MM but is currently under-utilised in Australia/New Zealand. ASCT is utilised less frequently in less fit patients (older, higher ECOG) and is associated with a poorer PFS. Consideration of an ASCT may benefit patients in this group.

PS-051
EDO-S101, an alkylating-HDAC-inhibitor, is synergistic with proteasome inhibition against multiple myeloma through activation of multiple pathways

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Background. EDO-S101 is a first-in-class cytotoxic agent with bi-functional alkylating-histone deacetylase-inhibiting (A-DAC) mode of action. It combines DNA-damaging effect of the alkylating agent bendamustine with a pan-HDAC inhibitor, vorinostat, in one single molecule currently tested in Phase I. Bendamustine combined with the proteasome inhibitor (PI) bortezomib (BTZ) is active against multiple myeloma (MM) and likewise EDO-S101 has strong synergistic cytotoxicity with PI in vitro against hematological malignancies (MM, mantle cell lymphoma and ABC type diffuse large B-cell lymphoma). We aimed to characterize the molecular mechanism of the synergy of EDO-S101 with PI in comparison to its structurally related drugs, bendamustine and vorinostat. Methods. Activity of EDO-S101 in combination with BTZ and other PIs was assessed in vitro using RPMI-8226 and several other MM cell lines. HDAC-inhibiting activity, accumulation of poly-ubiquitinated proteins and induction of ER stress, apoptosis and autophagy were assessed by quantitative PCR and western blotting. Proteasome activity was measured with activity based probes (ABP). Apoptosis was assessed by flow cytometry. Cell viability was evaluated by MTS assay. Results. Combination of BTZ with EDO-S101 showed superior cytotoxicity compared to melphalan, bendamustine or cyclophosphamide combinations and had higher HDACi-activity, compared to BTZ + vorinostat, as demonstrated by increased α-tubulin acetylation, providing a potential mechanistic basis for its superior synergy with PI. Consistent with this, EDO-S101 alone induced mild accumulation of poly-ubiquitinated proteins, which was potentiated by combination with BTZ. EDO-S101 induced activation of the UPR-regulators XBP1 and IRE1, in contrast to vorinostat or bendamustine alone. Co-treatment with BTZ and EDO-S101 or vorinostat resulted in highly synergistic triggering of the UPR (ATF4, CHOP, BIP). Interestingly, EDO-S101 in addition induced the pro-apoptotic machinery via upregulation of NOXA, downregulation of BCL2 and an increase of the BAX/BCL2 ratio. The pro-apoptotic signaling of EDO-S101 was highly synergistic with BTZ-induced apoptosis evidenced by annexinV/PI positivity in 90% of the cells. EDO-S101 reduced further c-Myc expression by 60%, which was potentiated by

BTZ leading to its reduction by 90%, while c-Myc levels remained unchanged during BTZ+vorinostat treatment. EDO-S101 further inhibited proteasomal and aggresomal proteolysis which led to autophagy induction, evidenced by upregulation of LC3A and LC3B. Conclusion. EDO-S101 is an alkylator-HDAC-inhibitor fusion molecule that combines key structural features of bendamustine and vorinostat. In addition it has potent ER stress-inducing, HDAC6-inhibiting, pro-apoptotic and c-MYC-antagonistic activity, in contrast to vorinostat or bendamustine.

PS-052

Expression of MDR1 Mediates Carfilzomib Resistance in MM and PCL Patients and May be Overcome by HIV Protease Inhibitors Nelfinavir and Lopinavir

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Background. The mechanism of multiple myeloma (MM) resistance to carfilzomib (CFZ) is poorly understood. In vitro models of CFZ resistance suggest upregulation of the multidrug resistance protein ABCB1/MDR1 as mediator of CFZ resistance. MDR1 is a druggable target; however, early clinical trials using verapamil for MDR1 inhibition in MM were not further developed due to insufficient drug plasma concentrations or severe toxicity, although significant improvement in patients' (pts) survival were shown. Thus, targeting MDR1 in advanced MM, assessing the functional role of MDR1 for the resistance of MM cells to CFZ and other drugs, and overcoming MDR1-mediated drug resistance in MM are a rational strategy to improve therapy of advanced MM. Methods. Gene expression data were obtained

from CD-138-selection MM PCs. Cell viability was evaluated by MTS. Proteasome activity was assessed by activity-based probes. ABCB1-ko was generated by CRISPR/Cas9 system. Inhibition of MDR1 was assessed by dye-efflux assay using MitotrackerGreenFM. Results. MDR1 was expressed in 7/29 CFZ resistant pts with available GEP data for CD138+ MM PCs. Furthermore, MDR1 was expressed in 29/44 primary and secondary plasma-cell leukemia (PCL) samples. Paired samples from one MM patient revealed that MDR1 was strongly upregulated at a later time-point when the disease was CFZ refractory. Consistent with this, analysis of in vitro cell line models for proteasome inhibitor (PI) resistance (AMO-1 and ARH77 MM cell lines adapted to either bortezomib (BTZ) or CFZ) revealed induction of MDR1 by CFZ, but not by BTZ. Inhibition of MDR1 increased sensitivity to epoxyketone-type PI, where the effect on CFZ was most prominent. CFZ concentrations sufficient to fully block intracellular b5 proteasome activity in control cells failed to affect proteasome activity in MDR1+ CFZ-resistant cells. In turn, MDR1-ko in AMO-1_CFZ restored the proteasome-inhibiting activity of CFZ and in addition identified several current MM drugs as MDR1 substrates, such as CFZ, Daunorubicin, Panobinostat, Lenalidomide, and Oprozomib. The HIV protease inhibitors Nelfinavir (NFV) and Lopinavir (LPV) have been suggested to modulate MDR1 function. Co-treatment with therapeutically relevant concentrations of NFV/LPV and CFZ in vitro inhibited MDR1 and re-established the intracellular proteasome-inhibiting activity of CFZ in AMO-CFZ MM cells and overcame CFZ resistance. Conclusion. MDR1 is present in advanced MM, in particular in PCL. It mediates CFZ resistance through drug export and likely plays an important role in resistance against CFZ and several other MM drugs. NFV and LPV are off-the-shelf drugs with MDR1-inhibiting activity at therapeutic plasma drug concentrations. They should be explored in MM to overcome resistance against CFZ and potentially other drugs for advanced MM.

PS-053
Multiple Myeloma: Experience in a tertiary center in Mexico City

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Worldwide survival for patients with multiple myeloma (MM) has increased substantially over the last decades. However, inequality in this trend between ethnic groups has been described. Disease-related features such as demographics and biology, socioeconomic status, and access to health care and novel therapies have been related to these differences. Data of MM Hispanic population, living, and being treated in Latin American countries is scarce. We present a MM cohort from a tertiary health care level institution in Mexico City. We prospectively collected data from 175 patients, from June 2006 to December 2014. The median follow-up was 20 months (3-104 months). Median age at diagnosis 62 years (35-92 years); 15% <50 years, 60% >64 years, and 19% >74 years. Poor performance status (ECOG 3 and 4) was found in 28% (n=49). Most patients were at an advanced stage of the disease, with 88% (n=154) being ISS II and III. Extramedullary disease (EMD) rate was high, presented in 25% (n=44). A total of 152 patients received therapy. Induction regimen was melphalan-based in 21% (n=32), thalidomide-based in 68% (n=104), and bortezomib-based in 11% (n=16). Only 9 patients (6%) received autologous hematopoietic stem cell transplant. A total of 132 patients were included in the survival analysis. Median OS was 45 months (95% CI, 40.9.-49.5) and PFS was 25 months (95% CI, 19.1-31.0). Univariate analysis for OS demonstrated that depth of response to induction therapy was related to shorter OS (p.001). On univariate analysis for PFS, poor PS (p=.007), ISS stage III (p=.001), creatinine clearance <30ml/min (p=.042), presence of osteolytic lesions (p=.004) and depth of response to induction therapy (p.001) were associated with a shorter PFS. On multivariate analysis ISS III

(HR=1.4, 95% CI 1.04-2.06, p=0.028) and depth of response to induction therapy (HR=0.61, 95% CI 0.52-0.72, p.001) remained significant. To our knowledge this is the first report of a MM cohort in a tertiary referral public health center in Mexico. We found a high rate of advanced disease, EMD, and poor PS, that might be related to delayed referral of patients and limited access to medical facilities. The OS and PFS in our study were significantly lower than the reported over the last decade by Western populations. These outcomes might reflect the distinct clinical features and limited availability of novel therapies and autologous transplant in our population. We acknowledge that there is an imperative need of promoting governmental and non-governmental strategies to seek universality on health coverage on developing countries.

PS-054
Association between baseline PET/CT findings and CD38, CD138 expressing myeloma cells in bone marrow and clinical parameters in patiens with multipl myeloma

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Backround: Plasma cells in multiple myeloma (MM) more expressed CD38 and CD138 antigens than normal plasma cells. PET/CT is very useful for detecting of skeletial or extramedullary lesions in myeloma. High uptake of 18F-FDG by tumor cells is associated with the metabolic activity of plasma cells in MM. In this study, we aimed to evaluate of relation between degree of F-18 FDG uptake and ratio of CD38 and CD138 expressing cells and clinical or parameters in patient with myeloma, as retrospectively. Methods: Newly diagnosed,

untreated 36 patients were enrolled to study. Immunohistochemical staining for immunglobins, light chains and CD38, CD138 were evaluated in the bone marrow biopsy samples, Head to toe whole-body 18F-FDG PET/CT scans were examined in all patients. For semi-quantitative evaluation, mean standardized uptake value (mSUV) of right anterior or posterior iliac crest or proximal femur were recorded by semi-automatic image registration software package. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 18.0. Results: The percentage of plasma cell ratio on bone marrow ranged from 5%-80% (mean 25.4±20.1) and there was also positive correlation between percantage of plasma cell and FDG uptake of bone marrow (p=0,031). There was negative correlation between mSUV of bone marrow and hemoglobin and hematocrit values (p=0.023 and p=0,027). The positive correlation between beta-2 microglobulin values and bone marrow FDG uptake were also detected (p=0.05). There was not correlation between FDG uptake value and albumin, creatinine, calcium, lactate dehyrogenase, sedimentation and C-reactive protein value. Conclusion: Our results showed that increased FDG uptake of bone marrow is related to the percantege of plasma cell infiltration of bone marrow and hemoglobin and beta-2 microglobulin level in MM patients. PET/CT may be useful for tumor burden other than detecting of skeletial lesions or extramedullary lesions in patients with myeloma.

PS-055
Rapid MALDI-TOF method for detecting and isotyping M-Proteins: evaluation of paired samples of serum and urine in different clinical settings.

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INTRODUCTION: The detection and quantification of M-proteins (MP) are necessary for the diagnosis and evaluation of response to treatment in plasma cell dyscrasia. The repertoire of tests for identifying a MP includes serum and urine protein electrophoresis (PEL), immunofixation electrophoresis (IFE), and quantitative serum free light chain (FLC). A new assay based on matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS) has recently been described by our group to provide detection and isotyping data (MASS-FIX) suitable for monitoring patients (pts). In this study we compared the (MASS-FIX) method to PEL, IFE of both serum (s-) and urine (u-) and FLC ratios, for the identification of MP in different clinical settings. MATERIAL & METHODS: Samples from pts whose physician's had ordered s- & u- PEL and IFE sFLC in the Clinical Immunology Lab at Mayo Clinic were used. The paired samples were enriched for IgG, IgA, IgM, kappa and lambda using capture select resins. After disassociating the heavy and light chains by reduction, the 5 purified samples from serum and 5 from urine were spotted onto a Bruker Microflex MALDI plate. Automated acquisition (~10 seconds/sample) was performed, and the 5 LC mass spectra from each enrichment were overlaid. The presence or absence of the MC was determined by visual inspection. RESULTS: Paired samples from 259 pts were tested (Table). The median difference of the mass/charge (m/z) distribution between serum and urine was 0.3 daltons. Serum MASS-FIX detected 172/173 MP that were identified by s-PEL/IFE; the exception was a newly diagnosed AL patient (though u-MASS-FIX was positive). U-MASS-FIX detected 140/142 MP that u-PEL/IFE detected; the exceptions were 2 treated pts, one MM and one AL. In both cases that uPEL was negative, the MP was detected by s-MASS-FIX. Using serum testing only, a panel of IFE/FLC outperformed s-MASS-FIX by detecting an additional 12 MP [IFE positive (1), FLC positive (12); 2 MM, 7 AL, 3 MGUS]; however, when the combined results of s- & u-PEL/IFE plus sFLC were compared to the combined results of s- & u- MASS-FIX, there

were only 4 pts that the routine bundles detected over MASS-FIX: these 4 were only positive by a borderline elevation of the κ/λ ratio (range: 1.81-3.96): one IgAκ treated MM, two MGUS, and a newly diagnosed AL (κ). In contrast, MASS-FIX identified 18 pts that PEL/IFE/FLC did not: 1 treated MM and 8 AL. There was perfect agreement between MASS-FIX and IFE isotyping in 152/169 (90%) of serum and in 130/136 (96%) of urine samples. In most instances, the discordance was due to the presence of a biclonal gammopathy. DISCUSSION & CONCLUSIONS: Our study demonstrates that MASS-FIX can be used for detection and isotyping in all the clinical setting investigated and has a comparable sensitivity with PEL and IFE methods.

PS-056 (d)
Splicing factor SRSF1 is dysregulated in multiple myeloma with functional and clinical significance.

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The mechanisms modifying expression and function of genes, such as alternative pre-mRNA splicing need to be considered in order to provide a more accurate genomic framework for clinical correlation, as well as for high value therapeutic target discovery. Compelling data deriving from RNA-sequencing of purified myeloma cells from 420 newly-diagnosed, uniformly-treated and clinically annotated patients show that RNA splicing is frequently deregulated in MM compared to normal donor plasma cells, with 1534 genes with one or more splicing events observed in at least 10% or more patients. Unsupervised analysis identified clinically relevant MM subgroups with high and low splicing index respectively and showed significant impact of alternate splicing on overall clinical outcome. Based on these data, we focused on understanding the molecular mechanisms driving aberrant alternate splicing in myeloma. Several studies provide evidence that an abnormally expressed splicing factor (SF) can have oncogenic properties by impacting alternative splicing of cancer-associated genes. We have identified 28 SFs to be significantly dysregulated in MM compared to normal plasma cells with impact on overall survival, and further investigated role of Serine/Arginine Splicing Factor 1 (SRSF1) in MM. Enforced expression of SRSF1 in MM cells significantly increased proliferation, especially in the presence of bone marrow stromal cells. Conversely, downregulation of SRSF1, significantly inhibited MM cell proliferation and cell survival. To dissect the mechanisms involved in SRSF1-mediated MM growth induction, we used SRSF1 mutants lacking either of the two RNA-recognition motifs or the serine/argine-rich C-terminal domain involved in protein-protein interactions, subcellular localization, and recruitment of spliceosome components. We also used a C-terminal fusion of SRSF1 with the nuclear-retention signal of SRSF2, to force SRSF1 retention in the nucleus and assess the role of its nuclear versus cytoplasmic functions. We surprisingly found that even NRS1 mutant failed to promote MM growth, suggesting an important role of cytoplasmic SRSF1 in promoting MM cells proliferation. Finally, using genome wide chromatin and transcription landscape mapping techniques, we have found SRSF1 to be under the transcriptional control of E2F1, a transcription factor with significant impact on MM cell growth and survival. A significant reduction in SRSF1 at mRNA and protein levels was observed after E2F1 and/or DP1 gene silencing. Moreover, peptide-based strategy to abrogate interaction between DP1-E2F1 led to decreased SRSF1 expression levels. These results indicate a functional role and clinical significance of a gene involved in regulation of alternate splicing in MM, highlighting the need to further understand the splicing pattern in myeloma initiation and progression.

PS-057
Fate of Ikaros in multiple myeloma cells

upon treatment with lenalidomide and proteasome inhibitor

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Recent evidences suggest that the efficacy of Lenalidomide (LEN) depends upon its ability to degrade IKZF1 and IKZF3 proteins via cereblon dependent ubiquitin –proteasome pathway [Science. 2014 Jan 17; 343(6168): 301–305]. It was also shown that IKZF1 and IKZF3 degradation axis remains central to the efficacy of LEN in multiple myeloma. Based on this model it would theoretically be antagonistic to combine LEN with proteasome inhibitors (PI). However, it is well recognized that there is significant synergism when LEN is combined with PI and this combination is used routinely and effectively in the clinic. The mechanism of synergism and the fate of IKZF1 and IKZF3 is poorly understood when these two agents are combined. We undertook a series of experiments to study the fate of IKZF1 when this combination of drugs was used in multiple myeloma cells. Combining LEN (1µM) along with bortezomib (BTZ; 5nM) a PI showed a significant kill on U266 cells (n=3; P=0.02) when compared to either of the agents alone. In an MTT assay, the synergism was well documented [Combination index (CI) = 0.5]. Next we assessed the function of proteasome (chymotrypsin activity) when LEN was combined with PI. We observed that LEN alone does not interfere with proteasome activity while BTZ alone inhibited it. It was also observed that combining these two agents does not interfere with BTZ action in inhibiting proteasome complex (n=3). As a result of efficient proteasome inhibition, we observed an accumulation of ubiquitinated proteins in the BTZ and LEN + BTZ treated cells. Next, we looked for the fate of IKZF1 in U266 cells treated with LEN, BTZ and in combination of both the drugs. As reported, we observed a degradation of IKZF1 in U266 cells upon

treatment with LEN. While we did not see any degradation of IKZF1 in BTZ alone treated cells. It was noted that in combination treated cells (LEN+BTZ) there was a degradation of IKZF1 (further validation showed downregulation of IKZF1 target genes IRF4 and c-MYC- data not shown).The combined data suggested a proteasome independent pathway mediated degradation of IKZF1. As previously reported, where autophagy can degrade ubiquitinated proteins in the absence of proteasome machinery.We noted an upregulation of autophagy pathwayin U266 cells upon treatment with LEN and BTZ compared to either of the drugs alone treated cells(correlated with IKZF1 degradation).Further, pre-treatment with an autophagy inhibitor (3-methyladenine) followed by treatment with LEN and BTZ, inhibited the degradation of IKZF1 protein.Taken together, this data demonstrates that there is a significant in-vitro synergism between LEN and BTZ. Our data suggests that the combination of LEN and PI additively induces autophagy pathway and the IKZF1 protein can be degraded via this pathway in the absence of proteasome complex.

PS-058
Bone marrow DKK-1 levels identify patients with smoldering myeloma with higher risk of progression to active multiple myeloma

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Smoldering multiple myeloma (SMM) patients can be stratified for the risk of progression to active MM based on several factors , however

new parameters to identify patients with a high risk of progression need to be defined. Recently, we analyzed bone marrow (BM) levels of several cytokines and chemokines involved in the MM-induced alterations of the bone remodeling finding that BM levels of Activin A, C-C motif chemokine ligand 20 (CCL20), Dickkopf 1 (DKK-1) and osteoprotegerin (OPG) were significantly different among patients with Monoclonal Gammopathy of Undetermined Significance (MGUS), SMM and MM. In this study we focused on the potetial role of these soluble factors in the progression of SMM patients. We analyzed a total cohort of 87 patients with SMM as defined by the International Myeloma Working Group updated diagnostic criteria admitted to our Myeloma Unit between 2007 and 2015. The median age of the patients was 65 years (range 38-92). Standard risk factors evaluated were size of serum M protein, percentage of BM plasma cells (BMPCs) and immunoparesis. Free Light Chain (FLC) ratio and FISH analysis,was available in about 30% of the patients. DKK-1, Activin A, CCL20, and OPG BM plasma levels were measured by ELISA assay. With a median follow-up time of 42 months, 21 patients progressed to active MM; median time to progression was 16 months. We firstly analyzed the main clinical features at diagnosis, finding that the percentage of BMPCs, serum M protein > 3 g/dL and immunoparesis were statistically significant correlated with progression to active MM (p<0,0001, p=0.023 and p=0.0016 respectively). BM Activin A, CCL20 and OPG median levels were not significantly different between progressed and not SMM patients, conversely SMM patients progressed to active MM showed significantly higher DKK-1 BM levels as compared to patients who had not progressed (median levels: 1777.50 pg/mL vs 782.77 pg/mL, p=0.007). BM DKK-1 levels and BMPCs were not statistically significant correlated (p=0.25 by Spearman's correlation); Consistently BM DKK-1 median levels were not significantly higher in patients with more than 20% BMPCs as compared to those with minus 20% of BMPCs. In multivariate analysis, adjusted for standard risk factors such as the size of serum M protein, the percentage of BM plasma cells, the presence of the

immunoparesis, we found that BM DKK-1 levels remained an independent prognostic factor for progression to active MM (p=0.001). Finally, we found that time to progression (TTP) to active MM was significantly worse in patients with BM DKK-1 above the median (DKK-1 median level: 971 pg/mL; p=0.021 by log rank test). Our study indicates that BM median levels of DKK-1 identify the SMM patients with higher risk of progression to active MM, and represent a new independent risk factor for progression in SMM patients.

PS-059
Influence of predictor genes of TC classification on clinical outcome in Multiple Myeloma

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A set of TC classification signature genes with prognostic expression value for Multiple Myeloma (MM) were investigated in a cohort of 156 patients of MM with a median follow-up of 11 months (range 0 to 33 months). The patients were classified as ISS stages I (10.25%), II (17.3%), III (72.4%), and their response to treatment with Thalidomide/Lenalidomide/Bortezomib based therapies was examined. MM specific aCGH arrays were analyzed among 82 out of 156 patients while Taqman based quantitative Real Time PCR assays were performed on all the patients using Quant studio 12K Flex. Expression levels of a set of 10 genes (WHSC1, CCND1,CCND3, MAFB, CX3CR1, FGFR3, CCND2, MAF, ITGB7, CKS1B) and a house keeping gene (GAPDH) were studied among MM patients alongwith cDNA from a pool of sorted plasma cells obtained from patients with Hodgkin's disease which served as controls. Data obtained was co-analyzed in terms of its correlation with aCGH profiles, response to treatment and progression free survival (PFS). An attempt has been made to investigate gene expression based predictive analyses for TC

classification in analogy with international standards and algorithms. The main observations include (i) 46% patients were cytogenetically HD while 54% NHD as per aCGH analyses (ii) patients with gene expressions reflective of 4p16 and 11q13 TC classification were most frequent, (iii) analyses of FGFR3 or MMSET (reflective of 4p16) or CCND1 (for 11q13) or MAFB (20q12) or CCND3 (for 6p21) at individual expression levels did not indicate any significant correlation with PFS; in contrast, patients with both predicted 4p16 as well as relatively high expression of CCND3, in particular, indicated a cumulative unfavourable response with significantly poor PFS outcome, and (iv) patients with higher MAF expression levels showed poor outcome in terms of PFS. Based on above, and as expected, these set of genes can be used as important predictive biomarkers for prognosis of MM.

PS-060
Dissecting genetic aberrations in Multiple Myeloma using aCGH and MLPA

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Development of modern genome-wide screening techniques along with improved understanding of multiple myeloma (MM) pathogenesis suggests that common prognostic FISH panels alone are insufficient for description of genome heterogeneity of malignant plasma cells. Low number of neoplastic cells and low mitotic potential is a major constraint for molecular evaluation in MM. Recent advent of new high-throughput techniques such as aCGH has allowed detection of genetic lesions in more than 90% of MM cases. Multiplex ligation-dependent probe amplification (MLPA) has simultaneously emerged as a fast and robust alternative method to analyze copy number changes at multiple loci across multiple patients in a single experiment based setting. The main objective of the present study was to evaluate the utility of aCGH and

MLPA in identification of genetic aberrations in MM and to compare the results obtained from aCGH and MLPA. Genomic DNA isolated from purified CD138 cells from bone marrow of MM patients (n=108) was labeled using SureTag Complete DNA Labeling Kit and hybridized onto 4x180K sureprint G3 CGH+SNP array chip (Agilent technologies). Agilent Euro Female/Male was used as the normal reference in the hybridization experiments. aCGH data was screened for aberrations by CytoGenomics software ver. 4.0. DNA from patients (n=34) was subjected to SALSA MLPA kit P425 (MRC Holland, Amsterdam, The Netherlands). Data was analyzed with Coffalyser.NET Software (MRC Holland) using healthy donors as controls. Additional copies of odd numbered chromosomes were identified by aCGH, 47% cases were categorized into hyperdiploid subgroup and 53% cases were categorized into non-hyperdiploid subgroup. Most commonly observed copy number aberrations were: del13q14.2 (aCGH:38%, MLPA:50%) followed by gain 1q23.3 (aCGH:35%, MLPA: 44%) and gain 1q21.3 (aCGH: 32%; MLPA:35%). Del17p13.1 was identified in 15% of the cases by both aCGH and MLPA. The comparison of results obtained from aCGH and MLPA suggested a concordance range of 88-100% for the identified aberrations. The discordance observed in the results obtained from a CGH and MLPA related to ploidy status (12%), del1p32.3 (5%) del1p31.3(Nil), gain1q23.3 (9%), 1q21.3 (3%), del 13q (12%) and del 17p (Nil). This study has revealed that the frequency of hyperdiploid subtype and the genetic aberrations associated with prognosis such as del13q and del17p is similar to that reported in literature. The results showed high concordance between aCGH and MLPA for almost all the aberrations except ploidy status and del 13q14; this could be because of presence of only three chromosome probes for evaluation of ploidy status in MLPA. Taken together, both aCGH and MLPA are powerful tools to detect all the prognostically relevant molecular events except balanced translocations.

PS-061
Hepatitis B virus reactivation in HBsAg-

negative patients with multiple myeloma: can not be overlooked in the endemic area

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Hepatitis B virus (HBV) reactivation has been highlighted in rituximab treated patients with CD20-positive lymphoma, especially for those with resolved hepatitis B, i.e. HBV surface antigen (HBsAg) negative but antibody to HBV core antigen (anti-HBc) positive. As both multiple myeloma (MM) itself and anti-MM therapy may have caused more impairment of B-cell immunity, the study aimed to analyze HBV reactivation in MM patients of the HBV endemic area. For 663 HBV-unvaccinated with MM diagnosed between 1996 and 2016, 11.5% of 383 with available data were HBsAg-positive at diagnosis. For 339 HBsAg-negative MM patients, the anti-HBc serostatus at diagnosis was available in 163 patients, and 63.2% of these 163 patients (n=103) were anti-HBc seropositive, i.e. resolved hepatitis B. For these 103 with resolved hepatitis B at diagnosis, total 70 (74.5% of 94 with available date) were seropositive to the antibody to HBsAg (anti-HBs) at diagnosis, and HBsAg reverse seroconversion (HBsAg-RS) was once seen in 7 patients (6.8%), including 6 seropositive and 1 seronegative to anti-HBs at diagnosis. For 60 HBsAg/anti-HBc "double-negative" MM patients, total 32 (58.2% of 55 with available date) were anti-HBs seropositive, and 7 of them (11.7%) developed HBsAg-RS, including 2 seropositive and 5 seronegative to anti-HBs at diagnosis. Totally, 14 of 163 (8.6%) patients developed HBsAg-RS, especially for those who once achieved a good treatment response. The HBV genomes in two HBsAg/anti-HBc "double-negative" patients who developed HBsAg-RS were analyzed, and missense mutations (variants) mainly located in the S1/S and P genes rather than C gene. We concluded that, in Taiwan – one of HBV endemic areas, the rate of HBsAg-RS in unvaccinated MM patients who were HBsAg/anti-HBc "double-negative" at diagnosis was not inferior to those

with resolved hepatitis B. The impaired production of anti-HBc at diagnosis of MM rather than core gene mutation of HBV was speculated.

PS-062
Characteristics of chromosome 17p aberrations identified by metaphase cytogenetics, interphase FISH and sequencing in multiple myeloma

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Background: The detection of chromosome 17p abnormality containing TP53 locus is important for risk stratification to predict survival and to define a treatment strategy in multiple myeloma (MM). The purpose of this study was to investigate the characteristics of 17p abnormality identified by metaphase cytogenetics(MC), interphase fluorescence in situ hybridization (iFISH) and TP53 mutation by TP53 exome target sequencing in MM at diagnosis. Methods : The study group included 109 patients diagnosed as having MM between 2010 and 2015 in two institution ; 44 patients with HD, 41 with NHD and 24 with normal karyotype confirmed by MC and/or iFISH. For MC, unstimulated cells from bone marrow aspirates were cultured for 24 or 48 hour. The iFISH was performed using commercially available TP53/CEP17 probes (Abbott/Vysis, Downers Grove, Ill., USA). For the specimens with low purity of plasma cells (<60%), CD138 magnetic bead sorting method was used. TP53 mutation sequencing was performed using target exome sequencing reagent kit (Access Array TP 53 target-specific panel, Fluidigm corp. CA, USA) and next generation sequencer platform

(Illumina Hiseq2000). Results: The del(17p) identified by MC and/or iFISH was found in 9% of total patients. The 34% of non-HD and 21% of HD patients showed del(17p). The del(17p) was observed in 18% of patients with t(4;14), 50% with t(14;16) and 31% with 1q gain. The typical pattern of del(17p) identified by iFISH showed 2 green signals of CEP17 and 1 red signal of TP53 (G2R1) and monosomy 17 showed 1 green signal and 1 red signal (G1R1). In chromosome 17 gain, CEP17 and TP53 signals were increased (more than two signals of green and red, respectively). The atypical iFISH patterns of 17p were variable; one patient showed G1R2 pattern ; the other patient had both G2R1 and G3R1 ; one patient, G2R1 , G3R2 , and G4R2 ; one patient, G4R3 and G4R4 ; one patient, G3R3, G3R4 and G4R4, etc. We performed TP53 mutation target sequencing in 48 patients including 14 patients with del(17p) and 34 lacking del(17p). TP53 mutation was found in 4% of patients. In HD group, 10% of patients showed TP53 mutation, while there were no non-HD patients having TP53 mutation. Among the patients with del(17p), 14% showed TP53 missense mutation ; one with p.Asp281His (c.841G>C) and the other with p.Gly245Asp (c.734G>A). All patients without del(17p) didn't showed TP53 mutation. Conclusion: This study showed that the frequency of del(17p) varied according to cytogenetic group and atypical FISH patterns on 17p were also observed. The mutation in TP53 was exclusively associated with del(17p). The prognostic significance of del(17p) with or without TP53 mutation remains to be cleared.

PS-063
Suppression of normal B lymphopoiesis in bone marrow induced by myeloma progression.

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Signal-transducing adaptor protein-2 (STAP-2) was cloned as a protein which binds and interacts with c-fms, M-CSF receptor, in 2003. We and others have reported that STAP-2 interacts with a variety of signaling or transcriptional molecules including Myd88, IkB kinase, and STAT3, and modifies the inflammatory reactions. Interestingly, in transgenic mice that overexpress STAP-2 in B lineage cells from pre-pro-B stage under the control of the Eu enhancer, the numbers of pre-pro B and immature B cells are suppressed with statistical significance. It is known that multiple myeloma (MM) cells secret several types of inflammatory cytokines such as IL-6 and TNFa. We hypothesized that the inflammation induced by MM cells could influence normal B lymphopoiesis in bone marrow (BM) via STAP-2 signaling. First, we evaluated the distribution of normal B cell progenitors in MM patients with treatment indication. There were 57 patients newly diagnosed or relapsed after an interval of more than 2 months from the last chemotherapy or 1.5 years after high-dose chemotherapy with autoPBSCT. BM samples were collected after informed consent, using protocols approved by the Investigational Review Board of Osaka University Hospital, and analyzed with 5-color (CD34/CD38/CD10/CD20/CD45) flow-cytometry. MM cells were clearly detected with CD38, CD20 and CD45 intensities, and B progenitors were divided into 4 maturation stages: CD34+ CD10Hi, CD34- CD10Hi CD20-, CD34- CD10Low CD20Low and CD34- CD10- CD20Hi. In MM BM, the percentages of B progenitors were varied, but lower than healthy control. PCR experiments of STAP-2 in CD10+ B progenitors of MM patients showed that the expression was up-regulated in BM of patients with severe suppression of B lymphopoiesis. Furthermore, we sought correlations between B lymphopoiesis and disease or patient condition. Age, albumin, and creatinine showed no significant relevance. In contrast, patients with high β2microglobulin (B2M) (> 3.5 mg/dl) had significantly lower percentages of B progenitors, while mature lymphocyte counts in peripheral blood were not associated. The burden of MM cells (>30% in BM) and severity of anemia also affected the

distribution of B lymphopoiesis in BM. It is known that hematopoiesis is influenced by hematological malignancy, as well as nonneoplastic condition including infection or chronic inflammation. In this study, we show that myeloma progression inhibits normal B lymphopoiesis, and there was a negative correlation between B progenitors and the prognostic factor, B2M. As a possible mechanism, we propose the up-regulation of STAP-2 signaling in MM BM would influence the early development of B cells. Further study would clarify the detailed mechanisms to suppress B cell generation in MM patients.

PS-064
AUTOLOGOUS STEM CELL TRANSPLANT IMPROVES DEPTH OF RESPONSE AND OUTCOMES IN AFRICAN AMERICAN PATIENTS WHEN COMPARED WITH CAUCASIAN PATIENTS

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BACKGROUND: There appears to be stark disparity in the incidence of multiple myeloma (MM) in the African American (AA) population (2-3 times higher) compared with Caucasians (C) [SEER 1975-2008 Data]. The AA pts appear to have lower incidence of high risk cytogenetics [Greenberg G et al, Blood Cancer J 2015] and the outcomes have not improved in the novel era therapy compared to C pts [Ailawahdi S et al, Blood Cancer J 2016]. We prospectively examined newly diagnosed transplant eligible MM pts at our center for outcomes. PTS AND METHODS: The MM database was interrogated from March 2014-October 2016 for all autologous stem cell transplant (ASCT) eligible MM pts. Clinical features, induction regimens, treatment responses and ASCT outcomes were compared between AA and C pts. Continuous variables were compared using median two-sample median tests, while incidences and proportions were compared using Fisher's exact tests. Survival distributions were estimated using Kaplan Meier techniques and compared with a log rank test. The responses for each subject pre and post ASCT were paired and analyzed using a generalized McNemar's Test. RESULTS: A total of 93 consecutive ASCT eligible MM pts were identified (39 AA, 54 C). There is no significant difference in gender distribution between the cohorts (p = 0.409) but AA pts were diagnosed at a significantly younger age (median age 56 years) than C pts (median age 62.5 years) (p =0.016). There appears to be a trend towards a statistically significant difference in the proportion of deletion 13 (cytogenetics) between the cohorts but otherwise no major differences were observed. There were no statistically significant differences in any clinical variable at diagnosis (lab features, serum LDH levels, ISS staging, cytogenetics, etc.). There was a statistically significant difference in the number of pts achieving an optimal response (>VGPR) to induction treatment between C and AA pts (81% vs. 56%, p=0.015). Interestingly, there appears to be a strong and paradoxical trend towards statistical significance in post-transplant responses (p=0.087), with 97.4% of AAs achieving an optimal response compared to 86.4% of the C. For the AA subset, 26 of 38 (68.4%) increased their depth of response with ASCT. Comparatively, only 48.0% (24 of 50) in the C subset increased their depth of response with ASCT. There was no significant difference in 1-year progression free survival between the two cohorts (89.6% in AA, 84% in C MM pts, p=0.479). CONCLUSIONS: Although AA pts appear to be younger than C pts, there were no differences observed in disease features at time of presentation. The depth of response appears to be lower in AA pts but ASCT helps deepen the response to the same degree as C pts. This translates in to comparable PFS at the 1-year mark. When provided similar access to care, AA

pts appear to have similar post-ASCT response and PFS compared to C pts.

PS-065
The outcomes of Korean patients with primary plasma cell leukemia: Analysis of Korean Multiple Myeloma Working Party (KMM160)

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Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell neoplasm, with rapid clinical course. In this study, we evaluated the treatment status and survival outcomes of Korean patients with pPCL. Sixty-nine patients were diagnosed with pPCL between February 1998 and December 2015. Among the 69 patients, 59 patients were treated. Twenty-two patients (37.3%) were treated with novel agents-based regimen with high dose chemotherapy and autologous stem cell transplantation (HDT/ASCT), 44.1% with novel agents-based regimens only, and 18.6% of patients were treated with chemotherapy only. Twenty-two patients underwent upfront HDT/ASCT and one received the allogeneic stem cell transplantation.

After a median follow-up of 16.5 months, median progression free survival and overall survival (OS) was 10.5 months (95% CI 7.0-14.1), and 16.1 months (95% CI 12.0-20.2), respectively. The median OS of three treatment groups comprising conventional chemotherapy only, novel agents only, and novel agents + HDT/ASCT were 2.9, 12.3, and 31.1 months, respectively ($P < 0.001$). Overall response rates after initial therapy was significantly higher in patients treated with novel agents-based regimens compared with those treated with conventional chemotherapies (75% vs. 43.4%, $P = 0.026$). On multivariate analysis, increased lactate dehydrogenase level (HR 12.063, 95% CI 4.125-35.272, $P < 0.001$), low albumin (<3.5 g/dL) (HR 2.934, 95% CI 1.376-6.258, $P = 0.005$), novel agents during treatment period (HR 0.235, 95% CI 0.093-0.594, $P = 0.002$), and performance of HDT/ASCT (HR 0.283, 95% CI 0.110-0.725, $P = 0.009$) were significantly associated with OS. In conclusion, patients with pPCL had poor survival outcomes, and the use of novel agents-based therapy with HDT/ASCT and achievement of appropriate response to frontline therapy would be important for expecting improved OS in patients with pPCL.

PS-066
A prognostic scoring system for patients with multiple myeloma who were classified stage II by Revised International Staging System

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Revised International Staging System (R-ISS) is recently proposed risk stratification algorism based on ISS, cytogenetic risk, and lactate dehydrogenase in multiple myeloma (MM).

Although R-ISS had an improved prognostic power compared to ISS, there is a problem that patients with stage II increase to 1.7 times. In this study, we evaluated survival outcomes and a new prognostic tool for MM patients classified as R-ISS II. Retrospective data from 441 patients who were initially treated with a novel agent-containing regimens were analyzed. R-ISS staging system could discriminate survival outcome more clearly compared to ISS in patients treated with novel-agents [median overall survival (OS) times of R-ISS I vs. II. Vs. III was 76.3 vs. 51.3 vs. 30.3 months, $P < 0.001$]. By applying R-ISS, 6.2% of patients with ISS I, and 24.3% with ISS III were reclassified into R-ISS II. Overall, 290 patients (66%) was classified into R-ISS II and had wide range of survival outcomes (0.7-114.5 months). In multivariate analysis, poor performance status (PS) (HR 1.657, 95% CI 1.159-2.370, P =0.006), del (17p13) (HR 2.227, 95% CI 1.174-4.223), P = 0.014), and thrombocytopenia (HR 1.533, 95% CI 1.033-2.276, P = 0.034) were significantly associated with OS in patients with R-ISS II. Based on this analysis, we constructed a new prognostic model consisted of poor PS (1 point), del(17p13) (2 point), and thrombocytopenia (1point). Among the 290 patients, 152 patients (52.4%) were classified as low-risk (score 0), 109 (37.5%) as intermediate risk (score 1), and 29 (10%) as high risk (scores 2 or more). The median OS times for the corresponding risk groups was 57.5 months (95% CI 40.4-74.5), 30.2 months (95% CI 20.7-39.7), and 20.9 months (95% CI 6.4-35.3) (P <0.001). R-ISS is an excellent prognostic tool in MM in the novel-agent era, but there is a limitation that most of patients were classified into R-ISS II. A new prognostic model for patients with R-ISS II is needed, and prognostic scoring system based on poor PS, del(17p13), and thrombocytopenia may be useful to distinguishing survival outcomes of patients with R-ISS II.

PS-067
Serum soluble SLAMF7 is correlated with disease progression in multiple myeloma and may affect anti-SLAMF7 antibody therapy

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Introduction: Signaling lymphocytic activation molecule family member 7 (SLAMF7; CS1, CRACC, CD317) is a member of the immunoglobulin superfamily expressed on T, B, and natural killer (NK) cells and contributes to activation of these immune cells. SLAMF7 is also highly expressed on plasma cells from patients with multiple myeloma (MM) and involved in MM cell adhesion to bone marrow (BM) stromal cells via co-localization with CD138 molecules. We investigated the concentration of serum soluble SLAMF7 (sSLAMF7) and its clinical significance in MM. Furthermore, we examined whether sSLAMF7 could affect the antitumor activity of anti-SLAMF7 antibody. Materials and Methods: Serum sSLAMF7 concentrations were measured using ELISA in 16 monoclonal gammopathy of undetermined significance (MGUS) patients, 103 newly diagnosed MM patients (18 asymptomatic and 85 symptomatic), and 16 healthy controls. Next, we analyzed the characteristics of patients in whom serum sSLAMF7 was detected and the correlation with SLAMF7 expression levels in CD138+ myeloma cells. Finally, NK cell-mediated antibody-mediated antibody-dependent cytotoxic (ADCC) activity against the SLAM7-expressing MM cell line U266 was assessed in the lactate dehydrogenase (LDH)-based

cytotoxicity assay using NK cell line NK-92MI. Results: 33% of MM patients (n=34), but no MGUS patients or controls, had detectable sSLAMF7 in serum (range: 0.011–14.7 ng/mL). sSLAMF7 levels in symptomatic MM patients were significantly higher than those in asymptomatic ones (P=0.0316). Furthermore, sSLAMF7 levels in patients with International Staging System (ISS) and revised ISS (R-ISS) stage 2/3 were markedly increased in comparison with ISS and R-ISS stage 1 (P=0.0007 and 0.0177, respectively). Serum sSLAMF7 concentrations were not correlated with the percentage of plasma cells or SLAMF7 mRNA expression levels in CD138+ plasma cells in BM obtained from patients. When comparing the clinical characteristics between sSLAMF7-positive (n=34) and -negative groups (n=69), plasma cell percentage and LDH levels, and corrected calcium, creatinine, C-reactive protein, β2-microglobulin, and interleukin-6 levels were significantly higher but levels of hemoglobin and albumin and estimated glomerular filtration rate were markedly lower in the sSLAMF7-positive group. In the in vitro study, NK cell-mediated ADCC activity using anti-SLAMF7 antibody was inhibited by recombinant SLAMF7. Conclusion: Our data suggest that high levels of serum sSLAMF7 in MM patients are correlated with advanced disease, and therefore sSLAMF7 levels may be a useful indicator of disease progression in MM. Moreover, sSLAMF7 may suppress the therapeutic effects of elotuzumab in MM. Further studies are in progress to clarify the mechanism of sSLAMF7 production in MM.

PS-068 (d)
Growth Differentiation Factor 15 (GDF-15) Is a New Biomarker for Overall Survival and Renal Outcomes in Patients with Light Chain (AL) Amyloidosis

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Growth differentiation factor-15 (GDF-15), a member of TGF-beta family, is involved in several pathological conditions, including inflammation, cancer, cardiovascular and renal diseases. Serum GDF-15 levels adds prognostic information to conventional prognostic factors, such as NT-proBNP and troponins, in cardiovascular disorders and has been associated with risk of end stage renal disease in diabetics. We evaluated the prognostic significance of serum GDF-15 in two independent cohorts from the Pavia Amyloidosis Center and the Department of Clinical Therapeutics, Athens. Serum levels of GDF-15 were measured by a novel pre-commercial immunoassay (Roche Diagnostics) in stored serum. The Pavia cohort included 202 and the Athens cohort included 107 patients with AL amyloidosis. Median age and involved FLC levels were similar between the two cohorts but there were differences in other baseline characteristics including heart involvement (77% vs 62% for Pavia vs Athens, p=0.007), Mayo stage 3(42% in Pavia vs 31% in Athens cohort, p=0.04), but stage 3B was similar (22% vs 24%) and peripheral nerve involvement (11% in Pavia vs 25% in Athens cohort, p=0.001). Renal involvement (67% vs 72%, p=0.415), median eGFR and renal stage distribution were similar (p=0.544). Two year survival was 59% for Pavia and 56% for Athens cohort. Median GDF-15 levels was 3027 pg/ml in Pavia and 3854 pg/ml in Athens cohort (p=0.09). The upper quartile of GDF-15 levels, however, was ≥5658 pg/ml in the Pavia and ≥7553 pg/ml in Athens cohort, and 90% and 94% of patients in the two cohorts had GDF-15 levels >1200 pg/ml (the upper limit of normal for individuals without cardiovascular disease). We evaluated the prognostic significance of GDF-15 levels for survival in the two cohorts by applying the previously identified cutoff of 7575 pg/ml. GDF-15 above cutoff was associated with shorter survival both in Pavia (17 months vs not reached, p=0.003) and Athens cohort (13 vs 47 months, p=0.03). In separate multivariate models for each cohort, that included Mayo

stage, GDF-15 remained of independent prognostic significance over Mayo stage, with a hazard ratio (HR) of 1.9 (95% CI 1.2-3.3, p=0.01) in Pavia cohort and a HR of 1.8 (95% CI 1.2-3.6, p=0.03) in the Athens cohort. We then evaluated GDF-15 levels for prognosis of renal outcomes (dialysis): GDF-15 >4000 pg/ml was associated with a HR of 7 (95% CI 2015.6, p=0.001) in Athens cohort (progression to dialysis within 2 years in 7% vs 47%); and HR of 4.9 in Pavia cohort. In both cohorts GDF-15 levels were prognostic for dialysis independent renal stage. Thus, we validated and confirmed in two independent cohorts, with differences in their characteristics, the prognostic value of GDF-15, as a biomarker with prognostic implications for different outcomes in patients with AL amyloidosis. Importantly, GDF-15 emerges also as new biomarkers for renal outcomes in patients with AL amyloidosis.

PS-069
Indirubins: A Potential Therapeutic Target in Multiple Myeloma

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Current drugs in the treatment of Multiple Myeloma (MM) result in cell death via a number of mechanisms including a direct effect on plasma cells as well as alteration in the BM microenvironment. Among the FDA approved kinase inhibitors, few are based on natural scaffolds. 6-bromoindirubin-3'-oxime (6BIO) is a potent kinase inhibitor based on the natural 6-bromoindirubin scaffold. Indirubin and 6-bromoindirubin are two natural products that have found a particular interest in dye chemistry as the main constituent of indigo and Tyrian purple dyes. Recent findings discovered that 6BIO was a promising anti-cancer agent acting on the JAK/STAT signaling pathway mediating cell proliferation. A library containing 2000 natural molecules was constructed using several data platforms. Each molecule was processed through different filters such as tautomeric studies, protonation and steroisomerism status. Two approaches were followed: the structure-based virtual screening and the ligand-based virtual screening. The results of both approaches were combined, the molecules ranked, and 100 out of 2000 were identified as strong potential bioactive hits for the β5 subunit. Out of these 100 molecules, the chemical structures of high interest were the following: indole alkaloids derivatives (indirubins), flavonoids, secoiridoids, simple phenolic acids and acetophenone. Fifty indirubins derivatives were selected based on different criteria: structure, known/unknown targets, chemodiversity in substitution patterns. To explore the inhibitory effects of indirubins in MM, we performed the WST1 proliferation assay in three MM cell lines (H929, JJN3, L363). Initially, all the selected indirubins(~50 indirubins) were tested at 7.5μM in L363 cell line and proliferation results from the WST1 assay extracted after 24 hours of treatment. More than half of the indirubins tested displayed more than 50% reduction of the proliferation at 7.5μM. Interestingly, 10 out of the 50 indirubinstested reduced more than 80% proliferation after 24 hours. The most active indirubins were tested in H929 and JJN3 cell lines, where similar effects were seen after 24 hours of treatment. All tested indirubins acted in a dose-dependent manner. Among the most active indirubins, two molecules namely 805 and 673 emerged as attractive for further development. Compound 805 is an analog of MLS-2384 while compound 673 is an analog of MLS-2438. The latter derivative represents a promising candidate displaying an IC50 below the micromolar range on H929 and JJN3 cells. To determine the kind of cell death caused by one of the most active indirubins, 673, cell cycle analysis was performed before and after treatment in H929 cell line. In particular changes in RNA expression of 84 genes key to

cell cycle regulation were analyzed in H929 cell line. Our results show that among other genes, the ones which have a dramatic increase in their expression

PS-070

Real-World Data on Clinical Characteristics, Prognosis and Outcome of Primary Plasma Cell Leukemia: A Study of the Greek Myeloma Study Group in the Era of Novel Agents

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Primary plasma cell leukemia (pPCL) exhibits poor outcome. We and others have previously demonstrated that novel agents and mainly bortezomib-based regimens (BBR) improve response rates and survival, however the prognostic impact of current treatments and biological markers on the outcome of pPCL has not been sufficiently explored, outside clinical trials. We analyzed the medical records of 50 patients with pPCL (M/F: 25:25; median age 65.5 years, range: 32-86 years; IgG: 19, IgA: 9, light-chain: 14, IgD: 2, non-secretory: 6; ISS1: 5, ISS2: 16, ISS3: 29) out of 2711 myeloma patients (1.8%), registered in the Greek Myeloma study group database, between 2000-2015; 52% of patients had Eastern Cooperative Group (ECOG) performance status ≥ 2; 53% had abnormal lactate dehydrogenase (LDH), 28% had hypercalcemia, 68% had hemoglobin <10 g/dL and 65% had high risk cytogenetics; 49/50 patients received therapy: 38 patients received BBR, one patient received melphalan-prednisone-thalidomide and 10 patients received conventional chemotherapy (C/T); 15 patients underwent ASCT consolidation; 48 patients were evaluated for response: 79% achieved objective response (≥PR) and 35% had at least very good partial response (≥vgPR), including

17% complete responses. Achievement of ≥vgPR correlated with BBR+ASCT (p=0.02). After a median follow up of 61 months (95% CI: 34.5-87.4), 38 patients have died (disease progression: 18, infection: 16, other causes: 4). Early mortality (≤1 month) occurred in 3/38 deceased patients; 31/38 patients who responded to treatment progressed and 27/31 received 2nd line treatment (lenalidomide-based: 7, BBR: 16, C/T: 4). Progression-free survival was 12 months (95% CI: 8.5-15.4) and it was marginally longer in patients treated with BBR+ASCT vs. others (18 vs. 10 months, p=0.07). Median OS was 17 months (95% CI: 13-21 months) and it was double in patients treated with BBR+ASCT compared to others (33 months vs. 16 months); median survival after PCL progression was 7 months (95% CI: 3-11 months).

PS-071

Exome sequencing of AL amyloidosis reveals recurrently mutated genes

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Background Immunoglobulin light chain amyloidosis (ALA) is a plasma cell dyscrasia characterized by deposition of amyloid fibrils in various organs and tissues, leading to organ dysfunction. Until now, only one systematic study of genomic profile of ALA on exome level was published. The aim of this study was to reveal genomic profile of ALA patients, to identify the potential role of mutated genes in pathogenesis of ALA and to compare number of

mutations with other monoclonal gammopathies. Methods Library was prepared using SureSelect Human All Exon V5 Kit. Aberrant plasma cells and peripheral blood (to exclude germinal mutations) was collected from 8 samples. 6 ALA and 2 ALA+MM were sequenced on Illumina HiSeq 4000 platform with average coverage 50x. Somatic variations were called using VarScan v2.0. Only non-synonymous mutations, indels and splice site alterations were considered for further investigation. Results The median number of mutated genes in aberrant population was 292 (range 230-440) per patient. 73 genes shared mutations among 3 or more patients. The most mutated genes were PAK2, HLA0DRB1, MUC3A, DHFRL1, IGHV2070, where the SNV was present in all patients. PAK2 gene is involved in cancerogenesis and is related to migration of MM cells and can also serve as a potential drug target. The nonsynonymous mutations in in MUC3A gene may affect its efficacy as a barrier against bacterial and increase the risk of infection because of likely change the extracellular structure or the structure of the glycosylation site of this protein. Genes IGHV2070 and HLA0DRB1 play a central role in the immune system and can vary between individuals. Conclusion We identified relatively high number of mutation per patient compared to previously published study by Paiva et al., 2016 (median 292 versus 15 SNVs). The discrepancy can be caused by different sequencing technology and mutation calling algorithm. In contrast to the other study, we also identified many recurrently mutated genes, however some of those can be just artefacts caused by large gene sizes and thus generally higher polymorphism (e.g. mucins). Total number of mutations was comparable among ALA patients and ALA+MM patients. For ALA+MM patients we did not detect SNV in any of the most commonly mutated genes in MM (like KRAS, NRAS, FAM46C, DIS3 and TP53). In further detailed study further investigate whether ALA with MM represent one disease or two coexisting diseases, based on genomic profile and clonal evolution.

PS-072
Monoclonal immunoglobulin deposition disease and proliferative glomerulonephritis with monoclonal immunoglobulin disease- how do they differ clinically?

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Background: Among non amyloidogenic paraproteinemia, monoclonal immunoglobulin deposition disease(MIDD) and less common entity proliferative glomerulonephritis with monoclonal immunoglobulin disease(PGNMID) have been described. Both being monoclonal disease with almost similar clinical presentation are differentiated on electron microscopy by immune complex type deposits in PGNMID from randall type deposits in MIDD. Materials and methods: A retrospective 8 years database from Department of Histopathology and Central Registry Department, PGIMER were retrieved from July 2008 to June 2016. All cases which were diagnosed as MIDD and PGNMID and confirmed ultrastructurally were included and their clinical course were compared. Results: There were 19 MIDD cases (mean age 53.2years with M: F ratio 2.1) ; 7 PGNMID cases(mean age 43.4 years and M: F ratio 2.5). Among MIDD cases one case was of heavy chain deposition disease, one was heavy and light chain deposition disease and 17 cases were of light chain deposition disease. The clinical presentations were same with rapidly rising renal failure(RPRF) and nephrotic syndrome(NS) being common presentation in both. The mean 24 hour proteinuria was also comparable in both the groups with 3.8gm and

3.7gm respectively. On serum free light chain assay(sFLC), kappa restriction was dominantly seen in MIDD(13 cases compared to lambda in 6). Kappa was raised in all cases of PGNMID, however, k:λ ratio was within normal range(Normal 0.37-3.5) . Total of 10 MIDD cases had diagnosis of multiple myeloma either at the time of renal biopsy or later, 3 cases had renal limited disease, further data was not available in 6 cases. The clinical course in isolated MIDD and PGNMID were like monoclonal gammopathy of renal significance and were almost comparable in both. However MIDD associated with other paraproteinemia had poorer outcome. Five PGNMID patients progressed to ESRD within 6 months of diagnosis. One had partial response to prednisolone based therapy and one had recurrence and died of infection post transplant. Conclusion: Paraprotein induced kidney damage have varied morphology. Among glomerular paraproteinemia MIDD and PGNMID presents with almost similar clinical presentation. The pathology and clinical outcomes in PGNMID and MIDD are relatively less recognised pertaining to less awareness and limited number of cases. The overall outcome of isolated MIDD and PGNMID do not differ, however MIDD are often associated with multiple myeloma and is infrequently associated with other paraproteinemia like cast nephropathy and proximal tubulopathy have grave prognosis.

PS-073
Evaluating the role of Tregs in the progression of Multiple Myeloma

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Introduction: The role of regulatory T-cells (Treg) in multiple myeloma has been unclear despite a decade of work. There are conflicting reports of the Treg frequency being increased, decreased and unchanged as compared to controls. The reasons cited for the variability in frequency are differences in the compartment studied, Treg definitions and methodology. There is however consensus that Tregs remain functional. Methods: Specimens obtained from the The Hematology Cell Bank of British Columbia were used for this study. Peripheral blood (PB) and bone marrow (BM) samples of 10 treatment naive patients with monoclonal gammopathy of undetermined significance (MGUS), 10 patients with multiple myeloma (MM) and 5 healthy controls were included. T-cell subsets CD4, CD8, Treg and its phenotype were analyzed by multi-parameter flow cytometry. Treg function was analyzed using the BD FastImmune® regulatory T-cell function kit. Results: The mean % Treg in the BM was not significantly different between MGUS, myeloma and controls (p=0.24). The mean % Treg in PB was however significantly higher in MM than MGUS and controls (p=0.03). Treg phenotypes (CD45RA+, CD161+ & TH17 like Tregs) were not significantly different between MGUS, MM and controls PB and BM. Overall activated (CD69+) and proliferating (Ki67+) Tregs were higher in MM BM as compared to MGUS/ controls. Indirect Treg function as assessed by intracellular cytokine expression of IFN-γ and IL-17 showed no significant differences between the three groups. Direct cytotoxicity function of Tregs as assessed by contact dependent suppression of conventional T-cells (CD4+ and CD8+ T-cells) showed MM Tregs were as suppressive as the control Tregs. Discussion: Our study confirms that Tregs though increased in PB are unchanged in the BM when comparing MGUS, MM and controls. This was true for the pro-inflammatory Treg phenotypes CD161+ and Th17 like Tregs as well. Tregs in the MM BM were more activated and proliferating than the MGUS/ control Tregs. Functionally, the Tregs in MM were as suppressive as the healthy controls. Conclusion: This study shows that the Tregs are unaffected in number and function in plasma cell dyscrasias and are unlikely to play an important role in the progression of MGUS to MM.

PS-074
PROGNOSTIC VALUE OF DIAGNOSTIC BONE MARROW PLASMA CELL PERCENTAGE IN MULTIPLE MYELOMA

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Multiple myeloma (MM) shows great variability in clinical course of the disease, and survival varies considerably. Myeloma plasma cell percentage is a major diagnostic criterion of MM, however its prognostic value is uncertain and rather worthless in the era of modern prognostic factors. Nevertheless, bone marrow plasma cell (BMPC) percentage both pre- and post-transplant has been identified as a prognostic factor for disease progression and survival. Also, clonal BMPC involvement of greater than or equal to 60% is acceptable as a strong biomarker and a myeloma-defining event in the absence of CRAB features (revised diagnostic criteria for MM 2014). The prognostic impact of BMPC percentage was evaluated in 345 newly diagnosed patients with multiple myeloma. There were 154 women and 191 men with a median age of 65(29-88) years. Disease stage at diagnosis was III in 188 (54.5%) patients; paraprotein was IgG in 216 (62.6%), IgA in 70 (20%), IgD in 1 (0.3%), light chain only in 35 (10%), non secreting in 23 (7%). Sixty-one (18%) of them had renal impairment at diagnosis with creatinine levels higher than 2 mg/dl. All patients had bone marrow smear assessment by conventional morphology while a bone marrow biopsy result was available in 228 patients. Percentages of BMPCs were significantly correlated between biopsy and aspirate (r = 0.76, p=0.01). However, in 28 cases BMPCs were considerably underestimated by smear compared to biopsy,

while the opposite was observed only in 4 cases. Overall survival (OS, 5-year probability) was 55.5% and median OS was 65 months (95CI 56-73.7). After a median follow up of 48 months, patients with <50% BMPCs at diagnosis had a significantly better survival (OS) compared to those with ≥ 50% BMPCs (median 85 vs 48 months respectively, p <0.001). The prognostic impact of BMPC percentage was more apparent in patients with less extensive BM infiltration. Patients with BMPCs <25% had a survival advantage over those with 25-70% and >70% (median OS not reached vs 60 vs 53 months, p=0.004). However, the percentage of BMPCs was not an independent predictor of survival and progression-free survival in multivariate model analysis. OS was adversely affected only by lactate dehydrogenase, older age, renal impairment and disease stage. BMPC percentage correlated significantly with clinical stage, levels of albumin, LDH and hemoglobin (p<0.001 for all) and renal impairment (p=0.005). In conclusion, although BMPC percentage is not an independent prognostic factor for MM, it provides valuable diagnostic and prognostic information.

PS-075
IMWG ´14 DIAGNOSTIC CRITERIA TO INITIATE TREATMENT IN NEW DIAGNOSED MULTIPLE MYELOMA (NDMM): REAL-WORLD STADISTICS

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Introduction Diagnostic criteria for Symptomatic Multiple Myeloma (MM) Published in 2003 by the International Myeloma Working Group(IMWG'03) established for the presence of a bone Marrow infiltration by plasma cells (BMPC) in any percentage And / or the presence of a monoclonal component of any

amount Along with the presence of signs or symptoms of organ damage (CRAB) attributable to the proliferation of plasma cells. These criteria have not changed in the last decade until the Recent revision of diagnostic criteria and treatment that IMWG Published by the end of 2014, which proposes an initial Pathologic condition (> 10% BMPC or demonstration of a Plasmacytoma) as a preliminary condition before starting treatment Due to "CRAB redefined" and / or the presence of markers of Rapid progression to "classical-symptomatic" MM criteria. Material and Methods We have performed a retrospective analysis with all new MM cases diagnosed from Dec-2014 to Nov-2016 (2 years). 48 patients were diagnosed of MM. 24 were male and 24 female. The median age at diagnosis was 74 years (55-87), 8 were under 65 (U65) and 40 were over 65(O65). 3 were diagnosed after biopsy of plasmacytomas. None of them have Bone Marrow (BM) infiltration but no PET-CT multitopic involvement. 7 of these NDMM were smoldering MM (sMM). All of then completed initial staging with more sensitive imaging tests than conventional radiology (MRI and / or PET-CT) 2 of these sMM were under 65 years old and were included in a clinical trial. The other 5 were older than 65 and after a median of 16 months of follow-up did not meet criteria in initiate treatment. Of the 41 patients who started treatment, 9 of them were new criteria, the rest met criteria for classic organic disease (CRAB). 6 patients were diagnosed after performance of PET-CT (3 of them after plasmacytoma biopsy; initial diagnosis: solitary plasmacytoma), 2 with FLC ratio criterium and the last one with BM Plasmatic Cell (BMPC) >60%, MRI image and FLC criteria. Analysis There are few information about real-life statistics in NDMM according to new criteria to initiate treatment. This 2year analysis shows a percentage of patients (22%) who have initiated new treatments superior to those described in the literature. Conclusions One of the hypotheses for introducing new criteria for initiating treatment was that the initiation of adequate and early treatment may improve the prognosis of patients with symptomatic NDMM. In an aging population such as the one we present, we believe that these new criteria to initiate

treatment can improve the medium- and long-term prognosis of this group of people with few chance to start intensive or a lot of lines of treatment because of increasingly comorbidities by age. Further follow-up and evaluation of survival comparing the "classical" group vs new-criteria group are guaranteed to assess if these early treatment will improve survival.

PS-076
Methylation of multiple myeloma in activity and remission

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Tumor suppressor gene promoter CpG island methylation is a well-recognized mechanism in cancer pathogenesis, but its role in multiple myeloma is controversial. The present study investigated the methylation status and expression of P16, suppressor of cytokine signaling 1 (SOCS-1), P73, E-cadherin and Src homology region 2 domain-containing phosphatase 1 (SHP-1), as well as global methylation in patients with multiple myeloma during active disease and remission. Bone marrow samples were obtained from 43 patients during active disease and remission. Methylation-specific polymerase chain reaction was performed on bisulfite-treated DNA to determine promoter-specific methylation. Global methylation was assessed by ELISA. Gene expression was measured using reverse-transcription polymerase chain reaction. The results indicated that SOCS-1 methylation occurred more frequently during active disease than remission [29 vs. 3.2% (P=0.021)] and was associated with more advanced forms of the disease [international staging system (ISS) 3, 16.67% vs. ISS 1, 8.3% (P=0.037)]. SHP-1 methylation during active disease was associated with a lower probability of survival at

39-month follow up (median), 52.5 vs. 87.5% (P=0.025). The percentage of methylation was associated with active disease and remission, but this was not significant. Global hypomethylation at remission was a negative predictor factor for overall survival. The results indicated that methylated P16, SOCS-1 and SHP-1 were associated with clinical variables of poor prognosis in multiple myeloma, as was the persistence of global hypomethylation at remission. The negative impact on overall survival of global hypomethylation at remission must be confirmed in a larger sample. Future studies are necessary to investigate whether patients with global hypermethylation at remission should receive more aggressive treatments to improve their overall survival.

PS-077 (d)
Response assignment using Hevylite correlates with clinical outcome in multiple myeloma

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Introduction: Novel heavy+light chain (Hevylite®, HLC) immunoassays offer an alternative method to assess haematological response in multiple myeloma (MM). Here we compare the consistency of responses assigned by HLC and standard IMWG criteria and evaluate the clinical impact of discordance. Methods: Newly diagnosed IgG and IgA MM patients enrolled onto the IFM-2009 trial and with monoclonal immunoglobulin >10 g/L (n=509), were included. Median age was 59 [range: 33-66] years, follow-up 30 [3-56] months). Haematological responses were assigned before maintenance therapy using standard IMWG criteria or equivalent HLC criteria (based on dHLC [clonal – non clonal concentrations] and HLC ratio [HLCr]). A complete response (CR) by HLC assessment referred to normalization of HLCr with <5% BMPCs. HLC-pair suppression was defined as levels of non-clonal HLC (e.g. IgG kappa in an IgG lambda patient) below the reference range; severe suppression denoted non-clonal HLC levels suppressed by at least 50%. Minimal residual disease (MRD) was based on 7-color flow cytometry. Results: At diagnosis, HLCr was abnormal in 100% IgA and 99% IgG patients. Before maintenance, the agreement in responses assigned with HLC compared to IMWG criteria was moderate. The best agreement was observed for patients achieving ≤partial response (≤PR, 79%, 76/96) or ≥CR (92% 130/142). By contrast, for 225 patients with a very good PR (VGPR) by IMWG criteria, HLC responses were concordant in only 45% (102/225) patients, with the remainder assigned as PR (18/225) or ≥CR (105/225). Median PFS for patients achieving VGPR by IMWG criteria was 34.5 months; HLC-based responses further stratified these patients into ≤PR, VGPR and ≥CR, with significantly different outcomes (median PFS=21.3, 28.9 months, and not reached, respectively; p<0.0001). By contrast, patients achieving a VGPR by HLC criteria could not be stratified based on their IMWG response. Importantly, an abnormal HLCr before maintenance had a greater concordance with MRD+ assessment (72% positive) compared to IFE (51% positive); whereas both a normal HLCr and negative IFE displayed similar agreement with MRD- assessment (88% and 94% negative, respectively). Finally, 15(11%) and 7(5%) of 142 patients at CR had suppressed or severely suppressed non-clonal HLC levels; these patients had shorter PFS (35.1 months; p=0.060; and 22.9 months; p=0.004, respectively) compared to patients with no/moderate HLC-pair suppression (median PFS not reached). Conclusions: HLC response assignment allows further stratification of standard IMWG responses into different categories with significantly distinct clinical outcomes. For patients achieving CR by IMWG criteria, HLC-pair suppression identifies a small

group of patients with poorer prognosis; possibly a consequence of deficient immune reconstitution.

PS-078

A Widely Applicable Method for Resolving Therapeutic Monoclonal Drug Interference for Myeloma Patients

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Background: The dawning of the era of therapeutic monoclonal antibody (t-mAb) immunotherapy for multiple myeloma (MM) has resulted in treatment related interferences for traditional electrophoretic methods as it can be difficult to distinguish the t-mAb from the patient's M-protein. While t-mAb specific electrophoretic assays are available, there is a need for a more widely applicable method for resolving the ever increasing number of t-mAbs from M-proteins. Objective: The goal of this study was to evaluate the use of accurate light chain (LC) mass (miRAMM) measurements to discriminate between M-Proteins and t-mAbs. Methods: Residual serum samples for 6 IgG kappa plasma cell dyscrasia patients were obtained from our clinical lab. The 6 residual serum M-Protein levels were adjusted to 0.1, 0.5 and 1g/dL using normal human serum and each were spiked with 3 levels (0.05, 0.1 and 0.5 g/dL) of daratumumab, elotuzumab or isotuximab. Each sample was then enriched for IgG using resins with camelid-derived nanobodies against the constant region of the IgG heavy chain (HC). After washing, samples were eluted from the resin with 20 uL of 5% acetic acid containing 50 mM TCEP to disassociate immunoglobulis (Ig) into LC and HC components. The mass distribution of the Ig LCs was obtained by miRAMM as previously described [1]. Results: miRAMM measurements were capable of precisely measuring the mass of the each t-mAb light chain and M-Protein LC within +/- 0.5 Da. The average masses of daratumumab, elotuzumab and isatuximab were

23380, 23423 and 23488, respectively. In all cases, the method was capable of baseline resolving the mAb from the IgG kappa M-protein. The relative area of the LC signal was in proportion the relative amount of t-mAb and M-protein. Conclusion: The results of this experiment demonstrate that miRAMM could resolve M-proteins and mAbs if their light chain masses differ by as little as +/- 2 Da without the need for anti-mAb antibodies making the miRAMM broadly applicable to a number of t-mAbs. 1. Barnidge DR, Dasari S, Botz CM, et al. Using mass spectrometry to monitor monoclonal immunoglobulins in patients with a monoclonal gammopathy. Journal of proteome research. 2014;13(3):1419-1427.

PS-079

Combination bone marrow imaging using PET-MRI in plasma cell dyscrasias: correlation with prognostic laboratory values and clinicopathological diagnosis

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Background: Magnetic resonance imaging (MRI) is recommended by the International Myeloma Working Group as the imaging modality of choice in asymptomatic myeloma patients, in staging of solitary plasmacytomas, and in myeloma patients with suspected neurological or soft tissue involvement. However positron emission tomography (PET) has the capacity to reveal metabolic marrow changes, and in combination with low dose computed tomography (CT) has been shown to predict survival and may provide for a better definition of complete remission. Therefore, a combination imaging method using highly sensitive MRI, with PET to detect active lesions, may provide superior disease assessment, allowing clinicians to better guide patient management. Methods: We analysed 16 patients newly diagnosed with a plasma cell dyscrasia for associations between qualitative and quantitative PET-MRI findings and patient

baseline laboratory values, including bone marrow cellularity and plasma cell percentage, as well as their clinicopathological diagnosis. Results: Final diagnoses for the 16 patients were: symptomatic myeloma (n=10), asymptomatic myeloma (n=4) and monoclonal gammopathy of uncertain significance (MGUS) (n=2). In patients with symptomatic myeloma qualitative assessment of MRI is more likely to reveal bone marrow abnormalities (focal or variegated pattern) than qualitative PET (8/10 versus 4/10). Neither modality detected qualitative marrow abnormalities in patients with asymptomatic myeloma or MGUS. Quantitative analysis showed MRI marrow water fraction directly correlated with trephine cellularity ($r = 0.78$, $p = 0.00039$), but not trephine plasma cell burden. MRI marrow water fraction correlated with PET bone marrow maximal standardized uptake values (SUV) in patients with low plasma cell burden ($r=0.91$, $p=0.0015$) but not in patients with high plasma cell burden ($r=0.18$, $p=0.61$). PET bone marrow maximal SUV inversely correlated with serum albumin ($r=0.57$, $p=0.017$) but showed no correlation with trephine cellularity or plasma cell burden. Furthermore, MRI marrow water fraction and marrow cellularity directly correlate with platelet count ($r=0.56$, $p=0.019$ and $r=0.61$, $p=0.0013$ respectively). Conclusions: Qualitative MRI detected bone and marrow changes appear superior to PET for the identification of patients with symptomatic myeloma. The MRI parameter of bone marrow water fraction is a useful surrogate of marrow cellularity, but quantitative analysis of combined PET/MRI reveals a dissociation between bone marrow water and metabolism in the presence of high plasma cell burden, and demonstrates significant associations with prognostic laboratory values including albumin and platelet count.

PS-080
Diarrhea incidence in multiple myeloma patients treated with lenalidomide and pomalidomide

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Background: Immunomodulatory drugs (IMiDs) are pivotal in the treatment of multiple myeloma (MM), and are administered as a continuous treatment. Thalidomide is a well known constipation-inducing agent. In contrast, physicians are aware that lenalidomide (Len) may induce gastrointestinal (GI) disorders, in particular diarrhea, but little is known of this side effect. No specific data on GI side effects are reported on the third-generation IMiD Pomalidomide (Poma). Aims: Description of incidence and management of diarrhea in a retrospective cohort of Len-or Poma-treated MM patients (pts). Methods: 126 Len-treated, and 59 Poma-treated MM pts were retrospectively analyzed in terms of diarrhea occurrence. This analysis included Len pts consecutively treated from June 2005 to December 2015, and Poma pts consecutively treated from August 2010 to September 2015. A descriptive analysis of diarrhea incidence, onset time, and response to treatments was performed. Results: Median age of the 126 Len-treated pts was 65 years (range 35-87); 57 (45%) re-ceived 1 or 2 autologous stem cell transplants, and 12 pts (10%) received an allogeneic stem cell transplant before Len start; 55 pts (44%) received Len as first line therapy, 32 pts (25%) as second line therapy, and 39 (31%) as third or subsequent line of therapy. Thirty pts (24%) manifested diarrhea during Len treatment; 27 pts (90%) had grade 1, 3 pts (10%) had grade 2, and no pts manifested grade 3 or more. Seventeen pts (53%) had abdominal cramps and 2 pts (6%) had rectal tenesmus. Diarrhea occurred after a median of 10 cycles. Almost all pts (29, 97%) had a correlation of diarrheic episodes with assumption of food, and most pts (24, 80%) reported persistent diarrhea during the rest period. Loperamide was administered in all cases, and 19 pts (63%) had reduced symptoms. Since for 11 pts (36%) loperamide had a poor control, they were treated with cholestyramine, which was effective in all cases. Nine pts (30%) had Len dose reduction, which corresponded to a decrease of the diarrhea in 5 of them. In 19 cases Len was stopped, with a rapid resolution of diarrhea in all cases. The same analysis

conducted in 57 Poma-treated pts did not show any GI symptom. Conclusion: Adverse GI events are common in new targeted drugs; a better understand-ing of the physiopathological mechanism is essential. For example, IMiDs have a gastroin-testinal toxicity profile with peculiar characteristics for the different generations. The first-generation IMiD Thalidomide is well known to be associated with constipation, sometimes very severe. The second-generation IMiD Len has an opposed GI toxicity profile, charac-terized by diarrhea. In our study, diarrhea is mainly mild, but still disturbing. It seems that a combination of dietary counselling, along with loperamide and cholestyramine treatment may control this symptom. We confirm that Poma has not relevant GI side effects.

PS-081 (d)
High Sensitivity Detection of Residual Disease in Multiple Myeloma from Blood

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Background: As effectiveness of treatments for multiple myeloma (MM) continues to increase, a greater proportion of MM patients are achieving deep response. Since traditional serum based assays are not sensitive enough, bone marrow (BM) based MRD methods have become available: a molecular-based method and multicolor flow cytometry (MFC). Limitations to BM based testing include expense, discomfort and potential sampling error in instances of patchy disease. Currently there are no blood-based high sensitivity assays clinically available to detect MRD in patients. Objective: The goal of this study was to serially evaluate blood MRD detection using a more sensitive M-protein detection method (miRAMM) [1] in MM patients with strict complete response (sCR). Methods: Patient selection criteria included: available serum sample within 30 days of initial diagnosis, a day 100 serum sample; and attainment of sCR as evaluated by serum and urine immunofixation,

serum free light chain, and BM 6-color MFC with a sensitivity of 10^{-4} to 10^{-5}. The patient records were then examined for the progression–free survival (PFS) time. Serum immunoglobulin enrichment was performed using a 50:50 mix of camelid-derived nanobodies against the light chain (LC) constant domains of kappa and lambda. After washing, samples were eluted with 20 uL of 5% acetic acid containing 50 mM TCEP, to disassociate immunoglobulis (Ig) into LC and HC components. The mass distribution of the Ig LCs was obtained by miRAMM as previously described [1]. Results: Using miRAMM the accurate mass of the M-Protein LC was identified in 100% (30 of 30) of patients at diagnosis. Post-ASCT serum miRAMM MRD status was determined by assessing for a LC above the polyclonal background having the same mass as the diagnostic sample. At day 100 post-ASCT, miRAMM identified MRD in 63% (19 of 30) of the sCR patients. Day 100 miRAMM (-) status was more likely in patients who achieved CR after induction therapy (81% (5/7) vs 26% (6/23)). Twelve sCR patients also had an available negative serum sample at ~ 300 days post-ASCT, 4 patients achieved miRAMM (-), one patient had persistent miRAMM (-), 4 decreased LC level by >40%, 4 patients had stable or increasing miRAMM intensity including one patient who went from miRAMM (-) at day 100 to miRAMM (+) by day 300. The 8 patients with favorable miRAMM at day 300 had a superior PFS than the other 4 who had stable or increasing intensity miRAMM (39.4 months versus 18.5 months, respectively, P<0.019). Conclusions: miRAMM's increased analytical sensitivity was able to detect residual M-protein from serum in >50% of sCR patients. Since the method is blood based and quantitative, serial monitor of sCR patients allows for assessment of continued response beyond day 100. 1. Barnidge DR, et al. Journal of proteome research. 2014;13(3):1419.

PS-082
Heavy+light chain and free light chain assays at baseline and during follow-up in EMN02/HO95 multiple myeloma clinical trial

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Introduction - Heavy+light chain (HLC) assay is a recent method that provides individual identification and quantification of the different light chain types of each immunoglobulin class, i.e. IgGκ, IgGλ, IgAκ, IgAλ, IgMκ and IgMλ. It allows an accurate assessment of both the involved/uninvolved Ig and permits to quantify even small amounts of monoclonal protein. Free light chain (FLC) and HLC can be considered potential prognostic and monitoring tools for multiple myeloma patients. We evaluated the role of HLC and FLC tests in the assessment and evolution of the disease in newly diagnosed multiple myeloma (MM) patients. Methods - 1510 patients aged ≤65 years with symptomatic newly diagnosed MM were enrolled in the EMN02/HO95 study (Cavo M et al, abs8000, J Clin Oncol 34, 2016). Serum samples from each patient enrolled in Italy (n=718) were analyzed at diagnosis, and specimens from 244 patients between starting of maintenance therapy and every 6 months up to +18 months were studied by SPE (serum protein electrophoresis), IFE (immunofixation), HLC, FLC, and corresponding BM samples by flow-cytometry MRD. Involved HLC ratio (iHLCR) was calculated with the involved Ig as numerator (IgGK/IgGL, IgGL/IgG/K, IgAK/IgAL, IgAL/IgAK). Involved FLC ratio (iFLCR) was calculated as K/L or L/K with the monoclonal chain as numerator. Standard FLC ratio (FLCR) and HLC ratio (HLCR) were calculated as K/L and IgGK/IgGL, IgAK/IgAL, respectively. Results - At baseline, high iFLCR (≥Q1) was significantly associated with lower TTP (median 51.6 vs NR, HR 1.72 95% CI 1.22-2.42, p=0.002). At pre-maintenance, 12% of patients had an abnormal HLCR, whereas 88% had a normalization of HLCR; 55% of patients had an abnormal FLCR, whereas 45% had a normalization of FLCR. No significant correlation with response or outcome was observed for patients who had a normalization of FLCR. At the same time point, 67% of non-BJ MM patients were IFE negative. Among them, 9% had still an abnormal HLCR, compared to 35% with abnormal HLCR in IFE positive patients (p=0.001). To date, the predictive value of each parameter on disease progression was then evaluated in 42 patients who relapsed after pre-maintenance. A parameter was considered positive when two consecutive determinations were abnormal. HLCR predicted relapse in 20% of cases, FLCR in 40% of non-BJ MM and in 70% of BJ MM, IFE in 35.7%, whereas MRD in 43.5%. By considering the positivity of at least one between FLC and HLC, their combined predictive significance was 47%. Conclusions - This preliminary analysis confirms the prognostic role of high iFLCR in newly diagnosed MM patients and suggests that the combined determination of FLC and HLC can predict outcome in non-BJ MM in a percentage of patients comparable to that of MRD using a more easily feasible assay. We are currently evaluating patient samples up to 42 months of follow-up, in order to confirm the present data.

PS-083
HES1, a bHLH transcription factor regulate cell proliferation and promotes apoptosis in in Multiple Myeloma cells

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The interplay between the Notch pathway and cell cycle modulators such as CCND2 is currently unexplored and might offer novel therapeutic interventions. We report that a range of constructs that mimic Notch1 pathway down regulated CCND2 reporter activity. Chromatin immuno-precipitation (CHIP) assay showed enrichment of the HES1 protein on CCND2 promoter in HES1 transfected 293T cells. Consistent with this data, meta-analysis of selected databases reveals reciprocal expression between HES1 and CCND2 in tumor cell lines and subsets of normal hematopoietic cells. Wild type HES1 but not the DNA binding mutant reduces the proliferative activity of Multiple Myeloma (MM) cells and subsequently induces apoptosis. Combining an RNA sequencing platform and QRT-PCR assay, we found an induction of HES1 and repression of CCND2 expression levels, block in cell proliferation and subsequent induction of apoptosis upon HDAC inhibitor treatment in MM cells. Overall our data shows that the Notch pathway can negatively modulate CCND2 via HES1 with concomitant specific cellular outcomes. We suggest that small molecules enhancing HES1 expression might have therapeutic role in subsets of MM patients.

PS-084
EPIDEMIOLOGICAL STUDY OF MULTIPLE MYELOMA – RETROSPECTIVE ANALYSIS FROM A TERTIARY CENTRE

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Methods Retrospective analysis of 41 patients diagnosed with multiple myeloma between Jan 2012 and dec 2015 was done. Demographical data and clinical presentation were noted. All Pre-treatment investigations like pathology report, radiological findings and serum immunology were taken for analysis. Results

Incidence was high in men and male to female ratio was 2.1:1. Median age and mean age was 51 & 52.1 years. Seventy one percent (29) were farmers and remaining 29% (12) included painters, carpenters and weavers. Forty six percent (19) were smokers and 24% were alcoholics. Co-morbid illness was present in 25% (hypertension-10%, diabetes-15%). Presenting symptoms were bone pain (68.3%), neurological deficit (12.2%), low backache (12.2%) fatigue (2.4%), arthralgia (2.4%), oliguria/anuria (2.5%). Eighty two percent of male and 92% of female were range of calcium 8.5-10.0 mg/dl. Renal failure in 22%, anemia 87.5% below 10.0 g/dl and multiple bony lesions in 37% was seen at presentation. Serum protein electrophoresis was positive in 85.4% of patients. Bone marrow examination showed 10%-50% plasma cells at diagnosis. Highest plasma cell percentage was seen in female patients-62% ,in male patients highest were 46%. Fifty one percent were in stage IIA, 41.5% in stage IIIA and 7.3% (5) in stage IIIB as per Durie salmon staging system. Conclusion Our study results showed strong occupational exposure background (farmer) for plasma cell disorder mainly multiple myeloma. It is important to understand chemical carcinogenesis in multiple myeloma and to reduce the risk of disease by taking appropriate public health action.

PS-085
Changes in cytokine production and metabolism in bone marrow mesenchymal stem cells in MGUS and multiple myeloma are driven by hypoxia induced PADI2 expression altering the transcriptome

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Multiple myeloma (MM) is a disease of the bone marrow, requiring residence in this environment for survival and proliferation. Central to this effect are the bone marrow mesenchymal stem cells (BMMSCs), which provide supportive signals to the myeloma cells. It has been suggested that the oxygen tension in the bone marrow may become hypoxic with disease onset and progression. In solid tumours, hypoxia results in the acquisition of pro-malignant phenotypes, such as resistance to chemotherapy. We recently reported that peptidyl arginine deiminase 2 (PADI2) is upregulated in BMMSCs in patients with monoclonal gammopathy of undetermined significance (MGUS) and MM, and that this leads to enhanced resistance to chemotherapy through changes in IL-6 signalling. We present here that PADI2 expression is regulated by oxygen tension, with short-term hypoxia sufficient to result in increased PADI2 activity and target gene expression. We also show that PADI2 activity can regulate the metabolism of BMMSCs through upregulated expression of glycolytic enzymes, among others. As we have also previously shown that the metabolism of the bone marrow is altered in patients with MGUS and MM, we contend that some of this metabolic transformation is due to altered BMMSC function through PADI2 expression. In summary, we suggest that the upregulation of PADI2 in BMMSCs, which may be through increased bone marrow hypoxia, results in significant alterations to the transcriptome of the cells that includes changes in cytokine signalling and metabolism.

PS-086
Comprehensive analysis of transcript isoforms in primary plasma cell leukemia and multiple myeloma with del(17p) showed significant differences between both dyscrasias

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Primary plasma cell leukemia (pPCL) is an aggressive plasma cell dyscrasia, characterized by short remissions and poor survival. Deletions of 17p13 have been observed in 50% of pPCL, whereas the presence of del(17p) in multiple myeloma (MM) does not exceed 10% at time of diagnosis. Although del(17p) is associated with poor outcome and extramedullary disease in MM, the presence of this abnormality does not confer the degree of aggressiveness observed in pPCL. The comprehensive exploration of the transcriptome, including the transcript isoforms measurement, may help to reveal biological differences between both plasma cell dyscrasias carrying del(17p). Transcriptomic studies were carried out with the Human Transcriptome 2.0 array in 9 newly diagnosed pPCL and 10 MM, all of them harboring del(17p). An unpaired two class analysis was performed using the SAM statistical approach, considering a q-value cut-off < 0.05. Statistical analysis was carried out at gene and transcript levels. To investigate the impact of alternative splicing, we analyzed the deregulated transcript isoforms corresponding to non-deregulated genes. Enrichment analysis was conducted through the Webgestalt web tool using the KEGG database. We found 896 genes and 3017 transcripts deregulated in pPCL compared to MM. Pathway enrichment analysis at gene level revealed a significant overrepresentation of genes in 4 pathways: aminoacyl-tRNA biosynthesis; spliceosome (including 3 members of the SR protein family such as SRSF1); alanine, aspartate and glutamate metabolism; and protein processing in endoplasmic reticulum. The most differentially expressed genes of these pathways were upregulated in pPCL samples compared to MM. The analysis at transcript level was focused on those genes with a total expression not differentially modified, but whose isoforms were differentially expressed. We found that

1363 isoforms were significantly deregulated, involved in Notch signaling, metabolic pathways, proteasome, RNA degradation and transport pathways. Interestingly, 3 transcript isoforms of EIF3C gene (a component of the eukaryotic translation initiation factor 3 complex) that encoded proteins smaller in size than canonical EIF3C were upregulated in pPCL. Additionally, we found 7 transcripts of PSMD1 (proteasome 26S subunit) and one of HDAC2 (histone deacetylase 2) upregulated in pPCL, although total gene expression remained unchanged. The functional implications of the differentially deregulated isoforms between pPCL and MM will be investigated. In summary, our data revealed significant differences in the relative abundance of transcript isoforms between pPCL and multiple myeloma cases sharing del(17p). These findings highlight the potential relevance of alternative splicing in the pathogenesis of pPCL. Funding:Instituto de Salud Carlos III-Cofinanciación fondos FEDER (PI13/00111);GRS, Junta de Castilla y León (1344/A/16) and AECC (GCB120981SAN)

PS-087 (d)
Anti-Myeloma Effects of the Selective JAK1 Inhibitor INCB052793 in Combination with Active Myeloma Agents In Vitro and In Vivo

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Several studies have demonstrated constitutive activation of the JAK-STAT pathway in multiple myeloma (MM) through dysregulated signaling of cytokines such as IL-6. In addition to its crucial role in promoting the growth, proliferation and survival of myeloma cells, IL-6 is also a potent stimulator of osteoclastogenesis and influences the tumor microenvironment in the bone marrow of myeloma patients by promoting an immunosuppressive milieu. Since JAK1 has been shown to be important for IL-6 signaling, studies to assess the effect of JAK1 inhibition alone and in combination with other anti-MM agents were undertaken. RPMI8226, MM1S or U266 human MM cells were cultured in the presence of the JAK1 selective inhibitor INCB052793 and anti-MM agents including the alkylating agents' cyclophosphamide (CY), melphalan (MEL), and bendamustine (BEN), the proteasome inhibitor carfilzomib (CAR), dexamethasone (DEX) or the immunomodulatory agents' lenalidomide (LEN) and pomalidomide (POM). Cell viability was assessed after 48 hours. The combination of INCB052793 and CY, MEL, BEN, or CAR synergistically inhibited the viability of RPMI8226 AND U266 cells in vitro. INCB052793 plus CY or MEL also significantly decreased the viability of MM1S cells. SCID mice bearing the human MM LAGκ-1A tumor had significantly smaller tumors when treated with INCB052793 alone when compared to vehicle control at Day 35 post implantation. This was in contrast to mice treated with single agent DEX, LEN or POM. Although the combination of INCB052793 with DEX, LEN or POM did not synergistically inhibit MM cell line growth in vitro, mice receiving the doublets of INCB052793 and DEX, LEN or POM demonstrated an enhanced anti-MM effect on LAGκ-1A growth in vivo that was superior to the doublets of DEX with LEN or POM. Mice receiving the triple combination of INCB052793 + DEX with LEN or POM demonstrated the most pronounced anti-MM effect on tumor growth in vivo compared to all other combinations tested. The inhibition of tumor growth with these combinations was observed throughout the study (through Day 70) and all combinations were well tolerated. Concomitant with effects on tumor growth, a significant reduction in serum human IgG levels was also observed. Studies to further understand the mechanistic effects of these combinations on myeloma signaling and the tumor microenvironment are ongoing. In conclusion, these in vitro and in vivo studies demonstrate that the combination of the JAK1 inhibitor INCB052793 with a broad spectrum of anti-MM agents is effective, and provide further support

for the clinical evaluation of these drug combinations in MM patients.

PS-088
IMPACT OF FRAILTY ON OVERALL SURVIVAL OF ELDERLY PATIENTS WITH MULTIPLE MYELOMA

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INTRODUCTION: Worldwide, life expectancy continues to rise. Frailty is a geriatric syndrome associated with reduced functional reserve, impairment in multiple physiological systems, and reduced ability to regain physiological homeostasis. It is associated with increased mortality and poses unique therapeutic challenges. OBJECTIVE: To evaluate the impact of the level of frailty on overall survival of elderly patients with multiple myeloma. Materials AND METHODS: This retrospective, observational and analytical study included a cohort of 150 patients older than 65 years with a recent diagnosis of multiple myeloma from January 2006 to December 2012. A check list for frailty burden measurement was used based on Edmonton frailty score and included: cognitive impairment, depressive disorder, polypharmacy, urinary incontinence, functional impairment, gait disturbance or falls, low weight or weight loss and previous hospitalization. Level of frailty was scored as the sum of each area involved. Record of all the variables were obtained from a retrospective review of the centralized and computerized medical records by a hematologist and geriatrician, using predefined standardized criteria. Patients were classified as fit (0-1 frailty criteria), vulnerable (2-3 criteria) or frail ($\geq$ 4 criteria). OS and PFS were estimated using the Kaplan Meier method using Stata13 program Group differences according to frailty were investigated using the Cox proportional hazard model accounting for ISS, age, Charlson comorbidity index and treatment. RESULTS: From the 150 patients evaluated, 124 patients were included in the study. The median age was 77 years (range 65-98). Thirty one percent of the patients were older than 80 years, 51% were female. The median Charlson Comorbidity index was 2 (range 0-7), 28% had renal failure and 40% of the patients presented with Myeloma ISS 3. Most patients received treatment with IMIDs. Sixty five percent of patients met at least one frailty criteria. The most common findings were polypharmacy, gait and functional impairment. Patients with comorbidities were more likely to be vulnerable or frail [OR 2,5 (95% CI 1,15 – 5,66) p= 0,01]. The median overall survival time was 75 months (95% CI 53-110), 39 months (95% CI 19-64) and 17 months (95% CI 5-37) for fit, vulnerable and frail patients respectively (log rank p 0,0002). In the multivariate analysis a higher risk of death was observed related to age [HR 1,07 (95% CI 1,02-1,12) p 0,002] and the number of frailty criteria [HR 1,13 (95% CI 1 – 1,3) p 0,05]. The presence of ISS 1 was associated with a favorable outcome. The frailty criteria independently associated with death were incontinence polypharmacy and previous hospital admissions. Conclusion: This study shows that the prevalence of frailty syndrome is high and it is independently associated with a less favorable outcome.

PS-089
Stabilization of ATRIP by SHFM1 regulates homologous recombination and genome stability in myeloma

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Genomic instability is associated with disease progression and poor clinical outcome in myeloma (MM). Based on prior studies showing that dysregulated homologous recombination (HR) activity contributes to genomic instability in MM, we investigated mediators of aberrant HR activity. We have found that split hand/foot malformation type 1 gene (SHFM1) is highly elevated in MM cells and correlates with

dysregulation of HR. We have also observed that several CpG sites within SHFM1 were methylated in normal PBMC and normal plasma cells, whereas unmethylated in MM cell lines. Consistent with observations in cell lines, the targeted bisulfite sequencing in normal and MM patient samples (N=5) showed that loss of methylation is a prominent mechanism underlying elevated expression of SHFM1 in MM. In the process of HR, ssDNA generated by Exo1 is coated with RPA, and RPA-coated DNA recruits the ATR–ATRIP complex to initiate the signaling cascade for initiation of HR repair. RPA on ssDNA is then replaced by Rad51 through a mechanism involving BRCA2. It has been shown that SHFM1 interacts with BRCA2 and contributes to HR process. To further investigate the role of SHFM1 in HR in MM, we investigated the proteins interacting with SHFM1 in MM cells by mass spectrometry and identified that SHFM1 interacts with ATRIP in MM cells. Co-immunoprecipitation confirmed the association of SHFM1 with ATRIP. To evaluate functional significance of these interactions, we conducted a loss and gain of function study. SHFM1-knockdown inhibited, whereas its overexpression increased the expression of ATRIP in MM cells, indicating that interaction of SHFM1 with this protein in MM cells increases its stability, allowing completion of subsequent steps in HR. Consistent with these observations, SHFM1 knockdown was also associated with loss of RPA protein expression in MM cells. Our data, therefore, show that loss of methylation within SHFM1 promoter causes upregulation of SHFM1 expression in MM which through its ATRIP stabilizing effect contributes to increased HR activity at initiation step. Inhibition of SHFM1/ATRIP interaction can, therefore, be novel strategy to reestablish genome stability in MM.

PS-090
18FDG-PET positivity post radiotherapy is a biomarker for relapse in patients with plasmacytoma

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Solitary plasmacytomas are characterised by focal proliferation of monoclonal plasma cells in either soft tissue or bone. The management of solitary plasmacytomas is distinct from other plasma cell dyscrasias with radiotherapy forming the mainstay of treatment, with curative intent. Precise diagnosis of a solitary plasmacytoma is therefore essential, to ensure that the patient is treated on the appropriate pathway. Patients with solitary plasmacytoma can also progress with multiple plasmacytomas or Multiple Myeloma. Established risk factors for progression from solitary plasmacytoma to myeloma/multiple plasmacytomas are raised light chain ratio, aberrant plasma cells in marrow and size of plasmacytoma. Imaging biomarkers of relapse remains an active area of investigation. 18F FDG PET-CT has emerged as a useful tool to diagnose plasmacytomas and stage patients, but data is limited on use of 18F FDG PET-CT to measure treatment response. In Plasmacytoma patients, the role of residual PET positivity post therapy as a biomarker for disease burden and correlation with biochemical results, is not yet known. Likewise, the role of 18F FDG PET-CT as a biomarker to estimate the cure fraction and as a marker of disease progression requires further study. To answer these questions we conducted a retrospective analysis of twenty-four patients, referred with a histological diagnosis of plasmacytoma, over a three year period. We recorded patient baseline characteristics, size and location of their plasmacytoma, imaging findings, paraprotein/light chain and bone marrow results. We then compared their 18F FDGPET-CT and skeletal surveys to analyse what proportion of patients were subsequently upgraded to myeloma on imaging alone and whether their treatment pathway had changed. We also recorded the proportion of patients with solitary plasmacytoma who progressed with progression recorded on 18F FDG PET CT scan on follow-up imaging or until the first sign of biochemical relapse. Progression free and overall survivals were then calculated from time of diagnosis of plasmacytoma. Of the 24 patients, 9 patients were imaged with both skeletal survey and FDG PET-CT. On comparing the imaging findings,

FDG PET-CT detected additional lesions in 55.6% of cases (5/9 patients), which were missed by conventional radiography and significantly changed treatment pathway. Follow up post treatment PET/CT was performed in 15/24 (62.5%) of patients. During the follow up period we found that 50% (12/24) patients with plasmacytoma progressed to Myeloma. In 66.7% of these cases, (8/12 patients) post therapy FDG PET-CT was positive, and only 1 PET-CT negative patient progressed. Only 50% (6/12 patients) of patients had biochemical evidence of either persistent disease or relapse at the time of clinical progression suggesting that FDG PET-CT is a useful imaging tool to identify plasmacytoma patients at risk of progression to Myeloma.

PS-091

Flow cytometric immunophenotyping in lymphoplasmacytic lymphoma/Waldenstrom's Macroglobulinemia demonstrates characteristic antigen expression pattern

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Introduction: Flow cytometric immunophenotyping (FCI) is a powerful tool used in the diagnosis, classification and monitoring of hematolymphoid neoplasms. However, due to lack of well-defined immunophenotypic features,FCI based diagnosis of lymphoplasmacytic lymphoma/Waldenstrom'sMacroglobulinemia (LPL/WM) is challenging. In this study, we described the very characteristic immunophenotypic patterns for the FCI of LPL/WM with aim to widen the application of FCI in the diagnosis of this entity. Methods: We retrospectively evaluated seven cases of LPL/WM diagnosed according to WHO criteria. FCI was performed using 8-10 color comprehensive antibody panel on the Navios flow cytometer and data analysis was performed using Kaluza software-V1.3. Molecular testing for MYD88 L265P mutation was performed using Allele-Specific PCR. Results: Bone marrow aspirate (BM) samples of seven cases of LPL/WM (age, 37-72 years & M:F – 5:2) were studied. On FCI, lymphocytes were 2-67% (median, 5.8%) and plasma cells (PCs) were 0.1-2.3% ((median, 0.5%). Clonal B-cells expressed moderate CD19 (7/7), moderate CD20 (7/7), partial-dim CD10 (2/7), dim CD5 (1/7), dim-negative CD43 (2/7), IgD (4/6),bright CD45 (2/7), dim-negative CD200 (2/7), heterogeneous CD38 expression (negative-bright) and surface kappa-light chains (5/7)/lambda (2/7).Clonal-PCsgated with CD138 and CD38 characteristically revealed expression of dim CD19 (7/7), heterogeneous i.e. moderate to negative CD20 (7/7), moderate-bright CD45 (7/7), moderate CD81 (7/7),and surface kappa-light chains (5/7)/lambda (2/7). Clonal-PCs were characteristically negative for CD56, CD28, CD117 and CD200. PCs also showed variable expression i.e.bright to dim of CD27 (7/7) and dim CD10 (1/7). Conclusion: FCI of LPL/WM revealed a very characteristic pattern of antigen expression. Clonal B-cells characteristically showed heterogeneous expression of CD38 from negative to bright revealing differentiation of B-cells to PCs. In contrast to myeloma-PCs, PCs in LPL/WM characteristically demonstrated the expression of CD19, CD20, bright CD45, moderate CD81 and surface light chains but negative for CD56, CD117 and CD28.

PS-092

Hepatitis B virus reactivation in multiple myeloma patients in the era of novel agents: a nationwide retrospective study in Japan

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Background: An estimated 2 billion people have been or are currently infected with hepatitis B virus (HBV); HBV seroprevalence is particularly high in East Asia. Recently, HBV reactivation was noted in patients with resolved HBV infection (HBsAg negative and anti-HBc and/or anti-HBs positive) who have undergone immunosuppressive chemotherapy. We previously reported the incidence and characteristics of HBV reactivation in 641 symptomatic multiple myeloma (MM) patients at the International Myeloma Workshop 2015 in Rome (Tsukune Y, et al. Ann Hematol. 2016; 95: 1465-). We concluded that HBV reactivation was not rare, but could not identify the risk factors and optimal preventative strategy for HBV reactivation. Therefore, we performed a nationwide retrospective study in Japan to estimate the accurate incidence and determine risk factors for HBV reactivation in MM patients treated with either novel agents or autologous stem cell transplantation (ASCT). Patients and methods: We identified 3,084 MM patients who treated with either novel agents (bortezomib, thalidomide, lenalidomide, pomalidomide, carfilzomib and ixazomib) or underwent ASCT between January 2006 and February 2016 at 52 hospitals in board-certified member institutes of the Japanese Society of Hematology. Data obtained using questionnaires included age, gender, M-protein, stage (Durie-Salmon stage, international staging system), laboratory findings, treatment, and outcomes. All statistical analyses were performed using SAS software (version 9.4.; SAS Institute Inc., Cary, NC, USA). Results: Of 3,084 patients, 486 (15.8%) were positive for HBsAg or had resolved HBV infection. During a median follow-up of 101 (1-540) weeks, of 32 (3.1%) HBV carriers, 1 who had not been administered anti-viral agents developed hepatitis. Conversely, 36 of 454 (7.9%) patients with resolved HBV infection showed HBV reactivation; the cumulative incidence of HBV

reactivation at 2 and 5 years was 8.7 and 18.4%, respectively. HBV reactivation occurred in 23.2% (26/112) and 2.9% (10/342) of patients who did and did not undergo ASCT, respectively. Seven of 36 (19.4%) patients with HBV reactivation developed de novo hepatitis and one of them died of fulminant hepatitis in spite of administration of lamivudine. ASCT was significantly associated with HBV reactivation (p<0.0001). Conclusion: Our nationwide analysis in Japan revealed that HBV reactivation is not a rare phenomenon in MM patients. Therefore, long-term monitoring is required to prevent hepatitis that is related to HBV reactivation in these patients.

PS-093
Mortality by Frailty Status as Defined by a Claims-Based Disability Status in Elderly Patients Newly Diagnosed with Multiple Myeloma in the United States

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Introduction: Little is known about the prognosis of frail multiple myeloma (MM) patients in the real-world setting. In this study, we applied a claims-based definition of poor disability status (DS) as a proxy measure for frailty status and described patient characteristics and mortality by DS in a population-based cohort of elderly adults with MM in the United States. Methods: We identified elderly (aged ≥66 years) patients, from the Centers for Medicare & Medicaid Services 100% files (2007-2012) for patients with ≥1 claim carrying a diagnosis code for MM, who began first-(1L), second-(2L), third-(3L), and fourth-line (4L) therapy. We used a

validated claims-based model to estimate the predicted "probability of poor DS" (PDS) for each patient (Davidoff et al 2013; Davidoff et al 2014). Patients were classified as frail (predicted PDS ≥ 0.11) and fit (predicted PDS<0.11). Line of therapy was defined by a 90-day gap in all treatments or by a drug being added to a regimen >90 days after the line index date. Drug regimens were identified based on National Comprehensive Cancer Network MM treatment guidelines and classified as monotherapy, doublets, triplets, and other. Baseline comorbidity level was defined using Charlson Comorbidity Index (CCI). Patients were followed from line initiation date to the earliest of death, disenrollment from Medicare Parts A, B, or D coverage, line end date, or December 31, 2012. Baseline characteristics were described by fit or frail for 1L-4L therapy. Overall survival (OS) was estimated using the Kaplan-Meier (KM) method with log-rank test to assess the differences between fit or frail patients. Results: In total, 12,547 MM patients initiated 1L therapy; 5841 (46.6%), 2372 (18.9%), and 819 (6.5%) advanced to 2L, 3L, and 4L, respectively. By line of therapy, percent of frail patients was 16.7% at 1L, 21.8% at 2L, 18.4% at 3L, and 18.2% at 4L. Compared with fit patients at 1L, frail patients were older (mean age 78.9 vs. 76.5 years); more were female (66% vs. 51%) and black (23% vs. 12%); comorbidity level was higher (CCI ≥5: 42% vs. 16%); more received monotherapy (32% vs. 19%) and fewer received doublets (54% vs. 61%) or triplets (10% vs. 16%); line duration was shorter (mean 357 vs. 434 days). Patterns were similar for patients who began 2L-4L. OS was worse for frail than for fit patients consistently across 1L-4L (P<0.01; KM curves not shown; 3-year OS: 34% vs. 61% at 1L; 40% vs. 59% at 2L; 25% vs. 53% at 3L; 1-year OS at 4L: 59% vs. 71%). Conclusions: Our study demonstrates that the claims-based prediction model for DS is applicable for defining frailty in elderly Medicare patients with MM. Frail patients were older, had higher comorbidity level, and worse overall survival compared to fit patients. Further studies assessing whether claims-based poor DS (frailty) is an independent risk factor for mortality and predictor for choice of treatment are warranted.

PS-094

Hijacking myeloma metabolism to target cytotoxic chemotherapy to malignant plasma cells with decreased bone marrow toxicity

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Background: Overexpression of the L-type amino acid transporter 1 (LAT1; gene name SLC7A5) is a common feature of many malignancies to support increased protein synthesis demand. LAT1 is expressed at low levels on normal tissues and normal plasma cells but at higher levels on myeloma plasma cells. Increased LAT1 expression is also associated with decreased survival in myeloma patients. We have taken advantage of this metabolic dependency in myeloma to develop a novel therapeutic agent, QBS10072S (QBS'72S). QBS'72S allows for selective LAT1-dependent transport of a nitrogen mustard agent into myeloma plasma cells for tumor eradication, while sparing normal hematopoietic cells when compared to nitrogen mustards used routinely in myeloma therapy. Materials and Methods: Colony-forming assays were performed with CD34+ stem cells isolated from normal donor bone marrow. Human myeloma cell lines (HMCLs) were treated with QBS'72S under standard conditions in 384-well plates and viability measured by CellTiterGlo assay. In vivo tumor burden was measured by bioluminescence imaging. Results: At identical doses to the nitrogen mustard melphalan, QBS'72S demonstrated reduced toxicity versus normal hematopoietic stem cells ex vivo. Decreased myelosuppression was found in Sprague-Dawley rats treated with QBS'72S compared to identical melphalan doses. QBS'72S monotherapy induced apoptosis in a panel of HMCLs in vitro. In luciferase-labeled U266 cells injected I.V. into NSG mice, QBS'72S showed significantly increased

survival and decreased tumor burden versus both vehicle and bortezomib at the maximal tolerated dose. Mechanistically, as expected, we found a similar DNA damage and apoptotic response to both QBS'72S and melphalan as evidenced by RNA-seq transcriptional signature, phosphorylation of DNA-damage associated proteins, and generation of cleaved caspase 3. Conclusion: QBS'72S is a promising novel treatment in myeloma, allowing for delivery of efficacious doses of nitrogen mustard to tumor with reduced myelosuppression.

PS-095
REIIBP is a Histone Methyltransferase Overexpressed in T(4;14) Multiple Myeloma with Oncogenic Potential

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Multiple myeloma (MM) is characterized by recurrent chromosomal translocations. Patients with t(4;14) have poor prognosis. The histone methyltransferase (HMTase) MMSET is overexpressed in MM as a result of the t(4;14) chromosomal translocation. MMSET is capable of producing 3 major isoforms, MMSET II, REIIBP and MMSET I. MMSET II contains the full-length protein of 1365 amino acids and possesses HMTase activity for H3K36 and H4K20. MMSET I, a short isoform with 647 amino acids, is identical to MMSET II N-terminus. REIIBP, a short isoform with 584 amino acids, has identical sequence of MMSET II C-terminus. Although the short isoform REIIBP is overexpressed universally in t(4;14) MM, its role in t(4;14) MM is still poorly understood. In this study, MM cell line RPMI8266 was transfected with REIIBP vector and the cell line with ectopic expression of REIIBP was generated using puromycin selection. Immunoblot analysis indicated that REIIBP had HMTase activity centered on

H3K9Me3, H3K27Me3 and H3K79Me3 in MM cells. Liquid chromatography-mass spectrometry (LC-MS) analysis confirmed the increase of H3 methylation levels at H3K9, H3K27 and H3K79. HMTase assay in vitro showed that the direct effect of REIIBP on histone methylation was focused on H3K27Me3. Gene expression array analysis indicated that there were 256 genes up-regulated and 365 genes down-regulated upon REIIBP overexpression. Consistent with gene array data, qPCR analysis indicated REIIBP overexpression increased BTK (Bruton's tyrosine kinase) mRNA levels significantly. Immunoblot analysis indicated that REIIBP increased BTK protein levels greatly. BTK can activate NFkB signaling pathway. As expected, REIIBP increased protein levels of p-NFkBp65 and anti-apoptosis protein Bcl2 levels were also increased. MTS assay showed REIIBP could promote cell proliferation and FACS analysis indicated REIIBP reduced apoptosis in MM cells. These preliminary results suggested that REIIBP is a HMTase and might act as an oncoprotein in t(4;14) MM cells.

PS-096
AYA-MYELOMA: REAL WORLD, SINGLE CENTER EXPERIENCE OVER LAST 5 YEARS

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Introduction: Multiple myeloma (MM) is considered as a disease of the old with the reported median age of 60-70 years. The disease occurs a decade earlier in the Indian subcontinent as compared to the West with a median age ranging from 45-50y in different series. It is very uncommon for MM to affect adolescents and young adult (AYA) with limited literature on the subject. Aim: The purpose of this study was to analyze the disease characteristics and outcomes of the AYA-MM

in the real world setting. Patients and methods: It is a retrospective single center study conducted at a tertiary care center from North India. Records of all consecutive patients with AYA-MM (15-39y of age) who were managed from 01 Jan 2010 to 31 Dec 2015 were reviewed. Survival was assessed from the date of start of treatment to the last follow-up date or death due to any cause. Results: A total of 415 patients managed for MM in the last 5 years were included in the study. The frequency of the AYA-MM was 9.6% (40/415) of whom five patients were younger than 30y. There was male preponderance with a male: female ratio of (26:14; ratio-1.85). The median age of the patients was 38y (mean-36.025, 18-39.9, SD – 4.67). The main presenting features were bone pain (55%), fatigue (45%), extramedullary plasmacytomas (20%) and infections (12%). The mean duration from symptom onset to diagnosis was 269d (median – 122, 15-1503, SD – 382). Organomegaly was seen in 28% (hepatomegaly in 27%, splenomegaly 12%). The performance status of the patients was good (ECOG>2 – 24%). Hypercalcemia, renal impairment (eGFR<60ml/min/1.73m2), anemia and lytic lesions were seen in 27.7%, 31.6%, 63.15% and 56.25% of patients respectively. 77.8% patients had abnormal κ/λ ratio, 61.12% patients had raised M protein and only 4 patients had Bence Jones proteinuria. Amyloid was absent in all evaluable cases except one. On risk stratification, 25%, 50%, and 75% patients were in ISS I, II and III respectively. Only 22.5% patients were transplanted (all Auto SCT), whereas most of the patients were managed with the chemotherapy even after remission induction (77.5%). The median survival after diagnosis was 388d (11-2170 days; mean - 561±510d). The 3y median survival of the study population is 80.21%. Conclusion: AYA-MM patients have a higher prevalence of extramedullary disease, high-risk disease, but longer survival than that observed in series of all ages.

PS-097
Treatment Patterns and Outcomes in Clinical Practice Among Patients with Newly-Diagnosed Multiple Myeloma: Systematic Literature Review

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Novel agents (proteasome inhibitors [PIs], immunomodulatory agents [IMiDs]) improve disease control and survival rates in patients with newly diagnosed multiple myeloma (NDMM) compared to conventional chemotherapy. Results from clinical trials may not reflect outcomes in the real world. The objective was to summarize published data on treatment patterns and outcomes in clinical practice among patients with NDMM. Methods A systematic literature review of observational studies of NDMM treatment patterns and clinical outcomes was conducted. Published literature was searched from Jan 2010-Jun 2016 using Medline, Embase, and PubMed databases; select conferences between 2014-2016 were also reviewed. Eligibility included studies of patients with NDMM (n≥50) receiving first-line treatment. Results Included studies (n=107) were conducted in Europe (35%), Canada or US (31%), Asia Pacific (26%), Latin America (4%), and multi-national (3%). Most studies (88%) were retrospective. Of 82 studies reporting treatment type, 95% included novel agent regimens: 82% and 83% of studies reported PI or IMiD use, respectively. The percentage of patients receiving novel agents ranged from 3% (diagnosis [dx] year 1999, US) to 83% (dx years 2009-2013, Denmark), and varied by country and patient characteristics. Proportions of patients receiving triplet regimens increased with time, likely associated with the introduction of novel agents (0% [dx years 1995-2005] - 12% [dx years 2006-2014]). Median (Mdn) treatment duration ranged from 3.4-23 months (mo), although few studies reported this (16%). Clinical outcomes (overall survival [OS], progression-free survival [PFS], overall response rate [ORR]) were reported in 92 studies. Consistently, patients receiving a PI or IMiD had longer OS than conventional chemotherapy. The minimum Mdn OS reported

was 6 mo in patients with high-risk cytogenetics not treated with a PI, while 7 studies reported Mdn OS was not reached (NR, Mdn follow-up [f/u] 23-71 mo; f/u not reported in 2 studies) in patients treated with novel agents or stem cell transplant (SCT). Mdn PFS ranged from 7 mo in SCT-ineligible patients with no response to first-line novel agent treatment, to NR in patients treated with first-line PI-based triplet regimens (Mdn f/u: 23-43 mo). ORR ranged from 31% in those with high-risk cyotgenetics treated with novel agents to >90% in those receiving PI or IMiD triplet regimens or SCT. Conclusions As targeted NDMM therapies have become available, treatment patterns have shifted. In this review, treatment durations were not well reported and varied substantively. Studies of novel agent regimens including PIs or IMiDs reported longer survival and higher response rates versus conventional chemotherapy, mirroring clinical trial results. Clinical outcomes were poorer in some patient subpopulations, including those with high-risk cytogenetics, indicating unmet need in these populations.

PS-098
Rates and Predictors of Stem Cell Transplant in Elderly Medicare Beneficiaries with Multiple Myeloma in the United States

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Objective: This study identified patient and contextual factors associated with the receipt of autologous stem cell transplantation (ASCT) among elderly Medicare beneficiaries with newly diagnosed symptomatic MM (NDMM). Methods: This retrospective cohort study used Surveillance, Epidemiology, and End Results registry and linked Medicare claims (SEER-Medicare) data. We identified individuals aged 66+ with an incident diagnosis of MM between 2007 and 2011, and evidence of CRAB symptoms (hypercalcemia, renal insufficiency, anemia and bone disease) based on ICD-9 diagnosis codes found in claims from six months pre- to one month post-MM diagnosis. Patients were followed until death or censoring due to non-continuous Medicare Parts A and B enrollment six months after diagnosis (individuals who died within 6 months were excluded from the study). ICD-9 and HCPCS codes were used to identify ASCT. Charlson Comorbidity Index (CCI), derived from medical claims, was used to measure comorbidity burden at the time of MM diagnosis. Baseline demographic and clinical characteristics among those who received ASCT were compared to those who did not using t-tests and Chi-square tests for continuous and categorical variables, respectively. Multivariable logistic regression was used to evaluate predictors of ASCT. Results: Among 2,698 individuals with NDMM who met our inclusion criteria, 173 (6.4%) underwent ASCT during the follow-up period. ASCT recipients were younger, more likely to be male, married, white non-Hispanic, and have fewer comorbid conditions. The rate of ASCT among recipients aged 66-69 was 22.1%, 7.2% among recipients aged 70-74, and 2.4% among those aged 75+ (p<0.001). The rate of ASCT was higher among males (7.8%) than females (5.1%) (p=0.005). Rates of ASCT were higher among those who were non-Hispanic white (7.2%), compared to those who were non-Hispanic black (3.8%) (p=0.004). Among those with CCI=0, 9.2% underwent ASCT, while 7.4% of those with CCI=1 underwent ASCT and 3.0% of those with CCI>1 underwent ASCT (p<0.001). Rates of ASCT were higher in the Northeast (7.7%) and South (8.0%) (p=0.04). Multivariable analysis showed that patients who were married, younger, and of white non-Hispanic race had significantly increased odds of ASCT, while those with Medicaid dual eligibility (proxy for low income), greater comorbidity burden and cardiovascular disease at baseline had significantly decreased odds of ASCT. Among the ASCT recipients, 14 (8%) died within one year of ASCT and 39 (23%) died after one year. Conclusion: ASCT is

performed in fewer than 1 in 10 patients aged 66 and older. A greater proportion of ASCT recipients were non-Hispanic white, married, diagnosed at a younger age, and had a lower comorbidity burden compared to non-transplant patients. Future studies should investigate the implications of comorbidity, age and race differences on post-transplant outcomes among older MM patients.

PS-099
The Real-World Characteristics and Outcomes of Newly Diagnosed Myeloma Patients Ineligible for Clinical Trials

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Background: Most prospective clinical trials in Multiple Myeloma (MM) exclude patients with low performance status or impaired renal function or marrow reserve. Thus, relatively little is known about these patients. We reviewed the disease manifestation, treatment, and prognosis of these patients. Methods: Data was extracted from the open-access MMRF Researcher Gateway corresponding with interim analysis 9 from the CoMMpass study. The CoMMpass study is enrolling 1000 newly diagnosed MM patients who will be tracked longitudinally for 5 years. Eligibility requirements for CoMMpass include: symptomatic MM with measureable disease by SPEP (>1.0g/dL), UPEP (>200mg/24 hours), or SFLC (>10mg/dL); receiving a proteasome inhibitor- (PI) and/or an immunomodulator (IMID)-based regimen a for initial MM treatment; and no prior malignancies in the past 5 years. We defined ineligibility for clinical trials as one or more of the following at time of MM diagnosis: ECOG performance status 3 or 4; creatinine >2.0mg/dL or receiving dialysis; absolute neutrophil count (ANC) <1.0x109/L or receiving growth factor support; or platelet count <50,000 x109/L or receiving platelet transfusion support. We compared the demographics, baseline presentation, and first-line treatment of these patients with the overall population using bivariate analyses. We then performed a multivariate Cox regression analysis to compare event-free survival (EFS) defined as the interval from diagnosis to disease progression or death. Results: 848 patients were available for analysis. 22% (189) met the study definition of ineligibility for clinical trials. 5% had low performance status, 15% impaired renal function, 3% impaired marrow reserve. Ineligible patients tended to be older (average age 65.1 compared to 63.9, p = 0.0111), have more advance stage (68% stage III compared to 20%, p <0.0001), and were less likely to receive IMIDs (37% compared to 65%, p < 0.0001). After controlling for first-line treatment and SCT utilization, patients ineligible for clinical trials had a 91% (aHR 1.91 [95% CI 1.45 - 2.52], p < 0.0001) increase in risk of disease progression or death. Conclusions: In the CoMMpass study, 22% of patients were unlikely to be candidates for clinical trials due to low performance status or impaired renal function or marrow reserve which are common exclusion criteria. These patients had a 91% increase in risk of disease progression or death compared to the overall population. The proportion of patients who are ineligible for trials is likely even higher in the general population as patients not receiving IMIDs or PIs and those with a history of other malignancies were excluded from the CoMMpass study. Additional research is needed to better understand the needs of these patients and improve their outcomes.

2. Therapy and Outcomes

PS-100 (d)
A Phase II Study of Carfilzomib, Pegylated Liposomal Doxorubicin, and Dexamethasone [CDD] for Relapsed or Refractory Multiple Myeloma

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Background: CDD [carfilzomib (CFZ), pegylated liposomal doxorubicin (PLD), and dexamethasone (DEX)] was well tolerated in our phase I dose escalation trial. An MTD was not reached despite administering the currently approved single-agent doses. The overall response rate (ORR) was 72% (5/7) in a heavily pre-treated population at the maximum dose level tested. Based on the promising results, we conducted a phase II expansion to further evaluate the efficacy of the regimen. Patient/Methods: Patients with relapse or refractory MM (RRMM) after ≥ 1 lines of therapy, with measurable disease, and good performance status, organ function and hematological reserve were eligible. CFZ was given on days 1, 2, 8, 9, 15 and 16 in 28 day cycles at a dose of 56mg/m2, PLD on day 8 at a dose of 30mg/m2, DEX on days 1, 2, 8, 9, 15 and 16 at a dose of 20mg. Following 6 cycles of combination therapy, PLD was discontinued and patients were treated with once weekly CFZ and DEX maintenance. Response was assessed per IMWG criteria. Overall response rate (ORR) was defined as partial response (PR) or better, event-free survival as the interval from start of therapy to discontinuation. Results: 24 patients were enrolled. The median age was 64 years (range 27-70) and 54% were female. 46% were stage I by ISS, 25% were stage II, and 29% were stage III. By mSMART criteria, 4% were high risk and 25% were intermediate risk. 63% were IgG subtype, 17% were IgA, and 20% had light chain only disease. The median number of prior therapies was 2 (range 1-13); median time from diagnosis to start of protocol was 40 months (range 7-200). All had prior exposure to lenalidomide and 67% were refractory; 92% had exposure to bortezomib and 42% were refractory, (25% were double-refractory), 13% had exposure to CFZ, and 9% had exposure to PLD or doxorubicin. 96% had undergone autologous transplantation. The overall response

rate was 83% with 25% achieving a complete response (CR/sCR). The estimated median number of cycles administered was was 11; the estimated median event-free survival was 13.4 months at a median follow-up of 15 months. Grade 3/4 non-hematologic toxicity was uncommon but included: infections (11), hypertension (4), reversible posterior encephalopathy syndrome (1), and MI (1). Grade 3/4 hematologic toxicity included: thrombocytopenia (11), anemia (8), neutropenia (7), TTP (1), and hemolysis (1). Conclusion: This is the first trial to report on a triplet regimen with high-dose CFZ (56mg/m2). CDD is well tolerated and efficacious in RRMM. The estimated ORR of the combination is 83% (95% CI 68%-98%), comparable to high-dose CFZ and DEX; however, CDD seems to elicit deeper responses. The CR/sCR rate of CDD is 25% compared to 13%. (Dimopoulos, et al, Lancet, 2015). Responses are durable with once weekly CFZ and DEX maintenance; however, PFS may be improved further with a more intensive maintenance regimen.

PS-101
Repeated lenalidomide treatment in patients with relapsed multiple myeloma

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Lenalidomide is an effective antimyeloma drug. The combination of lenalidomide with dexamethasone is nowadays the gold standard for treatment of relapsed multiple myeloma. The aim of this study was to analyze efficiency of repeated lenalidomide treatment in patients with relapsed and refractory multiple myeloma. From 2009 to 2015, 41 heavily pretreated patients were retrospectively evaluated. Lenalidomide was administered at the standard dose, and in combination with corticosteroids and chemotherapy. Before the second lenalidomide treatment, median of previous therapy lines was 3, all patients were refractory to the last

treatment, 95 % of patients were bortezomib-refractory and 48 % had previous autologous transplantation. In the first lenalidomide treatment, 82.8 % of partial response or better response was reached and median progression-free survival was 15.2 months. In the second lenalidomide treatment, 14.2 % of partial remission or better response was reached. Median progression-free survival was 4.8 months and median overall survival was 11.9 months. No success-predicting risk factor in lenalidomide retreatment was found. Treatment results were significantly affected by a limited lenalidomide coverage in the Czech health care system. Repeated lenalidomide treatment is an effective therapeutic alternative for heavily pretreated patients with relapsed and refractory multiple myeloma. For indirect comparison, the results are comparable to treatment by pomalidomide or daratumumab.

PS-102
Efficacy and safety of VTD-PACE regimen in relapsed or refractory multiple myeloma

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Background: VTD-PACE regimen is widely used for relapsed or refractory multiple myeloma as salvage therapy. However, only a few reports were reported. Therefore, we studied the safety and efficacy of VTD-PACE, retrospectively. Methods: We reviewed medical records of patients who received VTD-PACE regimen as salvage therapy for relapsed or refractory multiple myeloma between 2010 and 2016 in National Center for Global Health and Medicine hospital. Patients received several courses of treatment regimens as a consolidation or maintenance after VTD-PACE regimen. Adverse events were graded using the National

Cancer Institute's Common Terminology Criteria for AEs, version 4.0. Myeloma disease response was done in accordance with the International Myeloma Working Group uniform criteria. Results: Forty patients were treated with VTD-PACE regimen. The median duration of follow-up was 14.5 months (1-59 months). The median duration from diagnosis to VTD-PACE regimen was 17.0 months (2-164 months). The median age was 53.5 years old (34-66 years old). Patients with t(4;14), t(14;16), and del(17p) by FISH were 6 (15%), 2 (5%), 6 (15%), respectively. The median courses of VTD-PACE regimen were 2 (1-6) courses. Overall, 26 of patients (65.0%) achieved a confirmed partial response (PR) or better, PR were 19 patients (47.5%), very good partial response (VGPR) were 5 (12.5 %), complete response (CR) were 2 (5 %). The median progression-free survival(PFS) and overall survival(OS) was 8.0 months (95%CI, 2.0-14.0) and 20.0 months (95%CI, 17.1-22.9) , respectively. Fifteen patients were primary refractory or cyclophosphamide stem cell harvest failure cases. In this group, the overall response rate was 80 %, 7PR (46.7 %), 4VGPR (26.7 %), and 1CR (6.7 %). The median progression-free survival (PFS) and overall survival (OS) was 12.0 months (95%CI, 2.2-21.8) and 20.0 months (95%CI, 7.9-32.0), respectively. Grade 3/4 hematologic AEs were found in most cases, neutropenia (100%), anemia (60%), and thrombocytopenia (95%). Grade 3/4 non hematologic AEs were febrile neutropenia (52.5%), lung infection (12.5%) and diarrhea (10%), sepsis (7.5%), and electrolyte disturbance (92.5%). Conclusion VTD-PACE is an effective and tolerable salvage regimen for relapsed or refractory multiple myeloma.

PS-103
VTD IN OLDER PATIENTS COMPARATIVE WITH YOUNGER

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OBJECTIVES Assess the efficacy and safety of VTD (bortezomib plus thalidomide plus dexamethasone) as induction therapy before autologous stem-cell transplantation (ASCT) in both newly diagnosed and relapsed multiple myeloma, including patients (pt) over 65y. MATERIAL AND METHODS Retrospective analysis of toxicity of 23 VTD induction treatment in 22 pt (1 pt was retreated with VTD scheme) from June 2012 to December 2015 outside of clinical trials and comparision between under vs over 65 years old groups. PATIENTS Gender: female/male = 14/8 Age: global median 62 years (45-72). 13 patient under 65y(U65y): 57y (45-63) and 9 patients over 65y(O65y): median 70y (67-72).1/27 Disease characteristics. Myeloma subtype: IgG 10 pt, IgA 8 pt, light chain 2 pt, no secretor 2 pt, ISS disease stage: 1: 11 pt; 2: 4 pt, 3: 4 pt, (3 ND). Cytogenetics: High risk (del(17p) (p53), t(4;14),) t(4;16):5 pt. Standard risk: 17 pt 17 patients received treatment in 1st line (O65y: 9 ; U65y : 8) and 6 2nd line (O65y: 1 ; U65y :5) ASCT were performed in 9 U65y pt (4 as 2nd line treatment) and 6 O65y pt all as first line of treatment. ADMINISTRATION SCHEDULE Cycles every three weeks. U65y: subcutaneous bortezomib (sc-BTZ): 1,3 mg/m2 on days 1, 4, 8, and 11; thalidomide (Thal) 50 mg daily for the first 14 days, if well tolerated 100 mg for the next 14 days and therefore 200 mg; dexamethasone 40 mg the day of and the day after bortezomib. O65y: maximum dose of Tha: 100 mg and maximum doses of dexamethasone: 20 mg. Antithrombotic and antiviral prophylaxis was prescribed: low molecular weight heparin was administered for the first two to three months and then aspirin until the end of the treatment and acyclovir (800 mg/d) until 1 month after the last dose of Thal and sc-Bort respectively. RESULTS All the pt received the planned doses of sc-BOR. The median number of cycles completed VTD delivered was 4.5 for U65y vs 6 for O65y groups. Tha dose reduction was require in 5 pt (2 U65y and 3 O65y) and

discontinuation in 6 pt (5 U65Y); the most common reason was neuropathy. We didn´t observe any differences in the number of aphaeresis needed to reach the CD34 target or in the amount of CD34 cells collected The overall best confirmed response rate (CRS:Stringent complete response; CR: Complete response; VGPR: Very good partial response; PR: partial response) was 69,2% (n:9) for U65y and 77,7% (n:7) for O65y. After ASCT (+100) was 100% in each group. CONCLUSIONS VTD offers excellent safety profile and tolerance in both under and over 65 years old pt The low toxicity of sc-BTZ let us administrate cycles every three weeks without increasing neuropathy. Because of the adjustment dose of Tha in pt O65y we recorded not significant differences in the adhesion of treatment Tolerance and response before ASCT was similar between groups There were no differences on the number of aphaeresis needed to reach the CD34 target

PS-104
COST-EFFECTIVENES OF AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN OVER 65 YEARS NEW DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENTS

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INTRODUCTION Eligibility of candidates of ASCT in NDMM patients is defined in most health institutions by the age at diagnosis (generally under 65y) and not by biological or functional age. In the last 2 decades we have seen a substantial improvements in the prognosis of these patients, especially in young people, based on the better induction schemes, more effective and less toxic, and an intensification treatment that improve the depth

and duration of response with high dose chemotherapy supported by ASCT. MATERIAL Retrospective and comparative study of efficacy in patients (pts) between 66 and 75 years of age according with an "optimal" induction treatment (Thalidomide-THAL, Bortezomib-BTZ, or Lenalidomide-LEN based schemes) and the that inemployed (ASCT vs non-ASCT) of our cohort of patients diagnosed from Jan-1998 to Oct-2016 (n: 346) 129 pts (37%) meet the age criteria. 72 were man. Median age of this group were 71.5 (66-75). 75 of them received an optimal induction treatment. 32 were man. Median age: 71 (66-75) 20 of these patients received an ASCT after a BTZ induction treatment (VELDEX or VTD). The conditioning schemes administered were MEL200 in all of them. Toxicity were mild without mortality. Median age from diagnosis differed from ASCT group (68 y) than non-ASCT (72 y) OBJECTIVES: determine progression free survival (PFS), overall survival (OS) and number of lines after induction treatment. RESULTS After a median Follow-Up (FUp) of 48 months for the NON-ASCT group vs 26m for ASCT-group, we observed these differences - PFS were of 20m vs not reached (p.042) - OS were 53 m vs not reached (p.0489) - median number of lines employed after induction (+/- ASCT) treatment were 3 (0-6) vs 1 (0-3) CONCLUSIONS ASCT in over 65 years NDMM patients is feasible, without differences in toxicity or efficacy vs under-65 years patients and may be better PFS and OS and cost-effectiveness. Ageing with an excellent quality of life and lack of comorbidities is a usual NDMM population scenario. Clinical trials that compares these two approaches can answer part of these questions.

PS-105
Efficacy and Safety of Once-Weekly Carfilzomib and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma: Secondary Analysis from the CHAMPION-1 Study by Prior Lines of Therapy

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Introduction: In the phase 1/2 study CHAMPION-1, once-weekly carfilzomib (K) (20/70 mg/m2) with dexamethasone (d) showed acceptable safety and efficacy with an overall response rate (ORR) of 77% and median progression-free survival (PFS) of 12.6 months among patients (pts) with relapsed or refractory multiple myeloma (RRMM) (Berenson, et al. Blood 2016; 127:3360-8). In this secondary analysis, we used data from the final analysis of CHAMPION-1 to report on the efficacy and safety of once-weekly Kd at the 70 mg/m2 dose based on prior lines of therapy. Methods: Pts with RRMM who had 1-3 prior lines of therapy received K as a 30-min IV infusion on days 1, 8, and 15 of 28-day cycles. The phase 1 part of study used a standard 3 + 3 dose-escalation plan to establish the maximum tolerated dose (MTD) of weekly K following an initial 20 mg/m2 dose. In phase 2, pts received K on the same schedule at the MTD. Pts received d (40 mg) on days 1, 8, 15, and 22; d was omitted on day 22 starting with cycle 9. The primary objective was to determine ORR and secondary objectives were to determine PFS and safety. Results: A total of 104 pts (15 phase 1b and 89 phase 2) received K at the MTD of 70 mg/m2; of these, 54 and 50 pts had 1 or >1 prior line of therapy, respectively. The frequency of prior bortezomib (BTZ) exposure was 74.1% (1 prior line) and 94.0% (>1 prior line). The proportion of patients refractory to BTZ was greater in the >1 prior line vs 1 prior line subgroup (66.0% vs 44.4%). ORRs were 85.2% (1 prior line) and 68.0% (>1 prior line). The rates of achieving a complete response or better were 25.9% (1 prior line) and 12.0% (>1 prior line). Median PFS (1 prior line vs > 1 prior line) was 19.4 months (confidence interval [CI]: 15.3–23.5) vs 10.0 months (CI:

6.3–14.3). Rates of grade ≥ 3 adverse events (AEs) were 63.0% (1 prior line) and 70.0 % (>1 prior line). Grade ≥ 3 AEs of interest including hypertension and cardiac failure occurred at similar rates in the 1 and >1 prior line of therapy groups. Rates of treatment discontinuation due to AEs were 11.1% (1 prior line) and 20.0% (>1 prior line). Two patients died on study resulting from treatment-related AEs (1 with one prior line and 1 with more than 1 prior line). Conclusions: Once-weekly K (70 mg/m2) showed higher response rates and longer PFS in pts who had 1 prior line of therapy vs those with >1 prior line of treatment. The incidence of AEs was similar in these two subgroups and comparable to those observed with twice-weekly K. Overall, once-weekly Kd had a favorable benefit-risk profile in pts regardless of the number of prior therapies.

PS-106 (d)
CARFILZOMIB, POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA PATIENTS: A MULTICENTER, OPEN LABEL PHASE 1/2 STUDY

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Background: Outcome in myeloma patients (pts) relapsed or refractory (RRMM) to immunomodulatory drugs and Bortezomib is poor. Carfilzomib and Pomalidomide monotherapy only slightly improved survival. Weekly Carfilzomib is as effective as the twice schedule. We assessed weekly Carfilzomib, Pomalidomide and Dexamethasone for RRMM. Methods: in the phase 1, the primary objective was to determine the maximum tolerated dose (MTD) of Carfilzomib; in the phase 2 to determine response rate. Pts who received 1-3 prior lines of therapy and were refractory to Lenalidomide were eligible. Treatment consisted of 28-day cycles of Pomalidomide 4 mg d 1-21 (1 week off), Dexamethasone 40 mg once weekly and Carfilzomib at escalating doses (from 36 to 54 mg/m2) d 1,8,15 until relapse or intolerance. Results: Fifty-seven pts were enrolled. Median age was 62 years, median time from diagnosis was 3.7 years. In the phase 1, 15 pts were enrolled. The first 3 pts received Carfilzomib 36 mg/m2 and did not have any DLT. In the next cohort with Carfilzomib 45 mg/m2, 1 G3 hypertension and 1 sudden death occurred. Three more pts were enrolled at 36 mg/m2: 1 had a G3 atrial fibrillation, 1 G3 hypertension and 1 G5 heart failure. Both the sudden death and the heart failure were preceded by an hypertensive crisis. The safety committee established new procedures to evaluate cardiac function of potentially eligible pts, including 24h blood pressure monitoring before enrolment and serial measurement of blood pressure during treatment. Six more pts were enrolled at 27 mg/m2, none experienced a DLT. The MTD was 27 mg/m2. In the phase 2, 42 pts were enrolled, thus 48 received the recommended phase 2 dose (RP2D). In RP2D pts, the most frequent drug related G$\geq$3 AEs were neutropenia (65%), thrombocytopenia (12%), infection (8%) and fatigue/asthenia (9%). All G cardiologic AEs were 19%, G3-4 were 8%. After introducing the new procedures cardiac AEs were significantly lower (all G, G3-4, hypertension and major events) with no new fatal events. The ORR was 64%, with 26% $\geq$VGPR and 6% nCR/CR. After a median follow-up of 13.6 months, median PFS was 9.2 months and median OS was not reached. Conclusions: This is the first phase 1/2 trial combining weekly Carfilzomib, Pomalidomide and Dexamethasone. The combination was highly effective as it doubled median PFS in comparison with Pomalidomide or Carfilzomib

alone. A simple and careful cardiologic assessment before starting treatment significantly reduced the incidence of cardiac AEs.

PS-107
TOWARDS RESPONSE-ADAPTIVE CHANGES IN INDUCTION THERAPY TO IMPROVE SURVIVAL OUTCOMES IN TRANSPLANT ELIGIBLE MULTIPLE MYELOMA PATIENTS

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BACKGROUND: Bortezomib (V) - based triplet regimens are considered the standard of care induction regimens for transplant eligible multiple myeloma (TEMM) patients in the US, achieving >VGPR rates of ~60-70%. Recently, two phase II studies of carfilzomib-lenalidomide-dexamethasone (KRd) induction for TEMM (Zimmerman et al & Roussel et al, ASH 2016) with >VGPR rates in over 90%. Suboptimal response to induction appears to influence post-transplant response and survival outcomes. Our center utilizes a response-adaptive change in proteasome inhibitor (from V to K) for suboptimal response pre-transplant. Herein, we are reporting the impact of this approach on post-transplant outcomes. PATIENTS AND METHODS: The MM database was interrogated from March 2014-October 2016 for TEMM patients. Sub-optimal response was considered a response of less than VGPR based on IMWG criteria. Original induction treatment responses were compared to K treatment responses. Additionally, we compared outcomes with TEMM patients who did not undergo an induction switch to compare overall induction response and progression-free survival (PFS). Continuous variables were compared using median two sample tests, while incidences and proportions were compared using Fisher's exact tests. Survival distributions were estimated with Kaplan Meier techniques and compared using a log rank test. Paired responses were analyzed using McNemar's test to evaluate optimal response rates before and after K treatment. RESULTS: A total of 93 TEMM patients were identified, median age 59 (50 females, 43 males). Of these 93 patients, 15 patients (5 females, 10 males) were identified as receiving a treatment switch from V to K during their induction treatment. The majority of the V◊K treatment switch patients were considered to have ISS II (60.0%)/R-ISS II (76.9%) disease staging which is similar to the cohort of patients who did not undergo treatment switch (ISS II 43.1%, p=0.567; R-ISS II 74.0%, p=.181). In the treatment switch cohort, 33.3% of patients had high-risk cytogenetics which was higher than bute not significantly different than the comparable cohort of TEMM patients (18.0%, respectively; p=0.394). After V induction, 80.0% (12 of 15) had a partial response (PR), 13.3% (2 of 15) had a marginal response (MR), and 6.7% (1 of 15) had stable disease (SD). 53.3% (8 of 15) had VGPR, 46.7% (7 of 15) had PR after K-based induction. A paired comparison of these results suggests that there is improvement in depth of response with K-based induction treatment (p=0.002). Compared to the 78 non-induction switch TEMM patients, there was no significant difference in PFS (p=0.883). CONCLUSIONS: The response-adaptive strategy improve pre-transplant and post-transplant depth of response in TEMM with suboptimal response. This approach appears feasible and may help more TEMM patients benefit from upfront transplant as part of their treatment plan.

PS-108
From plateau to MRD-negative CR: outcomes in the MRC/NCRI series of randomised trials in newly diagnosed patients with multiple myeloma from 1980 to 2016

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Background: Since 1980 the MRC/NCRI series of randomised trials has enrolled 9588 patients with newly diagnosed multiple myeloma (MM). During this period high-dose melphalan with supporting autologous stem cell transplant (HDM+ASCT) and treatment with novel agents were introduced and transplant eligible (TE) and ineligible (TNE) populations defined. Methods: MRC IV, V, VI and VIII investigated low dose melphalan (+/-corticosteroid), cyclophosphamide and combinations including ABCM. MRC VII investigated HDM+ASCT after C-VAMP v ABCM. MRC IX TE investigated CVAD v CTD induction, HDM+ASCT and MRC IX TNE CTDa v MP; and in both pathways, clodronate v zoledronate, and thalidomide maintenance v observation. NCRI XI TE/TNE investigated CTD(a) v CRD(a) and sequenced CVD induction and HDM+ASCT(TE); and in both pathways, lenalidomide(+/-vorinostat) maintenance v observation. NCRI XI+ TE investigated the quadruplet KCRD v other treatments in NCRI XI TE. The median age of patients entering MRC IV, V, VI and VIII was 63y (range 31-74). MRCVII and VIII were sister trials for younger/fitter and older/unfit patients resulting in median ages of 55y (33-66) and 68y (35-74), respectively. MRC IX introduced pathways for TE and TNE patients with median age TE: 59y (31-78) and TNE: 73y (57-89), which were similar in NCRI XI TE: 61y (28-75) and TNE: 74y (54-92) and NCRI XI+ TE: 61y (33-88). Outcomes and baseline characteristics have been collated and response and progression reassessed/assessed according to IMWG criteria.

Results: Clear paradigm shifts in treatment are apparent, showing improved outcomes over low-dose chemotherapy delivered in MRC IV, V, VI, VII (low-dose arm) and VIII (>=VGPR: 6.5% (95%CI: 5.63-7.43), 1y PFS: 66.7% (65.0-68.4), 5y OS: 22.6% (21.1-24.2). The first of these is the introduction of HDM+ASCT in MRC VII TE (>=VGPR: 44.1% (37.1-51.2), 1y PFS: 78.2% (72.5-83.9), 5y OS: 48.0% (41.1-54.9). These improvements have been amplified in the TE pathways of MRC IX (>=VGPR: 45.8% (42.9-48.8), 1y PFS: 75.5% (73.0-78.1), 5y OS: 53.8% (50.7-56.8)), NCRI XI and NCRI XI+. Effective bisphosphonates in MRC IX, immunomodulatory drugs in MRC IX and NCRI XI, more effective maintenance in NCRI XI and the inclusion of novel quadruplets significantly improved outcomes (data will be presented). Prior to MRC VII, response was not associated with improved OS. Markedly increased depth of remission, as demonstrated by minimal residual disease (MRD) as assessed by flow cytometry (MFC), was shown to be a powerful predictor of outcome in MRC IX and NCRI XI. Analysis relating to patient characteristics, tumour load and renal function shows heterogeneity of treatment effect; cohorts of long-surviving patients have been identified (data will be presented). Conclusions: Outcomes in the MRC/NCRI series have greatly improved. Data from the linked investigatory studies continues to inform our therapeutic strategies.

PS-109
BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN THE MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA : A REAL-LIFE EXPERIENCE

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Bendamustine is a bifunctional alkylating agent, with low toxicity, proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM). It has been evaluated efficacy and tolerance of Bendamustine, in combination with bortezomib-dexamethasone (BVD) in patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. A regional retrospective real-life analysis of patients with rrMM who had been treated with BVD as salvage therapy has been performed. 56 patients (31 M/25 F), with rrMM, median age at diagnosis 57.3 years (r. 36-82), median age at start of treatment 61.8 years (r.37-83) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (Bendamustine 90 mg/sqm days 1,2; Bortezomib 1.3 mg/sqm days 1,4,8,11, Dexamethasone 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. ISS was equally distributed, and cytogenetic was evaluable in 12 patients, and in particular one del13q and one t(11;14). All the patients had previously been treated with schedule containing bortezomib and IMIDs, and 30% had also received radiotherapy. 67% of them had undergone at least to a single auSCT. All patients were relapsed and refractory to last therapies received before BVD. Bendamustine was well tolerated, with grade 3 transfusion-dependent anemia in 41% of patients, and 37% grade 3 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, after a median follow-up of 14 months (r.2-36), ORR was 64% (36/56 : 4 CR, 7 VGPR, 16 PR, 9 MR) with 8 PD and 12 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Median time to response was 1.2 months (r.1-3), median OS from diagnosis was 62.7 months (range 6-151), median OS from start of Bendamustine was 9.8 months (range 2-36). BVD has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT.

PS-110
A phase I/IIa study of the CD38 antibody MOR202 in combination with pomalidomide or lenalidomide in patients with relapsed or refractory multiple myeloma

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Introduction: CD38 is a type II transmembrane glycoprotein expressed in multiple myeloma (MM). MOR202 is a human IgG1 CD38 monoclonal antibody that has shown high single-agent antitumor activity in preclinical models of MM and synergy in combination with immunomodulatory drugs (IMiDs), lenalidomide (LEN) and pomalidomide (POM). Methods: Preliminary safety and efficacy data from a multicenter, dose-escalation phase I/IIa study of MOR202 in relapsed or refractory (RR)MM patient cohorts treated with clinically

relevant doses of MOR202 (2-hour IV infusion) + low dose (≤40 mg) dexamethasone (Dex) or with an IMiD/Dex, are presented. MOR202 dose levels evaluated were 4, 8 and 16 mg/kg q1w with Dex, and 8 or 16 mg/kg q1w with LEN/Dex or POM/Dex. Primary objectives were to evaluate the safety, maximum tolerated dose (MTD) and recommended phase II dose of MOR202. Results: 76 patients have been treated, 41 in clinically relevant cohorts: 18 patients received MOR202/Dex, 14 received MOR202 + LEN/Dex and 9 received MOR202 + POM/Dex. Patients had a median of 3 prior lines of therapy. The MTD was not reached. MOR202 combinations were well tolerated, with mainly hematological toxicity. A 2-hour MOR202 infusion was feasible in all patients. In the clinically relevant cohorts, only 2 patients discontinued due to a MOR202-related adverse event (grade 4 thrombocytopenia and serious grade 3 bacterial infection); no deaths related to any of the study drugs occurred. Infusion-related reactions (grade 1/2) were seen in only 3/41 (7%) patients, mainly occurring during the first infusion. In these cohorts, 35/41 patients were evaluable for response. In the MOR202/Dex cohort, 5/17 (29%) patients had a response, including 3 with partial (PRs) and 2 with very good PRs (VGPRs). In the MOR202 + LEN/Dex cohort 10/11 patients (91%) had a response; 9 PRs (2 unconfirmed), 1 VGPR. In the MOR202 + POM/Dex cohort 4/7 (57%) patients had a response; 2 complete, 2 PRs. Median time to response was 4 weeks; the longest duration was 14 months (MOR202/Dex). Preliminary analysis showed preservation of high CD38 levels on MM cells under MOR202 therapy. Conclusions: A 2-hour infusion of MOR202 (up to 16 mg/kg), with Dex, or with POM/Dex or LEN/Dex, showed a very good safety profile; particularly, excellent infusion tolerability, in heavily pretreated patients with RRMM. Promising preliminary efficacy and long-lasting tumor control was seen. CD38 expression on tumor cells was maintained during treatment.

PS-111
European Post-Approval Safety Study (EU Pass) of Relapsed/Refractory

Multiple Myeloma (RRMM): Safety In Patients (Pts) Treated With Pomalidomide (POM)

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Introduction/Background EU PASS is an observational, non-interventional registry designed to characterize the safety profile of POM treatment (Tx) in pts with RRMM in a real-world setting. Here, we report the incidence of adverse events (AEs) of special interest, including neutropenia, thrombocytopenia, venous thromboembolism (VTE), peripheral neuropathy (PN), and second primary malignancies (SPMs), in pts with RRMM treated with POM according to current clinical practice. Patients and Methods Pts with symptomatic RRMM were enrolled at the investigator's discretion and after the decision was made to treat with POM. Thromboprophylaxis was administered per local standard practice. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0). The study is ongoing and open for recruitment in centers across Europe. Results As of October 2016, 295 pts across 100 institutions in 8 European countries were included in the safety population. At the time of this abstract, Tx is ongoing in 183 pts (62.0%). Median age was 68 yrs (range, 37-88 yrs), with 36.6% of pts < 65 yrs, 36.3% between 65 and 75 yrs, and 27.1% ≥ 75 yrs;

54.9% were male. Median time from diagnosis was 4.7 yrs (range, 0.4-26.0). Median number of prior Txs was 3 (range, 0-10); 77.6% of pts had ≥ 3 prior lines. Most pts (97.6%) received prior lenalidomide. Prior bortezomib was administered in 97.2% of pts. Almost half of the pts (46.1%) had a good Eastern Cooperative Oncology Group performance status (0-1). In this analysis, median Tx duration was 15.9 wks (range, 0.0-92.0) and 4.4% of pts (n = 13) discontinued Tx due to AEs. AEs (all grades) occurred in 258 pts (87.5%). Overall, 164 pts (55.6%) had grade 3/4 AEs: neutropenia (n = 40, 13.6%), anemia (n = 15, 5.1%), thrombocytopenia (n = 14, 4.7%), and febrile neutropenia (n = 11, 3.7%). Infections (grade 3/4) occurred in 70 pts (23.7%); of those, 9.5% were pneumonia. PN (all grades) was uncommon (12 pts [4.1%]). Acute myocardial infarction (grade 3) occurred in 1 pt. VTE (deep vein thrombosis and venous thrombosis limb; all grades) was observed in 2 pts. The following SPMs were observed: basal cell carcinoma (2 pts), breast cancer (1 pt), and rectosigmoid cancer metastatic (1 pt). Conclusions Results of this ongoing non-interventional study in RRMM on the use of POM in the real-world setting show a similar AE profile to that of the pivotal randomized phase 3 trial published by San Miguel et al (Lancet Oncology, 2013), which investigated POM in pts with a greater number of prior Txs than pts enrolled in this study (median, 5 vs 3). POM was generally well tolerated, and the overall safety profile is similar to that seen in pivotal trials. Updated data will be presented at the meeting.

PS-112
Outcomes of Consecutive Patients With Newly Diagnosed Myeloma Requiring Dialysis: Dialysis Independence is Associated with Rapid Myeloma Response and Predicts for Longer Survival

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Renal failure (RF) commonly complicates symptomatic myeloma and may be severe enough to require extrarenal hemodialysis (HD). Immediate effective anti-myeloma therapy and vigorous supportive care are required to improve renal function. High cutoff HD to rapidly reduce the load of nephrotoxic light chains may offer some additional benefit in selected patients treated with bortezomib-based therapies (Cook M et al EHA 2016, Bridoux F et al ASH 2016). Outside clinical trials, there are limited data on the contemporary management and outcomes of NDMM patients requiring HD. Between 1995 and 2016, 50 patients (6.2% of 796 consecutive NDMM), who were treated in the Department of Clinical Therapeutics, presented with severe RF requiring HD, at the time of diagnosis. All patients received HD with regular filters. Median age was 69 years (37-88), 68% were >65 years; 92% had Hgb<10 gr/dl, 24% had hypeprcalcemia, 48% had elevated LDH, all had elevated β2-microglobulin (median 21.7 mg/L, range 6-60), and all were ISS stage 3. High risk cytogenetics (N=40) were present in 38%; per R-ISS, 75% were R-ISS-3 and 25% R-ISS-2. Median Bence Jones proteinuria (in patients who retained urine flow) was 2.2 gr/24h (range 0.1-8.8) and median level of involved free light chain (iFLC) was 9080 mg/l (range 119-201000 mg/l). Treatment was bortezomib-based in 41 (82%): 22% received bortezomib+dexamethasone (VD), 42% VD+cyclophosphamide (VCD), 16%

VD+thalidomide (VTD), 2% VD+doxorubicin (PAD); 9(18%) patients received non-bortezomib containing regimens. Twenty five (50%) patients became HD independent at a median of 158 days from start of therapy (range 4-336); age ≤65 years was associated with higher probability (75% vs 38%) and shorter time to dialysis independence (51 vs 336 days) (p=0.027). Bortezomib-based triplets vs VD alone were associated with higher probability of HD independence (57% vs 27%; p=0.06). Median survival is 29 months; early mortality (<2 months from start of therapy) was 16%, mostly due to infectious complications. On intent to treat, 64% of the patients achieved ≥PR (CR:6%, VGPR: 32%, PR: 26%). At landmark analysis, patients who with ≥PR within the first 2 months had higher HD independence rates (68% vs 27%, p=0.004). At landmark analysis, discontinuation of HD was associated with a significant improvement in survival (median OS 63 vs 22 months for patients who remained on HD, p=0.002) and was similar to that of the rest of MM patients (57 months). High dose therapy (HDT) followed by ASCT was performed in five patients while on dialysis; 4/5 became dialysis independent approximately one month after HDT. In conclusion, about 6% of NDMM present severe RF requiring HD but half of them can become HD independent and this chance increases with bortezomib-based triplet therapy, without the use of special filters, and independence from HD is associated with a significant improvement in prognosis.

PS-113
Efficacy and Safety of Daratumumab-Based Regimens in Patients with Relapsed/Refractory Multiple Myeloma – A Systematic Literature Review and Network Meta-analysis

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Introduction: Multiple myeloma (MM) is an incurable, life-limiting disease that accounts for approximately 1% of all cancers and 13% of haematological malignancies. Daratumumab is a new monoclonal antibody aimed to improve outcomes in relapsed/refractory MM (RRMM), and has been investigated in combination with lenalidomide plus dexamethasone (DRd), POLLUX, and with bortezomib plus dexamethasone (DVd), CASTOR, in randomized controlled trials (RCTs). Although DRd and DVd have been compared against current standard of care (SOC), namely Rd, and Vd, it is not known how daratumumab plus SOC compares with other key treatment options available on the market. A systematic literature review (SLR) and network meta-analysis (NMA) was therefore conducted to determine the comparative effectiveness of daratumumab plus SOC with other relevant options. Methods: An SLR based on searches of Medline, Embase, and the Cochrane Library was conducted to identify and then assess RCTs of treatments for RRMM. The specific studies of interest were those that had investigated the efficacy and safety of other treatment options considered to be comparators to DRd or DVd. Data from trials that met the SLR's inclusion criteria and the most recent data from POLLUX and CASTOR were extracted and then included in a Bayesian NMA to allow for indirect comparison. Results: RCT data from the SLR, POLLUX (DRd vs. Rd) and CASTOR (DVd vs. Vd) allowed formulation of two evidence networks. Network 1 included DRd and other Rd-based treatment, and Network 2, contained DVd and other Vd-based treatments. Analysis using a fixed-effects model found that DRd had a high probability of improving progression free survival (PFS; 99.9% to 100%) and overall survival (OS; 80.0% to 91.9%) versus the following treatments: • Carfilzomib+Rd – PFS: hazard ratio (HR) 0.54, 95% credible interval (CrI) 0.37–0.78 and OS: HR 0.80, 95% CrI 0.50–1.28 • Elotuzumab+Rd – PFS: HR 0.54, 95% CrI 0.37–0.80; and OS: HR 0.82, 95% CrI 0.51–1.30

• Ixazomib+Rd – PFS: HR 0.50, 95% CrI 0.33 to 0.74; and OS: HR 0.70, 95% CrI 0.42 to 1.15. Also, DVd had a high probability of improving PFS (94.7% to 100%) and OS (80.2% to 95.7%) versus the following treatments: • Panobinostat+Vd – PFS: HR 0.57, 95% CrI to 0.39–0.81; and OS: HR 0.67, 95% CrI 0.42–1.06 • Carfilzomib+dexamethasone – PFS: HR 0.74, 95% CrI 0.51–1.07; and OS 0.80, 95% CrI 0.48–1.34 • Cyclophosphamide+Vd – PFS data not reported; OS HR 0.53, 95% CrI 0.23–1.23. Of note, OS data for daratumumab are not yet mature and are still being collected. Conclusion: Evidence suggests that the combinations of DRd and DVd are effective in improving PFS in patients with RRMM with similar trends found for OS when compared with other established and new regimens. The results indicate that daratumumab in combination with SOC may be considered an effective treatment option in this indication.

PS-114 (d)

Final Survival Analysis From the FIRST Trial: Lenalidomide Plus Low-Dose Dexamethasone Until Progression (Rd Cont) v Melphalan, Prednisone and Thalidomide (MPT), and Rd for 18 Cycles (Rd18) for Transplant-Ineligible (TNE) Patients (Pts) With Newly Diagnosed Multiple Myeloma

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Background In FIRST, treatment (Tx) with Rd cont improved outcomes for TNE pts with NDMM v Rd18 and MPT. We present the prespecified final overall survival (OS) analysis. Methods TNE pts with NDMM were randomized 1:1:1 to Rd cont, Rd18, or MPT;

Rd18/MPT Txs were 72 wks in duration. The primary endpoint was progression-free survival (PFS). Secondary endpoints included OS (key secondary), overall response rate (ORR), time to second therapy (TTST), and safety. The primary comparison was Rd cont v MPT. Investigator response assessment (IMWG criteria) was used for PFS. Results As of Jan 2016 (final OS analysis), 52/535 pts in the Rd cont arm and 0 in the Rd18 (n=541) and MPT (n=547) arms continued Tx. The median follow-up for surviving pts was 67.0 mo (range, 0-86.8 mo). A statistically significant advantage in OS was shown with Rd cont (median, 59.1 mo) v MPT (49.1 mo; HR=0.78; 95% CI, 0.67-0.92; P=.0023); Rd18 median OS was 62.3 mo. Results remain consistent nearly 3 years after the original PFS analysis, with a continued PFS advantage for Rd cont (median, 26.0 mo) v MPT (21.9 mo; HR=0.69; 95% CI, 0.59-0.79; P<.00001) and Rd18 (21.0 mo); 4-y PFS was 32.6%, 14.3%, and 13.6% in the Rd cont, Rd18, and MPT arms, respectively. Median TTST was 36.7 v 26.7 mo for Rd cont vs MPT (HR=0.63; 95% CI, 0.54-0.73); Rd18 median TTST was 28.5 mo. In CR/VGPR pts, median TTST was 69.5 v 37.7 mo for Rd cont v MPT (HR=0.42; 95% CI, 0.32-0.54); Rd18 median TTST was 39.9 mo. 377 pts (Rd18 arm) and 381 pts (MPT arm) started second-line Tx v 299 in the Rd cont arm. Second-line bortezomib (BORT)–based Txs were most common (Rd cont, 179 pts [59.9%]; Rd18, 208 [55.2%]; MPT, 170 [44.6%]). Median time from second-line BORT to third-line Tx was improved following Rd cont vs MPT (16.4 v 10.6 mo). Grade 3/4 AEs occurred in 86.3%, 80.2%, and 88.7% of the 532, 540, and 541 pts (safety populations) of the Rd cont, Rd18, and MPT arms, respectively; most common grade 3/4 AEs were neutropenia (29.5%, 26.5%, and 44.9%) and infections (31.6%, 21.9%, and 17.2%). No new safety signals were seen. Discontinuation (D/C) was most commonly due to progression (50.7% [Rd cont], 66.9% [Rd18], 61.6% [MPT]). D/C due to AEs was similar across Rd cont, Rd18, and MPT arms (12.0%, 13.1%, 13.9%). Solid tumor second primary malignancies (SPMs) occurred in 6.0%, 6.9%, and 5.9% of pts, and hematologic malignancies occurred in 0.8%, 0.4%, and 2.6% of pts in the Rd cont, Rd18, and

MPT arms, respectively. Conclusions Rd cont significantly prolonged OS v MPT in TNE pts with NDMM. Rd cont and Rd18 had comparable OS results. Secondary endpoints were improved; the PFS advantage was maintained with Rd cont v MPT. Rd cont showed a PFS benefit v Rd18, delaying TTST. Few hematologic malignancies occurred with Rd Tx; the incidence of SPMs was similar between Rd cont and Rd18. The final analysis of this trial reaffirms Rd cont as a standard of care for TNE pts with NDMM.

PS-115

Elevated neutrophil-to-lymphocyte ratio at Day+100 is associated with decreased progression-free survival after hematopoietic stem cell transplantation in multiple myeloma

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Introduction: Consistent evidence has shown that the systemic inflammatory response, and consequently the interaction of immune cells and plasma cells, is of prognostic value in multiple myeloma (MM) patients. Recent studies, such as Shi et al. (2016), suggested that peripheral blood (PB) neutrophil-to-lymphocyte (NL), platelet-to-lymphocyte (PL) and monocyte-to-lymphocyte (ML) ratios, at diagnosis, can be useful surrogate markers of prognosis; however, there is no information about their prognostic role after treatment. Our objective was to evaluate the predictive value for survival of NL, PL and ML in MM patients submitted to autologous hematopoietic stem cell transplantation (aHSCT). Patients and Methods: We analyzed all 129 consecutive aHSCT performed in MM in our center between January/2009 and December/2015. We analyzed progression-free survival (PFS) and overall survival (OS); and neutrophil, lymphocyte, monocyte and platelet counts, and their

respective ratios, on Day -2 before aHSCT and on Day +100. We used the published cutoffs of 4, 100 and 0.3, respectively, and defined normal PB cell counts using CTCAE v4.03. Results: The median age of the cohort was 58 years, with 58.8% of males; the most common MM subtype was IgGκ (41.9%). The median follow-up time after aHSCT was 23.7 months. The mean±SD of NL, PL and ML at Day-2 were 4.1±2.7 G/L, 241.4±140.5 G/L and 3.0±27.7 respectively. There was no difference in PFS and OS between groups with NL<4 vs ≥4, PL <100 vs ≥100 and ML <0.3 vs ≥0.3 at Day -2, as well as at D+100 for PL and ML (p=NS). However, there was a significant difference in PFS by NL ratio at D+100 (PFS median NL<4 was 57.4 months vs 22.3 months for NL≥4; p=0.013), which was not reflected in a decreased OS (p=NS). These differences in the ratio were not explained by altered absolute counts: in fact, there was no difference in PFS and OS according to the presence of neutropenia at Day+100, while OS (but not PFS) was significantly increased (58.6 vs 72.6 months, p=0.03) with Grade 1 lymphopenia; no patients presented with lymphocytosis, and only 2 patients had neutrophilia. Conclusions: In our cohort, we failed to find the reported prognostic relevance for OS with the published ratios. Nevertheless, we observed that NL at D+100 correlates inversely with PFS, although this does not have an OS impact, which suggests that patients with MM and high NL ratios who relapse can be effectively salvaged with second-line treatment. Considering the absolute counts of the determinants of the NL ratio, only Grade 1 lymphopenia was of prognostic value for OS, although it failed to explain the impact of NL on PFS. Our results suggest that NL can be useful as surrogate predictor of relapse likelihood, when applied to Day+100 post-aHSCT evaluation.

PS-116

European Post-Approval Safety Study (EU Pass) of Relapsed/Refractory Multiple Myeloma (RRMM): Safety, Including Second Primary Malignancies, in a Large Cohort of Patients (Pts) Treated With Lenalidomide (LEN),

Thalidomide (THAL), and Bortezomib (BORT)

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Introduction EU PASS is an observational, non-interventional study to investigate the safety of LEN and other agents in the treatment (Tx) of RRMM in a real-world setting. Here, we assess the incidence of adverse events (AEs) of special interest (ie, neutropenia, thrombocytopenia [TCP], venous thromboembolism [VTE], neuropathy, and second primary malignancies [SPMs]). Patients and Methods Pts with RRMM initiating LEN Tx were enrolled at the investigator's discretion into the LEN cohort (LEN + dexamethasone, the approved combination for the Tx of RRMM); pts who received ≥ 1 prior Tx initiating a non–LEN-based Tx were enrolled into a background cohort (all other Txs, including novel agents).

Thromboprophylaxis was per local standard practice. AEs were graded per to National Cancer Institute-Common Terminology Criteria for AEs (v3.0). SPMs were defined using MedDRA terms, and SPM assessments were to be conducted up to 36 mos after Tx discontinuation (Protocol amendment 2011). Results As of March 1, 2016, 3630 pts were included in the safety population; 2151 (59.3%) received LEN, 1187 (32.7%) received BORT, 137 (3.8%) received THAL, and 155 (4.3%) received other therapies. The median duration on study Tx was 6.6 mos (range 0.1-79.9 mos) for pts receiving LEN, 4.1 mos (range 0-61.4 mos) for BORT, and 4.6 mos (range 0.2-36.9 mos) for THAL. At the time of analysis, 3557 pts (98.0%) had discontinued Tx and 73 pts (2.0%) were ongoing (63 LEN, 6 BORT, 0 THAL, and 4 others). Baseline characteristics were similar across cohorts. Median age was 70 yrs (range 25-95 yrs); 54.0% of pts were male. Of 2985 pts with available ECOG scores, 2865 (96.0%) had an ECOG score 0-2. The median number of prior therapies was 1 (range 1-6); the proportion of pts with only 1 prior Tx was lower in the LEN (44.2%) vs BORT (70.8%) and THAL (56.2%) cohorts. Overall, 1843 pts (50.8%) had grade 3/4 AEs, including neutropenia (20.0%, 4.5%, and 7.3% in the LEN, BORT, and THAL cohorts, respectively; febrile neutropenia in 1.5%, 0.4%, and 1.5%) and TCP (10.0%, 8.4%, and 3.6%). All grade neuropathy occurred in 9.8%, 28.2%, and 17.5%, and VTE occurred at 6.0%, 1.3%, and 0% of pts in the LEN, BORT, and THAL cohorts. Overall incidence of SPMs per 100 pt-years was 3.87 overall and 3.45, 5.41, 2.73, and 6.51 for LEN, BORT, THAL, and others, respectively. Tx discontinuation rates due to AEs were similar in each cohort (LEN: 22.4%; BORT: 20.1%; and THAL: 21.2%). Tx-emergent AEs leading to dose reductions were similar across cohorts (LEN: 23.9%; BORT: 21.2%; and THAL: 17.5%). Conclusions LEN was generally well tolerated and the safety results were similar to published data. As expected, the occurrence of neutropenia, TCP, and VTEs were higher in pts in the LEN cohort, whereas neuropathy was more frequently reported in pts in the BORT cohort. VTEs were

low in all cohorts. The occurrence of SPMs was generally low and comparable between cohorts.

PS-117
Addition of Cyclophosphamide and Higher Doses of Dexamethasone Do Not Improve Outcomes of Patients with AL amyloidosis treated with Bortezomib

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Bortezomib as single agent or in combinations with dexamethasone (VD) or with cyclophosphamide (VCD) induces high rates of hematologic CRs and organ responses in patients with AL amyloidosis. VCD is considered a "standard" regimen for primary therapy of patients with AL, but, it is not clear whether the addition of a third drug (cyclophosphamide) to bortezomib/dexamethasone (VD) further and significantly improves efficacy, given the substantial activity of bortezomib itself. Furthermore, patients with AL are frail due to multisystemic involvement and data from the treatment of elderly frail patients with myeloma have shown that addition of a third agent to VD does not improve outcomes and may increase toxicity. We compared the outcomes of 101 consecutive patients with AL amyloidosis who received VD or VCD. All patients received similar supportive care and were treated in two consecutive periods (up to 2010 received VD and after 2011 received VCD). Treatment was VD in 59 and VCD in 42 patients. Patients who received VD were older (median age 67 vs 60.5 years, p=0.024), had more often Mayo stage 3 (42% vs 29%, p=0.03), had lower eGFR (median 54 vs 86 ml/min/1.73 m2) but both groups had similar distribution in renal stages. Heart, renal and nerve involvement were similar between the two groups (p>0.5 for all). Weekly bortezomib was given in 41% of patients who received VD and in 40% with VCD; the starting dose was 1.3 mg/m2 in 90% and 92.5% respectively. The median dose of dexamethasone for VD treated patients was 240 mg/month and 144 mg/month for VCD (p=0.01). Early mortality was 36% vs 29% in Mayo stage 3 patients. On intent to treat, a hematologic response was 68% for VD and 78% for VCD (p=0.26); after adjustment for Mayo stage there was still no difference in response rates. Regarding CR+VGPR, it was 47.5% with VD and 35% with VCD. Higher doses of dexamethasone or twice-weekly bortezomib schedule were not associated with significantly higher or deeper hematologic responses rates. Cardiac and renal response rate was 29% and 43% for VD, and was 21% and 41% for VCD respectively (p>0.5 for all comparisons). Median follow up is 3 years and median overall survival (OS) is 34 months and was similar for patients treated with VD vs VCD (33 vs 36 months, p=0.45). There was no difference after adjustment for the dose and schedule of bortezomib and dexamethasone, and Mayo stage; no prognostic effect of higher doses of dexamethasone and twice weekly bortezomib was found. In conclusion, bortezomib even with low doses of dexamethasone is effective for the treatment of AL amyloidosis and higher doses of dexamethasone or addition of cyclophosphamide does not have a profound effect on efficacy and survival. New agents either targeting the plasma cell clone (like monoclonal antiCD38) or targeting the amyloid deposits are needed in order to further improve outcomes after bortezomib-based regimens.

PS-118
Upfront Tandem Auto-Allo Transplant in Multiple Myeloma: long-term follow-up and impact of "new drugs" at relapse

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We report the long term clinical outcomes of a multicenter trial, designed prior to the introduction of new drugs, where treatment of newly diagnosed multiple myeloma (MM) patients with an autograft followed by a nonmyeloablative allograft or with double autografts was exclusively based on the presence or absence of a HLA identical sibling (Bruno B et al. N Engl J Med 2007). Of 162 consecutive MM patients, 80 were assigned to tandem autograft-nonmyeloablative allograft and 82 to tandem autografts. Fifty-eight patients in the allograft-arm and 46 in the tandem autograft-arm completed the protocol. After a median follow-up of 12.2 years (range 7.7-15.4+), median overall survival (OS) was 11.4 (CI 95% 11.4-not reached) in the allograft-arm and 3.9 years (CI 95% 2.1-7.6+) in the tandem autograft-arm (HR 0.51, CI 95% 0.31-0.83; P=0.007), whereas progression-free survival was 3.6 and 1.5 years (HR 0.46, CI 95% 0.29, 0.74; P<0.001), respectively. Incidence of non-relapse mortality was 17.2% (95%CI: 7.4 to 27.1) in the allograft-arm and 4.3% (95%CI:0 to 10.3) in the autograft-arm. Two-year cumulative incidence of chronic graft-versus-host disease (cGVHD) was 67.2% (95%CI: 54.9 to 79.5), however 26.8% and 39% of cGVHD patients discontinued immunosuppression at 24 and 60 months respectively, considering both death and relapse as competing events. In both arms, main reason for treatment failure remained disease recurrence. Thirty-three/58 patients in the allograft-arm relapsed at least once. Two patients had a biochemical relapse without reaching criteria for treatment and were alive at 11 and 13 years from diagnosis. At follow-up patients were treated as follows: 15 patients with donor lymphocyte infusion, 28 with new drugs, 5 with radiotherapy, 10 with conventional chemotherapy (CC), 2 received a second allografting. In the autograft-arm 39/46 relapsed, and overall 35 received new agents, 10 CC, 13 a third autograft, 3 an allograft. Interestingly, median OS from 1st relapse was 7.5 years in the allograft-arm vs 2.0 years in the autograft-arm (HR 0.47, CI 95% 0.26-0.84; p=0.01). Our update showed that many patients developing cGVHD were MM-free and cGVHD-free at 5-years post-transplant, and that a synergism between graft-versus-myeloma and new agents exists. Given that MM remains an incurable disease, the combination of new drugs and allografting should be prospectively explored in high risk patients.

PS-119
Improved PFS and OS with ixazomib plus lenalidomide-dexamethasone (IRd) vs placebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Final data from the phase 3 China continuation of TOURMALINE-MM1

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The global, randomized, double-blind, placebo-controlled, phase 3 TOURMALINE-MM1 study (NCT01564537) demonstrated a 35% improvement in PFS (HR 0.74, p=0.012) with IRd vs placebo-Rd in MM pts with 1–3 prior therapies (Moreau et al NEJM 2016). The phase 3 continuation study reported here assessed the efficacy and safety of IRd vs placebo-Rd in pts with RRMM in China as a separate regional expansion of the global study. Eligibility criteria and study design were as in TOURMALINE-MM1. The primary endpoint was PFS, assessed by the same independent review committee as in TOURMALINE-MM1. Pts were analyzed separately from the global study. Sample size was based on Chinese regulatory requirements. 115 pts were randomized (57 IRd, 58 placebo-Rd; stratification was as in the global study). Compared to the global study, pts had more advanced disease at diagnosis (63% ISS stage II/III vs 46% in the global study), were more heavily pretreated (60% vs 41% had 2/3 prior therapies), and more frequently had refractory MM (43% vs 11%). At the preplanned final analysis for PFS (median follow-up 7.4 vs 6.9 mos), there was a significant 67% improvement in PFS with IRd vs placebo-Rd: HR 0.598; p=0.035; median PFS 6.7 vs 4.0 mos. This benefit was seen across prespecified subgroups. Median time to progression was 7.3 vs 4.1 mos with IRd vs placebo-Rd; HR=0.583, p=0.032. Overall response rates were 56% vs 31% with IRd vs placebo-Rd, including 25% vs 12% VGPR. At the final PFS analysis, OS data were not mature and the study continued blinded until a subsequent preplanned final analysis for OS. At the final OS analysis (median follow-up 20.2 vs 19.1 mos), there was a significant 139% improvement in OS with IRd vs placebo-Rd (HR 0.419, p=0.001), and a 10-month improvement in median OS (25.8 vs 15.8 mos). This OS benefit was seen across prespecified subgroups defined by age, disease status and prior therapy exposure. Results from sensitivity analyses of OS adjusting for potential confounding effects of subsequent therapies were consistent with a significant OS improvement in the IRd arm. Based on the OS findings, following unblinding of the study, pts in the placebo-Rd arm have the option to cross-over and receive IRd. At data cut-off for the final OS analysis, pts had received a median of 9.0 and 6.5 cycles of IRd and placebo-Rd; 67% vs 74% had grade ≥3 AEs (all-cause), 33% vs 31% had serious AEs, 9% vs 10% discontinued treatment due to AEs, and 7% vs 9% died on treatment. Common grade ≥3 AEs with IRd vs placebo-Rd included thrombocytopenia (25% vs 19%), neutropenia (25% vs 21%), anemia (12% vs 28%), and pneumonia (19% vs 17%). 18% vs 21% of pts had rash (no grade ≥3 events); 7% vs 10% of pts had peripheral neuropathy (no grade ≥3 events). In Chinese pts with RRMM, the addition of ixazomib to Rd was associated with a significant improvement in both PFS and OS, with limited additional toxicity.

PS-120
Daratumumab for the treatment of

Relapsed/Refractory Multiple Myeloma: A single center experience

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Introduction Daratumumab is a human monoclonal antibody that targets CD38; a surface protein expressed in myeloma cells. Daratumumab has a favorable profile and has been recognized as an important drug with encouraging clinical activity as a single agent and in combination with novel agents in heavily pretreated relapsed or refractory (RR) MM patients. Based on the above mentioned, we aimed to evaluate the clinical outcomes for our patients with RRMM treated with Daratumumab-based therapy. Methods All consecutive patients treated with Daratumumab-based regimens at our center from 01/2010 to 10/2016 were evaluated. Definitions of response and progression were used according to the EBMT modified criteria. Two-sided Fisher exact test was used to test for differences between categorical variables. A p value of <0.05 was considered significant and survival curves were constructed according to the Kaplan-Meier method and compared using the log rank test. Results Briefly, 32 consecutive RRMM cases receiving Daratumumab-based combinations were evaluated. Median number of prior lines of therapy was 4 (1-9). Treatment regimens are shown in Table 2. At the time of analysis, 65% (21 patients) are still alive and 15 (48%) have already progressed. Grade 1-2 infusion reactions were seen in 40.6% of cases but no severe reactions were observed. Grade ¾ neutropenia and thrombocytopenia were seen in 37.5% and 28.1% of cases. Blood transfusion was required in 13 patients (40.6%). Furthermore, median OS has not been reached yet (Estimate 18 months, CI95% 11.8-24.4) and median PFS was 5.7 months for the entire group (2.9-8.6). Twelve-patients had flow cytometry data available before starting Daratumumab and at disease progression. In conclusion, Daratumumab is an efficacious drug for the treatment of RRMM patients. Our data shows results in the setting of heavily pretreated RRMM with no major toxicity associated to the different regimen combinations. Table 1. Treatment regimens containing Daratumumab for patients with RRMM Treatment Regimen Lenalidomide/Dexamethasone/Daratumumab (LDD) N=12 ORR 12 (100%) >/=VGPR (75%) CR 5 (41.6%) VGPR 4 (33.3%) PR 3 (25%) SD 0 (0%) Pomalidomide/Dexamethasone/Daratumumab (PDD) N=8 ORR 2 (25%) >/=VGPR 0 (0%) CR 0 (0%) VGPR 0 (0%) PR 2 (25%) SD 3(37.5%) PD 3 (37.5 Pomalidomide/Bortezomib/Dexamethasone/Daratumumab (PBDD) N=2 ORR 1 (50%) >/=VGPR 1 (50%) CR 0 (0%) VGPR 1 (50%) PR 0 (0%) SD 0 (0%) MR 1 (50%) Bortezomib/Dexamethasone/Daratumumab (BDD) N=4 ORR 2 (50%) >/=VGPR 1 (25%) CR 0 (0%) VGPR 1 (25%) PR 1 (25%) SD 2 (50%) Single Agent N=12 ORR 5 (41.6%) >/=VGPR 4 (33.3%) CR 0 (0%) VGPR 4 (33.3%) PR 1 (8.3%) SD 3 (25%) MR 1 (8.3%) PD 3 (25%)

PS-121

Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) compared to Lenalidomide and Dexamethasone (LD) for the treatment of non-transplant eligible MM

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Introduction: Cyclophosphamide, bortezomib and Dexamethasone (CyBorD) has become the standard frontline approach for the treatment of multiple myeloma in many centers across Canada. In the non-transplant eligible setting, a recent a randomized controlled trial reported on the impact of Lenalidomide and Dexamethasone (LD), showing that this double-therapy is a

feasible and efficacious combination. Based on the above mentioned, we aimed to compare the effect of CyBorD and LD for the treatment of non-transplant eligible MM (NTE) patients in Alberta. Patients and Methods: The primary objective was to assess ORR, PFS and PFS2 for NTE MM patients treated with CyBorD and LD from 01/2010 to 10/2016. The recommended CyBorD regimen was as follows: Bortezomib 1.3-1.5 mg/m2 SC or IV (3-4 weeks out of 4), cyclophosphamide 300 mg/m2 PO days 1, 8, 15 and 22 and dexamethasone 20-40 mg PO days 1, 8, 15 and 22 with an aim to deliver a minimum of 9 cycles of treatment. Bortezomib maintenenance given every two weeks without cyclophosphamide or dexamethasone for up 2 years was recommended but left to the discretion of the treating physician. Lenalidomide was given at 25 mg days 1-21 of a 28-day cycle with Dexamethasone 20-40 mg PO days 1, 8, 15 and 22. Dose-adjustments were allowed to maintain patients on therapy and done at the discretion of the treating physician.Two-sided Fisher exact test was used to test for differences between categorical variables. A p value of <0.05 was considered significant and survival curves were constructed according to the Kaplan-Meier method and compared using the log rank test. Since bortezomib was used more in patients with kidney dysfunction, patients with creatinine >250 µmol/L were excluded from both groups. Results 130 consecutive patients with MM received CyBorD and 71 have received LD. At the time of analysis, 109 and 50 patients in the CyBorD and LD are alive, and 16 and 13 have already progressed, respectively. With a median follow up of 18 months for CyBorD and 39 months for LD, ORR and VGPR or better rates were 84.8% and 56.8% for patients treated with CyBorD, and 82.8% and 54.2% for LD (p=0.3). Median OS has not been reached for both groups but seemed to be similar (p=0.4). In addition, median PFS was 29 months for LD compared to 22.5 months for CyBorD (p=0.2). Lastly, median PFS2 was similar between both groups (45.7 months for CyBorD vs 39.2 months for LD, P=0.8). In conclusion, CyBorD and LD appeared to be effective treatment options for NTE myeloma patients with similar response rates. Even with the caveat of having

most of LD patients on clinical trials (97%) and the use of bortezomib in real world setting with more kidney dysfunction, this data shows comparable outcomes.

PS-122
Safety and Engraftment Parameters for Bloodless Transplants among Myeloma Patients

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Background: High dose therapy (HDT) and autologous stem cell transplant (ASCT) is a standard treatment approach with the goal of improving survival among myeloma patients. The myelo-ablative dose of melphalan used prior to stem cell infusion suppresses hematopoiesis, and supportive transfusions of red cells and platelets are utilized until engraftment. Most transplant centers do not offer HDT/ASCT to patients who decline to receive blood products, due to safety concerns associated with an increased risk of cardiovascular (CV) complications and mortality during the period of aplasia. We present data from our institutional experience of the safety and the engraftment parameters following bloodless transplants among myeloma patients. Methods: We performed a case-control study among myeloma patients that underwent HDT/ASCT (bloodless transplant-BT vs transfusion supported transplant-TST) at the Winship Cancer Institute of Emory University Hospital. Patients underwent ASCT from August 2006 until August 2016. For each patient that underwent BT, three matched TST controls were selected from the same database that underwent ASCT in the same period, matched by age (±5 years), sex, race and risk stratification. Non-parametric Mann-Whitney U test compared engraftment parameters and log-

rank test compared PFS and OS between two groups. Results: Twenty-four consecutive BT patients and 71 TST patients were analyzed. Median ages at time of ASCT for BT and TST patients were 56 years (range 37-71) and 54 years (range 27-68); p=0.222, respectively. Median times from diagnosis to HDT-ASCT for BT and TST were 8 months (range 1-47) and 9 months (range 2-117); p=0.419, respectively. Median times to neutrophil engraftment between BT and TST were 14 days (range 8-21) and 14 days (range 11-22), respectively, p=0.821; median times to platelet engraftment were 16 days (range 10-29) and 16 days (range 9-28), respectively, p=0.863; and median hospital stays were 15.5 days (range 12-24) and 16 days (range 12-29), respectively, p=0.802. Median PFS for BT and TST from ASCT was 36 months (95% CI 17.39-54.61) and 44 months (range 33.92-54.1), respectively, p=0.132. None of the BT patients received PRBC transfusions, and only one BT patient required 1 platelet transfusion. Amongst the control cohort, median PRBC transfusions given was 3.21 units and median platelet transfusions was 1.49 units. At a median follow up of 59 months after ASCT, median OS has not been reached. There were no transplant-related mortality or CV complications in either group. Two (8%) menorrhagia and 1 (4%) thrombosis was seen in the BT group, while no such episodes were observed in the TST group.

PS-123
Analysis of efficacy and predictive factors for treatment response of thalidomide-containing regimens in patients with relapsed/refractory multiple myeloma who have received prior chemotherapy including bortezomib and lenalidomide

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Background For patients with multiple myeloma who relapsed after treatment with bortezomib- and lenalidomide-based regimens regardless of whether autologous stem cell transplantation (ASCT) is received, there has not been any option for introducing new drugs such as pomalidomide, daratumumab, or carfilzomib due to unavailability of such drugs by national insurance coverage in Korea. In this situation, we can use only thalidomide-based combination treatment or old drugs such as melphalan plus prednisolone for these relapsed patients even though they were already exposed to thalidomide previously. Thus, we designed this study to determine the efficacy and predictive factor for treatment response of thalidomide-containing regimens in these relapsed or refractory multiple myeloma (RRMM) patients. Methods We conducted a retrospective analysis for group using subsequently thalidomide-containing regimens of RRMM patients who have received previous chemotherapy including bortezomib and lenalidomide in multi-centers of Korea. The primary objective was overall response rate (ORR) and the secondary objectives were complete response (CR) rate, progression free survival (PFS), overall survival (OS) and predictive factors for treatment response. Results A total of 27 eligible patients were enrolled at nine centers in Korea. The median age of the patients was 67 years (range, 50-84 years) and the median number of previous treatments was three (range, 2-5). Ten patients (37%) had undergone ASCT before thalidomide-based treatment. Of 27 evaluable patients, 1 patient achieved CR and 8 patients showed treatment response more than partial remission. Thus, CR rate was 3.7 % and ORR was 29.6 %. The median PFS was 5.9 months (95% CI, 1.3-10.5 months) and median OS was 9.2 months (95% CI, 7.3-11.1 months). In univariate analysis for treatment response, age at diagnosis (p=0.028) and prior ASCT (p=0.015) were significant clinical characteristics. But, there was no significant predictive factor for treatment response in multivariate analysis.

Conclusion Thalidomide-containing regimen seems to be a potential salvage treatment option in a group of patients with RRMM who were exposed to bortezomib and lenalidomide previously.

PS-124
Bortezomib-melphalan-prednisone (VMP) versus MP as initial treatment for very elderly patients with newly diagnosed multiple myeloma

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Background Although bortezomib-melphalan-prednisone (VMP) therapy is a well-established standard treatment for patients with multiple myeloma (MM) who are ineligible for high-dose therapy, it is not clear whether very elderly patients should be treated with VMP in clinical practice, considering the toxicities. The purpose of this case-control study was to compare the efficacy of VMP versus melphalan-prednisone or cyclophosphamide-prednisone (MP/CP) as initial therapy for very elderly patients. Methods We retrospectively studied 233 patients aged 75 years or older with newly diagnosed multiple myeloma between March 2007 and February 2015. One-hundred thirty one patients received VMP and 102 patients received MP/CP regimen were enrolled from 15 institutions throughout Korea. Results Patient characteristics were comparable in these two groups. Overall response rate was 70.2% in VMP patients and 48.0% in MP/CP patients (P=0.001). Complete response rate was 22.9% in VMP patients and 7.8% in MP/CP patients (P=0.002). After a median follow-up for survivors of 28.5 months, progression-free survival (PFS) and overall survival (OS) were significantly different between the two groups (PFS, median 21.3 vs. 11.8 months in VMP and MP/CP group, respectively, P=0.018; OS, median 34.9 vs. 22.8 months in VMP and MP/CP group, respectively, P = 0.006). Nonetheless, for 61 patients who were aged ≥ 80 years, PFS and OS was not significantly different between the two groups (PFS, median 19.6 vs. 13.2 months in VMP and MP/CP group, respectively, P=0.378; OS, median 27.8 vs.17.8 months in VMP and MP/CP group, respectively, P = 0.443). Conclusion VMP therapy showed significant benefit for very elderly patients. Frailty and comprehensive geriatric assessment should be incorporated to guide treatment decisions for this population.

PS-125
The efficacy of salvage autologous stem cell transplant for patients with multiple myeloma who received maintenance therapy post an initial transplant

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Prospective studies have shown advantages to undergoing a second ASCT in comparison to conventional salvage therapy for patients with relapsed/refractory MM, but these studies have included few patients who received maintenance therapy following the initial ASCT. Previous studies have shown the 2nd ASCT results in a progression-free survival (PFS) of 40-50% of

what patients received in their 1st ASCT, but this data comes before lenalidomide maintenance was considered standard of care. Therefore, we performed a retrospective chart review of 28 patients with MM that relapsed following initial ASCT with maintenance therapy and subsequently underwent a second ASCT for salvage. Results: The median age of the study population was 59 years (range 48-69) at second ASCT. 64% (n=18) were males, 36% (n=10) females. Prior to initial ASCT, the median number of induction cycles was 4 (range 2-11). 86% (n = 24) of patients received bortezomib during induction, 39% (n =11) lenalidomide, 7% (n=2) cyclophosphamide, and 11% (n=3) received another agent. Maintenance therapy consisted mostly of lenalidomide (93%, n = 26); 7% (n=2) had bortezomib maintenance due to lenalidomide intolerance. The overall response rate (ORR) was 100% (n=28); the complete response rate (CRR) was 39% (n=11). The median progression-free survival (PFS) post-ASCT was 31 months (range 9-57), the median interval between initial and salvage ASCT was 38 months (range 22-63). At relapse, 93% (n=26) received reinduction chemotherapy while 7% (n=2) went directly to salvage ASCT. The median number of reinduction cycles was 4 (range 2-28). 54% (n=15) of patients received carfilzomib during reinduction, 46% (n=13) bortezomib, 32% (n=9) cyclophosphamide, 29% (n=8) lenalidomide, 14% (n=4) pomalidomide, and 7% (n=2) received another agent. Prior to second ASCT, 79% (n=22) received melphalan conditioning, while 21% (n=6) received BEAM. 79% (n=22) received maintenance therapy post transplantation; 39% (n=11) received bortezomib, 18% (n=5) pomalidomide, 11% (n=3) lenalidomide, 7% (n=2) carfilzomib, 21% (n=6) were observed off maintenance, and 4% (n=1) had progression post-ASCT prior to starting maintenance. The overall response rate (PR or better) was 86% (n=24); the CRR was 21% (n=6). The median estimated PFS was 12 months (95% CI 10-15). The median duration of follow-up was 18 months. Conclusion: In MM patients who relapse post-initial ASCT with maintenance therapy with lenalidomide, the PFS following a salvage ASCT is ~40% that of the initial ASCT, similar to the data for patients transplanted prior to the maintenance

lenalidomide era. Novel re-induction, conditioning, and post-transplant maintenance regimens may improve the outcomes of patients undergoing a second ASCT for salvage therapy.

PS-126
Relative Dose Intensity (RDI) of Lenalidomide affects the outcome of patients treated with VRD consolidation followed by autologous stem cell transplantation

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〈Background〉 The concept of dose intensity has been developed in the field of cancer therapy. It has been reported that relative dose intensity (RDI) affects the outcome of breast cancer, ovarian cancer, malignant lymphoma, and chronic myeloid leukemia. Despite of recent progress of novel agents, the prognosis of multiple myeloma is still poor. We investigated the impact of dose intensity of bortezomib and lenalidomide on the outcome of myeloma patients. 〈Method〉 A retrospective analysis of 46 patients treated with bortezomib based induction therapy and autologous stem cell transplantation (ASCT) followed by bortezomib-lenalidomide-dexamethasone (VRD) consolidation, and lenalidomide maintenance in National Center for Global Health and Medicine Hospital from January 2010 to the end of October 2016 were undertaken. Cumulative dose, RDI were calculated in each patient. Overall (OS) and progression free survival (PFS) was analyzed using Kaplan-Meier methods, and log-rank test. 〈Result〉 The median RDI of bortezomib and dexamethasone in the induction therapy were 0.72 (range, 0.00 to 1.36) and 0.74 (range, 0.00 to 1.40). In the consolidation therapy, median RDI of bortezomib, lenalidomide and dexamethasone were 0.89 (range, 0.17 to 1.11), 0.80 (range, 0.19 to 1.44) and 0.88 (range, 0.17 to 0.94), respectively. The median RDI of maintenance lenalidomide was 0.53 (range, 0.00 to 0.96). Cumulative dose of bortezomib was

45.3/m2 (range. 15.3 to 97.8), and of lenalidomide was 1900mg/body (range. 0.00 to 10130).The RDI of lenalidomide in the consolidation therapy≧95% was 9 cases (20%) and 36 cases (80%) were RDI <95%. The median age of the RDI ≧ 95% group was 53 year [38-66], and the median age of the RDI <95% group was 60 year [37-68]. The PFS of RDI≧95% group (median PFS was not reached) was superior to RDI <95% group (median PFS was 44 months) (P = 0.048). There was not significant difference of OS between both groups. 〈Conclusion〉 Our study suggests that RDI of lenalidomide in consolidation therapy after ASCT contributes the outcome.

PS-127
Incidence and timing of Graft versus Host disease (GVHD) after daratumumab(Dara) anti CD38 therapy post allogeneic transplant (alloHCT)for myeloma .

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Immune mediated therapy in myeloma may take the form of targeted antibodies such as Dara, or the older nonspecific form of allogeneic hematopoietic cell transplant(alloHCT). Dara also has effects on non myeloma CD38 positive cells, importantly including Tcells, a potent mediator of graft versus host disease. Regulatory T cells (TregS)are reduced with parallel increases in helper and cytotoxic Tcells counts in Dara treated patients. Deficiency in Tregs play a large role in development of acute GVHD. Therefore, use of Dara post allo HCT

may induce a flare in GVHD. Methods: Centers with a high volume of alloHCT for MM were contacted to identify patients receiving Dara for relapsed MM following allo HCT. Three centers responded with 23 cases. Using standardized data collection forms, patient related, MM related and transplant related data were collated and analyzed after IRB approval. Details of initial conditioning, GVHD prophylaxis, incidence of GVHD pre Dara and post Dara and routine demographics were recorded. Results: Dates of alloHCT were between 2001-2016. Median follow up for surviving patients is 38.7 months. The time from alloHCT to first dose of Dara was a median of 2.1 years (3months to 15years)Pt demographics are in table1. Median number of Dara infusions was 12 (range 1-19) Five pts developed GVHD after Dara. Median time to onset of GVHD from first dose of Dara was 207 days. One acute GVHD, 4 chronic GHVD. Of the 5 pts 2 received Dara alone and 2 Dara plus Pomalidomide and 1received Dara Lenalidomide Bortezomib. Response to Dara in all pts included 8 SD, 2 MR, 6PR,1VGPR,1CR, 3PD and 2 missing. Conclusions: Dara therapy post allo HCT was well tolerated. While the incidence of developing GVHD after Dara exposure was low, physicians should be aware that it may occur many months following the Dara exposure. Age at diagnosis 48 (33-55) Sex Female 10 (43) Male 13 (57) Race Caucasian 15 (65) Hispanic 5 (26) Asian 2 (11) African-American 1 (5) Number of lines of therapy prior to AlloHCT 2 (1-9) Conditioning Cy/TBI 1 (4) Flu/Cy 1 (4) Flu/Cy/TBI 3 (13) Flu/Mel 5 (22) Flu/Mel/ATG 2 (9) Flu/Mel/Bort 2 (9) Flu/Mel/Vel +/- ATG 6 (26) Flu/Mel/TBI 1 (4) TBI 2 (9) GVHD Prophylaxis FK/MTX 4 (17) MMF/Cyclosporine 3 (13) Tacro/MMF/Cy 4 (17) Tacro/MTX 11 (48) Tacro/Siro 1 (4)

PS-128
Single center experience with autologous stem cell transplantation for multiple myeloma: a retrospective analysis

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Background and objective: The use of novel agents for induction prior to autologous stem cell transplantation (ASCT) has considerably improved the overall response rates [stringent complete response (sCR), CR, very good partial response (VGPR), partial response (PR)] in multiple myeloma (MM) patients. It improves the overall survival and progression free survival. There are very few studies from the developing countries on the use of novel agents followed by ASCT. Methods: This is a retrospective data analysis of 53 patients who underwent ASCT for multiple myeloma as a part of their remission consolidation therapy from Aug 2012 to March 2016. All patients were conditioned with high dose Melphalan (140 or 200mg/m2). Either, Thalidomide or Lenalidomide or Bortezomib was used as post-transplantation maintenance treatment. Results: Total number of patients was 53 out of which 35 were males. Median age of the cohort was 57years (22yrs-66yrs). The most common myeloma subtype was IgG Kappa in 29/53 (55%) patients. Anemia, bone disease and renal failure were seen in 58%, 70% and 32% patients respectively. At the time of presentation 58% of patients were in ISS III stage. All patients received Bortezomib based three drugs induction chemotherapy and the most common regimen was VTD used in 79% of patients. The median number of cycles before ASCT was 6 (range: 5-7 cycles). Pre ASCT 4(8%), 20(38%), 23(43%) and 6(11%) patients were in sCR, CR, VGPR and PR respectively. Three months post ASCT 9(17%), 24(45%), 30(30%) and 3(6%) patients were in sCR, CR, VGPR and PR respectively. One patient (2%) had progressive disease 3 months post ASCT. The median days of engraftment for neutrophils and platelets were 11 (range 9-13) and 11 (range 8-50) days respectively. There was no peri-transplant mortality and median hospital stay was 17 days (range 13-33 days). Post ASCT 5-years overall survival was 86.8% and 3-years progression free survival was 49.2%. The outcome was independent of subtype of MM, dose of Melphalan (140 vs 200mg/m2) and renal failure. Conclusions: The Bortezomib based three drugs induction regimens were effective and well tolerated in this retrospective analysis. It significantly improved the post-induction and post-transplant response rates without affecting stem cell collection. ASCT in MM has treatment related tolerable morbidity and minimal mortality.

PS-129
Pre-treatment small fiber neuropathy by sympathetic skin response (SSR) does not predict treatment emergent neuropathy in newly diagnosed multiple myeloma (NDMM) patients receiving bortezomib based induction therapy

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Introduction: Bortezomib (BOR), the first in-class proteasome inhibitor is an key agent in induction therapy of NDMM. A predominantly small fiber, peripheral neuropathy is one of the dose limiting toxicities of BOR. We examined whether pre-treatment small fiber neuropathy (SFN) identified by sympathetic skin response (SSR) testing predicted treatment emergent neuropathy (TEN) in patients receiving BOR based induction. Methods: Our study consisted of 19 NDMM patients diagnosed and treated between January and December 2014 who received BOR (1.3 mg/m2 BSA subcutaneous), cyclophosphamide (350 mg/m2 oral) and dexamethasone (40 mg oral) on days 1,8,15 and 22 of a 28 day cycle. All patients were evaluated before starting treatment with symptoms, neurological examination, nerve conduction study and SSR. These were repeated when the patient developed grade 3 neuropathy, at the

termination of therapy or at the end of the study period, which ever was the earliest. Neuropathy was graded using NCI CTCAE v4.0, Total Neuropathy scores- reduced (TNSr) and clinical (TNSc) at baseline and after treatment. SSR was considered abnormal if the latency was more than 1700 ms in palm and more than 2200 ms in sole or if a response was not elicitable. Neuropathic pain was assessed using numerical response scale (NRS) for pain. TEN was defined by increment of 1 grade in NCI CTCAE, 2 units in TNSr and TNSc and 1 unit in NRS. The study was approved by institutional review board. Results: Nineteen patients underwent evaluation before and after diagnosis. Median age at diagnosis was 61 years (range, 37-74); 12 (63.2%) patients being male. One (5.3%), 6 (31.6%) and 12 (63.2%) patients belonged to ISS I, II and III stages at diagnosis.Eleven (57.9%) patients had abnormal SSR before treatment. Among patients with abnormal SSR (n=11), 5 (45.5%), 6 (54.5%), 5 (45.5%) and 5 (45.5%) patients developed TEN by NCI CTCAE, TNSr, TNSc and NRS respectively. Among patients with normal SSR at baseline (n=8), 5 (62.5%), 5 (62.5%), 3 (37.5%) and 3 (37.5%) patients respectively developed TEN respectively. There was no difference between patients who had normal or abnormal SSR before treatment with respect to their risk of developing TEN (p>0.05 for all comparisons). Conclusion: In this small single center study, SFN identified by abnormal SSR at baseline does not predict TEN in patients receiving subcutaneous BOR based induction therapy for NDMM.

PS-130
Outcome of the rare myeloma subtypes-An analysis of the Collaboration to collect Autologous transplant outcomes in Lymphoma and Myeloma (CALM) data

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Introduction Rare subtypes of myeloma remain challenging to treat and due to their infrequent incidence there is limited data on their outcome. The Collaboration to collect Autologous transplant outcomes in Lymphoma and Myeloma (CALM) study has provided an opportunity to compare the real world outcomes of patients with rare subtypes of myeloma. Methods The CALM database identified 2802 patients with newly diagnosed myeloma undergoing first autologous stem cell transplantation (ASCT). Patients were divided in to "usual" myeloma (IgG, IgA and light chain myeloma) and "rare" myeloma (IgD, IgM, IgE and non-secretory (NS)). Only one patient with IgE myeloma was identified, and was therefore excluded from analysis. This study compared the overall survival (OS) and progression free survival (PFS) of these patients and the impact of novel versus non-novel drug containing induction regimens prior to ASCT. Results 2,695 patients had "usual" myeloma, while 108 had "rare" myeloma (29 IgD, 17 IgM, 1 IgE and 61 NS). IgD myeloma was found to be associated with the worst OS and PFS. With a follow up time of 72 months the OS for "Usual,

IgD, IgM and NS myeloma was 56.4%, 24.5%, 65.8% and 61.2% respectively (p=0.002). Similarly at 36 months the PFS was 39.5%, 29.8%, 51.5% and 50.2% respectively (p=0.0374). PFS with a non-novel agent was shown to be inferior to induction with a novel agent (p0.0088) but the difference in OS was not statistically significant (p=0.3758). We postulate that patients receiving non-novel induction received a novel agent at the time of relapse which may have impacted on OS results. Four different combinations of novel based induction regimens were compared: Velcade, Lenalidomide, Thalidomide and combined induction with Velcade and either Lenalidomide or Thalidomide and compared with non-novel induction. No difference in OS was seen (p=0.3764). When non-novel drugs were excluded from the analysis of OS and PFS results similar to the whole group were observed. It was not possible to perform a sub-analysis comparing the novel agents within the rare myeloma subtypes as the numbers were too small. Multivariate analysis was carried out to evaluate the impact of both the subtype of myeloma and treatment on outcomes. Using "usual" myeloma as a baseline multivariate analysis confirmed that IgD myeloma had the worst OS with HR 2.53 (p0.001). There was no OS advantage in the novel induction agent group. With regards to PFS there is a trend towards superiority in the novel induction agent group hazard ratio (HR 0.89, p=0.070). PFS in NS myeloma was confirmed to be superior (HR 0.62, p=0.011). Conclusion Rare subtypes of myeloma have been associated with inferior outcomes and an aggressive clinical course. This study confirms that IgD myeloma is associated with a poorer outcome as expected, however NS and IgM myelomas have superior PFS and OS.

PS-131
Phase 2 study using intravenous busulfan and melphalan conditioning regimen for autologous stem cell transplantation in patients with multiple myeloma; final analysis (KMM150)

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The aim of this prospective study was to evaluate the efficacy and toxicity of intravenous (i.v) busulfan and melphalan as a conditioning regimen for autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM). Patients received i.v busulfan (9.6 mg/kg) and melphalan (140 mg/m2) prior to ASCT (NCT01923935; KMM150). A total of 99 patients with MM were enrolled at 18 institutes between January 2013 and March 2016. Median time to transplant was 6.2 months. The overall response rate after ASCT was 93.6%, including 44.1% with a stringent complete response/complete response, 25.8% with very good partial response, and 23.7% with partial response. The frequent severe non-hematologic toxicity (grade 3-4) was infection (25.8%) and stomatitis (16.1%). Venous–occlusive disease was developed in three patients (3.2%). No case of treatment related mortality was observed. In conclusion, i.v busulfan and melphalan conditioning regimen was tolerated, and disease control was encouraging.

PS-132
Cytoplasmic transduction peptide-fused recombinant tumor-associated antigens

can elicit a potent myeloma-specific cytotoxic T lymphocyte by loading onto dendritic cells

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Background: Dendritic cell (DC)-based vaccines are one of promising tools in patients with multiple myeloma (MM). However, the source of tumor antigens is still challenging in this field. Here, we evaluated the feasibility of tumor-associated antigens (TAAs) to be loaded onto DCs for improving the efficacy of immunotherapy against MM. Materials and Methods: Quantitative PCR was performed to evaluate the expression of TAAs from malignant plasma cells isolated from bone marrow mononuclear cells of MM patients. Then, we made 7 cytoplasm transduction peptide (CTP)-fused recombinant proteins (CTP-SSX2, CTP-SSX4, CTP-MAGEA3, CTP-MAGEC2, CTP-hTERT, CTP-BCMA, and CTP-CD38) for the efficient delivery of TAAs onto DCs. After determination of optimal protein dose for loading onto DCs, several functional studies were performed by the DCs. Results: Based on quantitative PCR analysis, 4 cancer testis antigens (SSX2, SSX4, MAGE-A3 and MAGE-C2), hTERT, BCMA, and CD38 were selected to make CTP-fused recombinant TAAs. The CTP-fused recombinant TAAs did not deteriorate the function of DCs in terms of phenotype expressions and cytokine productions, including a Th1-polarizing capacity of naïve T cells. DCs loaded with each CTP-fused recombinant TAA had successfully generated a myeloma-specific CTL to kill myeloma cell lines and primary myeloma cells.

Conclusion: This study showed that CTP-fused recombinant myeloma-associated proteins were a useful tumor antigen source to be loaded onto DCs for generation of myeloma-specific CTLs in vitro. Therefore, CTP-fused recombinant TAAs will become a feasible tumor antigen for the clinical application of DC-based cancer immunotherapy in the field of MM.

PS-133

The efficacy and safety of lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma in real clinical practice : a study of the Korean Multiple Myeloma Working Party (KMMWP)

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Background : Lenalidomide and dexamethasone (RD) is a standard of care for relapsed/refractory multiple myeloma (RRMM), but there is limited reported data on its efficacy and safety in the real clinical practice. The purpose of this study was estimate necessity of RD chemotherapy for improving survival in RRMM in real clinical fields. Methods : Data from patients at twenty two university hospitals in South Korea between

December 2012 and Oct 2016 were collected retrospectively. Clinical and laboratory data were collected retrospectively by review of medical records. The study protocol was approved by the institutional review board of each participating hospital. Patient characteristics were described at the status before lenalidomide treatment start except for cytogenetics and international staging systems, which were described from the data established at the time of diagnosis. The progression free survival (PFS) was defined duration from the date of starting RD chemotherapy to the date of disease progression, relapse, or death from any causes. OS was calculated from the start of lenalidomide treatment to the date of death or the date of last follow-up. Cox proportional hazard regression model was used for a multivariate analysis for PFS and OS. Prognostic factors significant in univariate analysis for PFS or OS were entered for multivariate analysis. Results : The median age of the 289 patients was 66 years (range, 30-85 years) and the male to female ratio was 1.07:1.0. Patients previously were exposed to bortezomib only (43.1 %), both thalidomide and bortezomib (15.4 %), and patients who had prior autologous stem cell transplantation were 41.0 %. Median number of cycles of RD were 6 (range, 1-32). The response rates were following: CR or stringent CR (sCR) in 24 (8.3%), VGPR in 65 (22.5%), PR in 88 (30.4%), MR in 11 (3.8%) and < PR in 60 (20.7%). Overall response rates (≥PR (partial response)) rate was 61.2 %. The differences of 3-year PFS of patients with achieved VGPR or more than VGPR and less than VGPR were 63.8% vs 28.0%, p<0.001. The 3-year OS were 73.0% vs 40.4%, p<0.001. The differences of 3-year PFS of patients treated with RD less than 6 cycles and 6 cycles or more than 6 cycles were 38.6% vs 45.8%, p<0.001. The 3-year OS were 49.9% vs 52.6%, p<0.001. In multivariate analysis, these two prognostic factors were shown significant prolonged survival (PFS; p<0.001 and p<0.001, OS; 0.012 and p=0.001). Adverse events of more than grade 2 were reported. Hematologic toxicities including cytopenia was observed only in 9.7 % of patients, infections including pneumonia in 16.9%, fatigue in 5.9%, skin rash in 2.4% and thrombosis in 1.7 %. Conclusions : Our study confirms that RD is effective and safe in RRMM. It produces prolonged survival especially in patients who received more than 6 cycles and achieved more than PR response. Toxicities from RD were tolerable for RRMM patients.

PS-134
Ixazomib in combination with thalidomide and dexamethasone as treatment for patients with relapsed/refractory multiple myeloma: An ongoing phase II trial

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Introduction Ixazomib is an effective oral proteasome inhibitor with favorable toxicity profile. Recent studies showed significant activity as single agent with dexamethasone and in combination with other agents. Here, we evaluate the activity and tolerability of the all-oral combination ixazomib-thalidomide-dexamethasone (IxaThalDex) in pts with RRMM. Methods Patients with RRMM with ≥ 1 prior line of therapy (TX) were enrolled. Eligibility criteria: measurable disease, ECOG PS ≤2, ANC ≥1000/μL, platelet count ≥50000μL, GFR ≥15mL/min. Treatment:

Ixazomib (4mg, d 1, 8 and 15), thalidomide (100mg/d), and dexamethasone (40mg once/week). Pts aged ≥75 years received lower doses of thalidomide (50mg/d) and of dexamethasone (20mg). 8 cycles were planned, followed by ixazomib maintenance TX (4mg, days 1, 8, 15 of a 28 cycle and 3mg in pts aged ≥75 years) for one year. Results Fifty-seven of 77 planned pts have been enrolled so far. Intent-to treat group (ITT) median age: 67, range 41 to 84 years, ISS stage I: 22, II 19, III: 15, not known: 1, median number of prior TX lines: 2 (range: 1-5). 11 pts discontinued TX before completion of 2 cycles. Presently, 8 pts are too early for evaluation per protocol (PP). Full documentation of ≥ 2 cycles is available for 35 pts, with a median number of 4 cycles and a median F/U of 5 mos. A PR or better was achieved in 17 pts (49%), nCR: 3 pts (8.6%), VGPR: 4 (11.4%), PR: 10 (28, 6%), MR: 2 (14, 3%), yielding a clinical benefit rate (CBR) of 62.9%. FISH data are available in 29 of the 35 PP pts. ≥PR was seen in 6/12 pts with t (4; 14) and/or t (14; 16) and/or del17p and in 7/17 with standard risk cytogenetics. Median PFS at the time of reporting is 11.6 mos., both in the ITT and PP group. Median OS has not been reached in neither group. Patients with high-risk cytogenetics showed a statistical non-significant tendency for shorter PFS (11.6 mos. vs. not reached, p=0.205) and OS (p=0.446). Global health status/QoL as assessed by EORTC QLQ C-30 instrument revealed clinical meaningful (>5 points) improvement in QoL, which was slightly more pronounced in pts with ≥PR. Neutropenia was noted in 18 pts (32%), (15 grade 1/2 and 3 grade 3). Leucopenia was seen in 14 pts (25%), (13 grade 1/2 and one grade 3). 7 pts (12%) had anemia (3 grade 1/2 and 4 grade 3). Thrombocytopenia was recorded in 15 pts (26%, 10 grade 1/2 and 5 grade 3). The most frequent non-hematological toxicity was fatigue observed in 17 pts (30%). Infections were noted in 20 pts (including 6 pts with pneumonia and 1 pt with sepsis). Polyneuropathy was seen in 9 pts (all of them grade 1 or 2). During the study, the incidence of new PNP was relatively low (8 new and one worsening PNP) with presently 9 (37.5%) pts with grade 1-2 PNP. Conclusion The exclusively oral IxaThalDex regimen showed an ORR of 49%, a CBR of 62.9%, and a

PFS of 11.7 mos in pts with RRMM, was well tolerated and led to an improvement in QoL.

PS-135
Response After Induction Therapy in Transplant-eligible Newly-diagnosed Myeloma - a Pooled Analysis from Three Subsequent Multicenter Phase III Trials

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Background: The aim of this pooled analysis is to assess the response to induction therapy (IT) in newly-diagnosed, transplant-eligible multiple myeloma (MM) in 3 subsequently conducted multicenter phase III trials. Patients/Methods: 1515 patients were included and analysed as treated. Three cycles of a 3-drug IT were applied in each trial: vincristine, doxorubicin (DOX), dexamethasone (DEX; VAD) vs. thalidomide, DOX, DEX (TAD) in the HD3 trial; VAD vs. bortezomib (BTZ), DOX, DEX (PAD) in the HD4 trial; and PAD vs. BTZ, cyclophosphamide (CYC), DEX (VCD) in the MM5 trial. Results on IT for every separate trial have been reported previously: GMMG-HD3 (Breitkreutz et al., Leukemia, 2007; present analysis n=529), GMMG-HD4 (Sonneveld et al., JCO, 2012; present analysis n=388) and GMMG-MM5 (Mai et al., Leukemia, 2015; present analysis n=598). Data on partial response or better (≥PR), complete response (CR) and progressive disease (PD) are uniformly defined between the EBMT (Bladé et al., BJH, 1998, applied in HD3) and IMWG criteria (Durie et al., Leukemia, 2006, applied in HD4 and MM5) and were compared. Logistic regression models were built to assess factors influencing response. Trial effect was accounted for in pooled analyses. Results: The PD/≥PR/CR

rates after IT were 5.9%/56.3%/2.3%, 3.1%/62.4%/4.4% and 2.5%/75.6%/5.7% in the HD3, HD4 and MM5 trial. The ≥PR rates increased through subsequent study generations (Odds ratio (OR) compared to HD3: HD4 OR=1.28, p=0.07; MM5 OR=2.40, p<0.001) whereas the rates of PD during/after IT decreased (OR compared to HD3: HD4 OR=0.51, p=0.05; MM5 OR=0.41, p=0.006). On pooled analysis, patients with adverse cytogenetics (CA, defined as del17p, t(4;14) and/or gain 1q21 >2 copies, n=457) had non-significantly improved ≥PR rates (73.1%) compared to patients without CA (n=478, 68.2%, p=0.16). The ≥PR rates were in particular higher in patients carrying the CA t(4;14) (n=111, 82.0%, p=0.03 vs. no CA). However, rates of PD were also increased in these subgroups: any CA 4.2% (p=0.01) and t(4;14) 4.5% (p=0.05) vs. no CA 1.5%. Renal impairment (RI, defined as serum creatinine > 2mg/dl, n=155) was also associated with inferior ≥PR (58.7% vs. 66.7%, p=0.03) and increased PD rates (7.7% vs. 3.3%, p=0.006). In multivariable analyses, BTZ treatment (OR=3.02, p<0.001) and presence of CA (OR=1.39, p=0.04) remained significant factors to achieve higher ≥PR rates whereas low platelets (<150/nl, OR=2.47, p=0.005), LDH (> upper level of the normal, OR=2.11, p=0.02), and treatment within the MM5 trial (OR=0.38, p=0.004) significantly influence PD rates. Conclusions: Response to IT improved over subsequent study generations applying novel agents, namely BTZ. Among high-risk subgroups as defined by CA, broad heterogeneity regarding response to IT was found with increased ≥PR as well as PD rates. This implies the need to further stratify MM beyond CA and adopt therapies.

PS-136
Low frequency of CD161+CD4+ T cells correlate with the occurrence of infections in refractory/relapsed multiple myeloma patients receiving lenalidomide plus low-dose dexamethasone treatment

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Background: Although the combination of lenalidomide and low-dose dexamethasone (Len-dex) is known to preserve the efficacy with reduced toxicity than lenalidomide plus high-dose dexamethasone (Len-Dex) in patients with refractory/relapsed multiple myeloma (RRMM), infection is still a leading toxicity. Moreover, the patterns and risks for infection in patients with RRMM during Len-dex treatment remain unclear and there is a need to identify contributing factors associated with increased risk for infection. Considering the disease-related and treatment-related immune deficits in patients with RRMM, we explored the predictive implications of the revelation of the immune cell populations prior to Len-dex initiation for the occurrence of infection. In addition, the various clinical and laboratory parameters were analyzed. Methods: Clinical and microbiology records of 90 RRMM patients during Len-dex treatment were reviewed and risk factors for infection were analyzed using the logistic regression. In addition, to develop the new immune cell biomarker, we prospectively examined immune cell populations (CD3, CD4CD161, CD8CD161, Lin-HLA-DR-CD11b+CD33+, CD14+HLA-DR-, NK and NKT cells) of the peripheral blood taken on baseline of Len-dex therapy. Results: Forty-eight men and 42 women were enrolled in this study. The median age was 61 years (range, 29-84 years). During a median 11 cycles of Len-dex treatment, 52 (57.8%) patients experienced at least 1 infection episode. Of a total of 92 episodes of infection, 58 (63%) episodes were clinically defined, 29 (31.5%) episodes were microbiologically defined, and 5 (5.4%) episodes were fever of unknown focus. Severe episodes were frequently observed during early 3 cycles. In the univariate analyses, lower Hb (<10 g/dL) and serum albumin (<3.5 mg/dL), and higher serum creatinine (≥2 mg/dL) were associated with increased risk of infections (≥grade 3) during early 3 cycles. After adjusting

for risk factors for infection on univariate analyses, multivariate analyses showed that lower Hb (<10 g/dL) was an independent factor for the occurrence of infections and lower frequency (P = 0.009) and absolute count (P = 0.072) of CD4+CD161+ cells in peripheral blood prior to Len-dex were associated with the occurrence of infection, especially during early 3 cycles of Len-dex therapy. Conclusions: We demonstrated several clinical predictive factors for the occurrence of infection in patients with RRMM receiving Len-dex treatment. And we found that the frequency and absolute count of CD4+CD161+ cells may provide additional information for predicting the occurrence of infection in early period of Len/dex therapy.

PS-137
Comparison of Bortezomib versus non Bortezomib regimens in the treatment of Multiple Myeloma: Experience from a Tertiary Care Centre in North India

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Background: In multiple myeloma (MM) autologous stem cell transplantation (ASCT) is the standard consolidation therapy for patients <65 years of age. However, in a country like India, a large proportion of patients are unable to undergo ASCT, because of financial reasons or non willingness for transplant or due to availability of transplant facility in only a few centres in the country. Hence, it is vital to achieve the best possible response with the current novel agents for the treatment of MM in these patients. The aim of this study was to compare the treatment response, outcome and toxicity of Bortezomib versus non Bortezomib based regimens in newly diagnosed patients of MM who could not undergo ASCT or were transplant ineligible. Methods: We retrospectively analysed the data of 179 newly diagnosed MM patients who were treated at our centre in the past 2 years (2014-2015) and could not undergo ASCT. Outcome with a Bortezomib based therapy consisting of Bortezomib (V) + Cyclophosphamide (C) + Dexamethasone (D)

(VCD) or Bortezomib (V) + Thalidomide (T) + Dexamethasone (D) (VTD) was compared with non Bortezomib based regimens consisting of Thalidomide (T)/Lenalidomide (L) + Dexamethasone (TD/RD). The overall response rate (ORR), complete remission rate (CR), very good partial response rate (VGPR), overall survival (OS), progression free survival (PFS) and treatment toxicity were analysed. Results: The median age of our patients was 56 years (range 29-87yrs). 82 patients (45.8%) received Bortezomib based while 97 (54.2%) received non Bortezomib based regimens. The ORR was 98.7% in the Bortezomib and 88.6% in the non Bortezomib arm (P=0.24). The CR was significantly higher in the Bortezomib (34.1%) as compared to non Bortezomib arm (12.3%) (P= 0.02). The median PFS was 21 months (95% CI: 18.36-23.63) in the Bortezomib arm and 8 months (95% CI: 7.19-8.80) in the TD/RD arm (P=0.0001). The estimated 3 year OS in the Bortezomib group was 81.2% and 50.1% in the non Bortezomib group (P=0.01). The incidence of thrombocytopenia (>Grade 2) and diarrhoea (>Grade 2) were significantly higher in the Bortezomib arm as compared to non Bortezomib arm (P=0.001 for both), but could be controlled well with drugs/ modification of dose of Bortezomib. Elderly patients (> 65 years) tolerated Bortezomib therapy well with no significant increase in adverse effects when compared to the younger patients (<65 yrs). Conclusion: Our data highlights that Bortezomib based regimens (VCD/VTD) in comparison to non Bortezomib based regimens (TD/LD) have a significantly better outcome (CR, PFS, and OS). Though higher incidence of thrombocytopenia and diarrhoea are seen with Bortezomib based regimens, but these are not treatment limiting toxicities. Elderly MM patients (>65 years) tolerate Bortezomib based regimens well, with no higher incidence of adverse effects when compared to non elderly patients given Bortezomib.

PS-138
Bisphosphonate induced osteonecrosis of the jaw (BONJ) in patients with multiple

myeloma undergoing autologous stem cell transplantation

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Introduction Osteonecrosis of the jaw (ONJ) is associated with the use of bisphosphonates in cancer patients. We analysed the incidence and risk factors of BONJ in multiple myeloma (MM) patients after high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT). Methods We retrospectively analysed the data of 120 MM patients after HDT and ASCT to evaluate the incidence and risk factors of BONJ. For statistical analyses we used the SPSS program, the Fischer-Yates-test and the Mann-and-Whitney-U-test. We compared the patient group with BONJ (n=23) with the group without BONJ (n=97). Results Twenty-three patients (19%) developed BONJ. Six patients suffered several events of BONJ. Thus, the total incidence of BONJ events was 24%. No significant impact on BONJ was observed for patient gender, disease stage, presence of osteolytic lesions, anaemia, beta-2 microglobulin, osteoporosis, diabetes mellitus, and for renal failure. Neither did the type of tumor treatment affect the development of BONJ, such as the use of prednisone, dexamethason, melphalan, bortezomib, thalidomide, cyclophosphamid, bendamustin, lenalidomide, or the use of local radiation. However, there was a significant association with patients' current age (p=0,04), the type and total duration of bisphosphonate treatment (p=0,014), number of bisphosphonates' rotations (p=0,013), rheumatism (p=0,0001). Furthermore, dental manipulations were observed in 65,5% of BONJ events (19/29). Conclusions This is the first study to systematically analyse the incidence and risk factors of BONJ in MM patients undergoing HDT and ASCT. The use of bisphosphonates is highly associated with the occurrence of ONJ. Length of bisphosphonate exposure, type of bisphosphonate, rheumatism and previous dental procedures seem to be the most important risk factors.

PS-139
Total dose but not combination of Bortezomib regimen influences outcomes in multiple myeloma

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Background Bortezomib has been used in relapsed/refractory myeloma since 2007 and more recently has been increasingly used to treat newly diagnosed myeloma in the UK. However, the real-word usage patterns and factors that influence long-term clinical outcomes have not been studied widely. Aim Does duration, dosage, and combinations of bortezomib-based regimen affect clinical outcomes in a real-world setting using local protocols? Do age, sex, relapse and transplant status have any influence? Methods We performed a single-centre retrospective audit using electronic patient records between 2010-2016 to evaluate myeloma patients who had completed ≥1 cycle of bortezomib therapy. We collated and analysed data on demographics, treatment regimens and disease status to identify statistically significant factors that influence overall survival(OS) and event-free survival(EFS). Results 272 patients had bortezomib therapy in this period, 59.7% male, median age at treatment initiation 69years (range 32-95). 64% of patients were aged<75. 25.7% have received stem cell transplant. Median OS was 37months(95% CI, 31-43), and estimated 5-year survival, 35%(95% CI, 25.4-44.6). 43.2% received Bortezomib-Dexamethasone only(doublet) and 56.8% had an additional agent in combination(triplet). 38.9% were newly diagnosed patients receiving bortezomib as first line therapy while 61.1% received bortezomib in relapse status(i.e. second

line or higher). Univariate analysis showed median OS was higher with triplets(42vs30months, p=0.03), ≥6 cycles of treatment(47vs21months, p=0.0001), total dose≥50mg(42vs33months, p=0.006), transplant(61vs29months, p=0.0001) and in patients aged<75(55vs20months, p=0.0001). Patients >75yrs survived longer on triplet regimens compared to doublet(30vs17months, p=0.04). Although median OS was longer in patients<75yrs(55months), both triplet and doublet regimens gave similar results. Multivariate Cox regression identified that only age<75((HR=0.67, 95% CI=0.45-0.99, p=0.05), transplant(HR=0.4 95% CI=0.2-0.7, p=0.004) and total dose<50mg(HR=1.7, 95% CI=1.2-2.5) were independently significant. In the 204 non-transplant patients only total dose<50mg has an independent impact(HR=1.7 95% CI=1.2-2.8). Similar analysis of event-free survival showed only dose<50mg(HR=1.7, 95% CI=1.3-2.3), transplant(HR=0.4 95% CI=0.3-0.7) and relapsed status(HR=1.9 95% CI=1.4-2.6) to be independently significant. Conclusion Our cohort provides the first data for long-term real world patterns of bortezomib usage in a UK centre. Although there appears some improvement in OS with triplet regimens, particularly in older patients, the overall impact is modest and likely explained by other factors. The caveat is that very few patients were on VRD, the most efficacious triplet regimen. However, the total dosage of bortezomib therapy has a significant impact on survival independent of age, regimen and transplant settings.

PS-140

Optimal timing of second transplant in myeloma patients without optimal response to first transplant

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Background: In several trials of tandem transplant, improved survival outcomes after tandem transplant is not consistently observed. Overall survival was significantly prolonged in only 1 trial and was limited to patients who did not achieve a very good partial response (VGPR). The reported data on the use of a second stem cell transplant as salvage for relapsed myeloma have recently been reviewed. If the response duration after the initial transplant was less than 1 year, stem cell transplantation could not be recommended as an effective intervention. In myeloma patients with suboptimal response (≤ VGPR) following first transplant with high-dose chemotherapy, the available data are needed regarding optimal treatment regimens to improve the depth of response, and lead to substantial improvement of clinical outcomes. Methods: We evaluated the clinical benefits according to treatment strategies, tandem transplant (≤ 6 months after first transplant) or secondary transplant (> 6 months after first transplant) in patients with PR to first transplant. Response evaluation was done around D+100 after transplant. A total of 43 patients who received tandem transplant (n=20) or secondary transplant (n=23) were recruited. Results: Median follow-up duration was 41 months. CR rate in tandem transplant was higher than the group of novel agents (65.0% vs 60.9%). The rate of deep response including very good partial response (VGPR) in tandem transplant was similar to that of secondary transplant (75% for tandem transplant vs 73.9% for secondary transplant). And the time to next treatment of the tandem transplant seemed to be shorter than that of secondary transplant (27.2 months vs 33.2 months). In patients who achieved CR, the time to next treatment was longer than in patients without CR (34.1 months vs 14.2 months). However, no different in overall survival was seen between two groups. Conclusions: In patients who achieve a partial response after first transplant with high-dose chemotherapy, there was no meaningful difference of clinical outcomes according to the transplant timing-tandem or secondary. Therefore, second transplant might

be delayed until progression. In addition, both tandem and secondary transplant are still an available treatment option and achieving deeper response is associated with a better clinical outcome.

PS-141
Induction therapy and thalidomide based maintenance in multiple myeloma - A retrospective analysis from a tertiary cancer center.

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Induction therapy and thalidomide based maintenance in multiple myeloma - A retrospective analysis from a tertiary cancer center. Arun ramanan. V (1), Prof. Dr. Kalaichelvi. K (2) (1) DM medical oncology Resident, (2) Professor & HOD, Department of Medical oncology, Madras Medical college, Chennai. Objective: To analyse the treatment results and maintenance with Thalidomide for multiple myeloma patients. Methods: Retrospective analysis of 41 multiple myeloma patients (2012-2015) treated with either Bortezomib,Dexamethasone,Thalidomide (BDT regimen) for 4 cycles followed by maintenance thalidomide and dexamethasone or cyclophosphamide,Vincristine,Prednisolone plus thalidomide (CVP-T regimen) for 6 cycles followed by oral cyclophosphamide with thalidomide maintenance (for 2 years). Adverse effects were analysed. Results: Out of 28 patients received induction therapy with BDT regimen, 54%(15 patients) achieved complete remission (CR), 46%(13) achieved partial remission (PR) and among 13 with CVP-T regimen, 31% (4) achieved CR and 69%(9) PR. 32 % (9) were progression free at 36 months with thalidomide and dexamethasone maintenance after BDT regimen and 28% (3) with oral cyclophosphamide and thalidomide after CVP-T regimen. Totally 11 out of 41 (29%) with thalidomide based maintenance were progression free at 36 months Grade 2 Neuropathy in 11 with thalidomide / dexamethasone and Grade 3 Neuropathy in 6 patients with Cyclophosphamide / thalidomide

when maintained for 2 years. 3 patients had Deep vein Thrombosis. Conclusion: Induction with BDT regimen results in 54% CR whereas CVP-T regimen results in 31% CR. 29% were progression free at 36 months with Thalidomide based maintenance after BDT regimen and CVP-T regimen. Thalidomide based maintenance is a valid option after induction chemotherapy where stem cell transplant is not considered an option.

PS-142
Global, Prospective, Non-interventional, Observational Study of Disease Presentation, Treatment Patterns, and Outcomes in Multiple Myeloma (MM) Patients (pts): The INSIGHT MM Study (NCT02761187)

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Advances in treatment have improved prognosis and increased disease-free and overall survival for MM pts. However, currently available data on disease presentation, treatment patterns and outcomes for real-world MM pts at the global level are limited due to the overrepresentation of medically fit pts in clinical trials, the large number of treatment options and combinations, and varying global access/practice patterns. INSIGHT MM is a global, prospective, non-interventional, observational study of real-world pts that aims to further understand disease and pt characteristics at presentation, treatment and clinical outcomes, plus the association of treatment with tolerability, effectiveness, health-related quality of life (HRQoL) and healthcare resource utilization (HRU). At least 5000 adult pts with newly diagnosed or relapsed/refractory MM will be enrolled and followed prospectively for ≥5 yrs or until death or end of study. Choice of therapy will be decided by the treating healthcare provider independent of study participation. The primary objective is to describe real-world disease and pt characteristics at presentation, therapies, and clinical outcomes in pts with MM. Secondary objectives include describing: real-world patterns by treatment facility type and country; patterns and duration of treatment combinations, sequencing, retreatment, and continuous vs fixed duration treatment strategies, plus association with clinical outcomes; factors associated with treatment initiation, modification or change at relapse; HRQoL and HRU; and associations between pt characteristics, clinical disease presentation, therapies and outcomes. Hospital/clinic records will be used to record baseline pt and MM-specific characteristics, diagnosis, comorbidities and prior therapies. MM management, disease status and safety data will be recorded quarterly by each site. Effectiveness of therapy will be assessed based on response, progression status, time to next therapy, vital status, and date and cause of death. Treatment tolerability will be assessed based on serious AEs and non-serious

AEs associated with treatment discontinuation/dose modification, as well as PRO surveys. HRQoL will be collected using the EORTC QLQ-C30 and the EORTC QLQ-MY20. The 9-item Treatment Satisfaction Questionnaire for Medication will be used to capture pt satisfaction with MM-directed therapy, including convenience. The Q-5D-5L instrument will capture self-reported preference-based measures of health status suitable for calculating quality-adjusted life year data. Comorbidity and frailty will be assessed using the Charlson Comorbidity Index, the Katz Index of Independence in Activities of Daily Living and the Lawton Instrumental Activities of Daily Living. HRU evaluations will incorporate inpatient and ICU admissions, length of stay, outpatient clinic visits, surgeries and emergency room visits. The study is ongoing and recruiting pts.

PS-143

Triplet Therapy & Overall Survival (OS) in Routine Practice among Transplant-Ineligible Patients (pts) with Newly Diagnosed Multiple Myeloma (NDMM) in the United States (US)

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BACKGROUND: Triplet therapy with novel agents (immunomodulators [IMIDs] & proteasome inhibitors [PIs]) improved OS in trials of NDMM pts; however, outcomes with these combinations in routine practice have not been well elucidated. We describe treatment (tx) patterns & outcomes in a US cohort of NDMM pts by 1LT type. METHODS: In this retrospective electronic medical records database study, adult NDMM pts starting 1LT between 1/1/2008 & 12/31/2015 were identified

using ICD-9/10 diagnosis (dx) codes. Pts were followed 1 yr prior to dx until death/loss to follow-up/or end of study. Pts having transplant during 1LT were excluded. Treatments received during 1LT were defined as: PI-based: bortezomib or carfilzomib +/- non-IMID; IMID-based: lenalidomide, thalidomide, or pomalidomide +/- non-PI; PI+IMID-based: any combination of PI + IMID; other: any non-PI/non-IMID tx (dexamethasone mono-tx >90 days, bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine). In addition, induction therapy in 1LT was categorized as a 3+ vs 1-2 drug regimen. CRAB symptoms (sxs) (renal insufficiency [RI], anemia, bone disease [dz], & hypercalcemia [HC]) were identified with ICD codes or lab values within 6 months (mo) prior to 1 mo post-dx. Kaplan-Meier method was used to analyze OS from start of 1LT. RESULTS: Among 2070 NDMM pts, mean age was 70.1 years (yrs). 1LT with novel drugs predominated (PI-based, 45.8%; IMID-based, 27.6%; PI+IMID-based, 17.1%; other, 9.5%). 631 pts (30.4%) initiated a 3+ drug combination: 35.8% PI+IMID+steroid, 62.0% cytotoxic agents+PI or IMID, 2.2% cytotoxic agents. Pts given an IMID-based or other regimen were older (mean age, 72.4 yrs for both) compared to pts on PI- or PI+IMID-based 1LT (mean ages: 69.1 & 67.7 yrs, respectively); P<0.01. More pts on a PI- or PI+IMID-based 1LT had anemia, HC, & bone dz vs pts on IMID-based or other 1LT type; P<0.02 for all. More pts on PI-based 1LT had RI than other 1LT types, P=0.01. Median OS was longer for pts treated with a PI+IMID combination (51.1 mo [95% CI: 48.1, not estimable]) vs PI-, IMID-, or other therapy at any time during 1LT (43.8 mo [95% CI: 33.6, 50.7]; 47.4 mo [95% CI: 40.1, 51.9]; & 35.0 mo [95% CI: 30.0, 43.8], respectively). Pts on 3+ drug 1LT in induction had a longer median OS than those who received 1-2 drugs (50.9 mo [95% CI: 46.0, 81.7] vs 41.1 mo [95% CI: 37.2, 47.3]). CONCLUSIONS: In this NDMM cohort, age & dz sxs influenced choice of 1LT regimen type. While more intensive 1LT appears to improve survival outcomes in univariate analyses, future work is needed for confirmation. A limitation of this dataset is that

information on reasons for discontinuing tx & adverse events was not available.

PS-144
Treatment (tx) Patterns & Outcomes by Line of Therapy (LOT) in a Large United States (US) Cohort of Transplant-Ineligible Patients (pts) with Multiple Myeloma in the Era of Novel Agents

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BACKGROUND: A prior analysis of newly diagnosed multiple myeloma (NDMM) pts between 1985 & 1998 at a US center reported a median overall survival (OS) from start of first (1LT) & second (2LT) line tx of 28.4 & 17.1 months (mo), respectively. We describe tx patterns & outcomes by LOT among NDMM pts treated in routine care in a contemporary US cohort. METHODS: This was a retrospective US electronic medical records database study. Adult NDMM pts starting 1LT between 1/1/2008 & 12/31/2015 were identified using ICD-9/10 codes. Pts were followed 1 year (yr) prior to diagnosis (dx) until death/loss to follow-up/or end of study. Pts undergoing transplant during 1LT were excluded. Regimens in each LOT were grouped into PI-based: bortezomib or carfilzomib +/- non-IMID; IMID-based: lenalidomide, thalidomide, or pomalidomide +/-non-PI; PI+IMID-based: any combination of PI + IMID; Other: any non-PI/non-IMID tx (dexamethasone mono-tx >90 days, bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine). Charlson comorbidity index (CCI) was derived based on ICD dx codes within 1 year pre-dx. High cytogenetic risk was defined as del(17p), t(4;14), t(14;16), &/or 1q21 gain. Kaplan-Meier method was used to analyze duration of tx (DOT), time to next tx or death

(TTNT) & OS from start of each LOT. RESULTS: Among 2070 NDMM pts, mean age at dx was 70.1 yrs; 51.3% were male; comorbidities were common (CCI=1: 17.2%; CCI=2+: 31.1%); & 10.5% had known high-risk cytogenetic disease (dz). 1LT with novel drugs predominated (PI-based, 45.8%; IMID-based, 27.6%; PI+IMID-based, 17.1%; other, 9.5%). Among 697 & 255 initiating 2LT & 3LT, respectively, use of novel agents was frequent in both LOTs (86.2% & 89.4%). In 2LT, 41.9% received IMID-, 37.0% PI-, & 7.3% PI+IMID-based therapy; in 3LT both PI- & PI+IMID combination tx increased but IMID-based tx decreased (43.5% PI; 17.65% PI+IMID; 28.2% IMID). Median DOT was: 1LT: 5.9 mo (95% confidence interval [CI]: 5.5, 6.2); 2LT: 7.1 mo (95% CI: 6.2, 7.9); 3LT: 5.5 mo (95% CI: 4.4, 6.1). Median TTNT decreased with each successive LOT; 1LT: 16.1 mo (95% CI: 15.1, 17.2), 2LT: 14.1 mo (95% CI: 11.7, 16.4), 3LT: 8.8 mo (95% CI: 6.6, 10.2). Median OS from initiation of each LOT also decreased; 1LT: 44.8 mo (95% CI: 40.3, 49.0); 2LT: 36.4 mo (95% CI: 29.4, 43.8); 3LT: 26.8 mo (95% CI: 18.7, 31.4). Pts with known stage I/II dz (n=169) had a 2-yr TTNT of 50.5% & a 2-yr OS of 80.6% compared to 43.9% & 67.6%, respectively, for pts with stage III dz (n=92) from initiation of 1LT. CONCLUSIONS: Median OS from start of 1LT & 2LT was longer in the present analysis of a contemporary cohort of pts with NDMM than previously reported. Still, successive relapses in MM are associated with diminishing disease control & worse outcomes. These data provide useful benchmarks for future analyses of recently approved therapies for MM.

PS-145
Association Between Treatment Regimen Type in Second-Line Therapy (2LT) and Duration of Therapy (DOT) & Time To Next Treatment (TTNT) in a United States (US) Relapsed/Refractory Multiple Myeloma (RRMM) Cohort

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BACKGROUND: In MM, extended DOT in clinical trials is associated with better outcomes. Data on DOT and outcomes in pts with RRMM treated in routine clinical care are limited. We evaluated the DOT & TTNT by regimen type in a US cohort of 2LT RRMM pts. METHODS: In a retrospective US electronic medical record database study, adult RRMM pts diagnosed between 1/1/2007 & 6/30/2015 initiating a bortezomib-, carfilzomib-, or lenalidomide-based (bort-, carf-, or len-based) 2LT were identified. The regimens in 2LT were grouped into mutually exclusive categories: 1) bort- (+/-len); 2) carf- (+/-len); and 3) len-based (-carf or bort). DOT of 2LT was calculated from the first to the last administration date of all drugs in the 2LT regimen or death. Kaplan-Meier method was used to analyze DOT of 2LT & TTNT from start of 2LT to start of 3LT. Cox proportional-hazards regression was used in multivariate analyses, adjusting for age, gender, comorbidities, anemia, bone disease, cytogenetic risk, dx year (yr), type of 1LT, treatment-free interval (TFI), prior transplant, time from index dx to 2LT, race, region, & insurance type. RESULTS: Among 492 RRMM pts, median age in the len- (n=227), bort-(n=213) and carf-based (n=52) groups was 69, 72, and 67 yrs, respectively. Median follow-up ranged from 3.3 mo (carf-based) to 14 mo (len-based). More pts in the carf group had anemia at start of 2LT and proteasome inhibitor + immunomodulator front-line triplet therapy, P<0.01. The proportions of pts with prior stem cell transplants were similar across the regimen types, P=0.50. The median TFI from 1LT to 2LT was 1.1 mo in the carf- vs 3.9 mo in the bort- & 5.4 mo in the len-based groups, P<0.01. Overall, unadjusted median 2LT DOT was 7.7

mo (95% CI: 6.6, 9.2) & TTNT was 14.7 mo (95% CI: 12.9, 17.7). The len-based group had the longest unadjusted median DOT (10.1 mo [95% CI: 7.9, 11.9]) vs the bort- (6.6 mo [95% CI: 5.1, 8.2]) & carf-based (4.6 mo [95% CI: 3.0, 7.5]) groups; P<0.01. The regimen type in 2LT was significantly associated with DOT (adjusted HR[bort] for treatment discontinuation: 1.41 [95% CI: 1.11, 1.79] & HR[carf]: 1.93 [95% CI: 1.25, 2.96] vs len-based 2LT). The len-based group had the longest unadjusted median TTNT (20.1 mo [95% CI: 17.7, 29.2]) vs the bort- (11.9 mo [95% CI: 9.5, 13.7]) & carf-based (5.7 mo [95% CI: 3.7, 8.2]) groups; P<0.01. After adjustment, TTNT was associated with regimen type (adjusted HR[bort]: 1.91 [95% CI: 1.45, 2.52] & HR[carf]: 3.21 [95% CI: 2.00, 5.17] vs len-based regimens in 2LT). CONCLUSIONS: In this RRMM cohort, TTNT was almost 2-fold longer than DOT in 2LT, suggesting that treatment is frequently discontinued for reasons other than progression. The all-oral lenalidomide-based regimen in 2LT was associated with the longest DOT & TTNT, even after adjusting for baseline patient characteristics. Future research is needed to confirm these results.

PS-146
Newly Diagnosed Multiple Myeloma (NDMM): Effect of Age, Renal Insufficiency (RI), & Cardiovascular (CV) Disease (dz) on Overall Survival (OS) & Treatment (tx) Patterns Among Stem Cell Transplant (SCT)-Ineligible Patients (pts) in the United States (US)

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BACKGROUND: Introduction of proteasome inhibitors (PIs) & immunomodulators (IMIDs) into MM tx in the last decade has led to prolonged OS. However, comorbid RI & CV dz and older age (75+ years [yrs]) negatively affect survival in relapsed/refractory MM. We aimed to describe tx patterns & outcomes in SCT-ineligible NDMM pts treated with first-line tx (1LT) in routine clinical practice in a US cohort based on age & presence of comorbid RI & CV dz. METHODS: This was a large retrospective US electronic medical records database study. Adult pts with symptomatic SCT-ineligible NDMM initiating 1LT between 1/1/2008 & 12/31/2015 were identified using ICD-9/10 diagnosis (dx) codes for MM. CRAB symptoms (RI, anemia, bone dz, & hypercalcemia) were identified within 6 months (mo) prior to 1 mon post-dx by ICD codes or lab values. Pts were followed from 1 yr prior to dx until death/loss to follow-up/or end of study. Other comorbidities were identified within 12 mo prior to dx. Overall survival (OS) & time to next tx (or death) from start of 1LT (TTNT: a surrogate for progression-free survival) were estimated using Kaplan-Meier method. Cox proportional hazards regression was used to estimate hazard ratios (HRs) & 95% confidence intervals (CIs) for OS & TTNT. RESULTS: 2070 NDMM transplant-ineligible pts (<75 yrs: 1209; 75+ yrs: 861) were analyzed. Most patients received IMID and/or PI-based 1LT (90.5% pts). Triplet therapy in 1LT was more common in younger pts (<75 yrs) than in older pts (75+ yrs): 36.8% vs 22.4%, respectively. PI-based 1LT was most common (>40%) regardless of age or presence of comorbidities. Elderly pts (75+ yrs) received IMID-based 1LT more often than younger pts (35.0% vs 22.4%). Median OS & TTNT from start of 1LT were 44.8 mo (95% CI: 40.3, 49.0) & 16.1 mo (95% CI: 15.1, 17.2). Controlling for race/ethnicity, stage, cytogenetic risk, diabetes, thromboembolic dz, geographic region, type of 1LT and year of dx, elderly patients (75+ yrs) had worse OS & TTNT in multivariate analysis (HR[OS]: 1.68 [95% CI:1.4, 2.0]; HR[TTNT]: 1.16; [95% CI:1.03, 1.31]; both P<0.02). Pts with RI and CV dz or RI alone had worse OS (HR[BOTH]: 1.5 [96% CI: 1.2, 1.9], HR[RI]: 1.3 [95% CI: 1.1, 1.5]; both P<0.02). At dx, RI,

CV dz, or both were found in 869 (42.0%), 142 (6.9%), & 297 (14.4%), respectively. More pts age 75+ yrs vs <75 yrs presented with RI (63.3% vs 51.4%; P<0.01) or CV dz (25.1% vs 18.4%; P<0.01). CONCLUSIONS: Despite introduction of PIs and IMIDs into US clinical practice, the median OS of 44.8 mo, in this US cohort of SCT-ineligible NDMM pts treated between 2008-2015 remains unsatisfactory. The majority (56.3%) had comorbid RI & CV dz or RI alone & 42% were 75+ yrs old at dx; our data confirm these factors are independently associated with worse OS. New efficacious & safe therapies for this population are needed.

PS-147
Re-immunization following Autologous Hematopoietic Stem Cell Transplantation (auto HCT) is Safe and Effective in Patients with Multiple Myeloma Receiving Lenalidomide Maintenance

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Introduction: CDC guidelines recommend vaccination starting 12 months after HCT, but there is varying practice regarding revaccination in patients on maintenance therapy, with some not vaccinating at all. Due to decreased vaccine rates among the general population causing decreases in herd immunity, we aim to establish the safety and efficacy of revaccinating patients on lenalidomide maintenance (LM). Methods: We retrospectively identified myeloma patients from the institutional registry who received their first Auto HCT between 2010-2014 within one year of diagnosis. Vaccine responses were determined based on comparison of pre- and post- vaccination titers. We classified patients as responders, non-responders, or immune by pre-vaccination titer. We used descriptive statistics to summarize the results for each vaccine and univariate analysis to compare between patients who were and were not on LM. Adverse events due to vaccination were retrospectively collected. Results: 122 patients met inclusion criteria (median age, 58 years; range, 34-75; 52% males). Median time to vaccination was 12.6 months (range 8.1-26.4) after Auto HCT with 71% on LM and 10% on steroids at initiation. 118 completed the Haemophilus influenzae type b (Hib) vaccine series per CDC guidelines. With 24% starting immune and 2% not evaluable, 71% responded (95% of evaluable). Complete pneumococcal vaccination with Prevnar 13 occurred in 119. All patients had lost their immunity prior to vaccination, but 58% responded to the vaccine (58% of evaluable). 109 patients completed the Polio vaccine series. With 69% retaining immunity, 27% responded to the inactivated polio vaccine (100% of evaluable). 106 completed the full Tdap vaccine series. Tetanus, diphtheria, and pertussis had 60%, 69%, and 75% responders (96, 74, 91% of evaluable), with 32%, 0% and 13% starting immune, respectively. Fewer patients received and completed the Hepatitis A and B vaccines with 76 patients receiving the Hepatitis A vaccine as single agent vaccine or as combined Twinrix (56 completing), and 87 patients receiving the Hepatitis B vaccine as either single agent or combined Twinrix (68 completing). Responses occurred in 30% and 40% (58 & 49% of evaluable), with 29% and 3% starting immune, respectively. Univariate analysis did not show any difference in response rates between the patients who were and were not receiving LM at the time of immunization. The response rates in our cohort are consistent with reports in patients without myeloma. No patients had related adverse events.
Conclusions: Re-immunization with inactivated vaccines in patients on LM is both safe and effective, offering this population immunity to vaccine preventable diseases.

PS-148 (d)
Predictors of Early Treatment Failure

following initial therapy for Systemic Immunoglobulin Light Chain Amyloidosis

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Introduction: The prognosis of patients (pts) with systemic light chain (AL) amyloidosis depends on number and severity of organ involvement, especially cardiac. Though the outcomes have improved over the decades, still the high early mortality remains unchanged. We analyzed the factors predicting early treatment failure (ETF) within 12 and 24 months after 1st therapy for AL amyloidosis. Methods: Pts with AL amyloidosis seen at our institute within 90 days of diagnosis, between 2006 and 2015, were identified. Their data was collected by chart review for retrospective analysis. Pts who died within 3 months of starting therapy were excluded. ETF was defined as relapse / progression requiring treatment change / re-institution or death within 12 (ETF 12) or 24 (ETF 24) months of starting 1st line treatment. Non-ETF included pts with a follow up of more than 12 or 24 months who had relapse / progression beyond 12 or 24 months or had continuing response. Results: A total of 794 pts met the study criteria and were included in the analysis. Among these, 265 (33.4%) pts had ETF12 and 418 (52.6%) had ETF24, while the rest belonged to Non-ETF12 and 24 cohorts. The median age (64.3 vs 62.3 years; p=0.01), proportion of males (70.5 vs 59.9%; p=0.003), cardiac involvement (81.3 vs 63.7%; p<0.0001), renal involvement (57.2 vs 68.2 %; p=0.006), multi-organ involvement (65.6 vs 52.7%; p=0.0008), presence of t(11; 14) (56.1 vs 42.9 %; p=0.008) and proportion of pts in higher mayo stage (59.8 vs 41.5; p<0.0001) were

higher in ETF12 as compared to Non- ETF12, while liver involvement (17.1 vs 12.1%; p=0.1) and bone marrow plasma cell (BMPC)% (32.4 vs 31.6%; p=0.8) were similar. The median follow up was 62.9 months (95% CI; 59.9, 67.3) from start of initial therapy. The variables included in the analyses for factors predicting ETF12 and 24 were age at diagnosis (≤ vs > 70 years), mayo stage (I+ II vs III+IV), BMPC (≤ 10% vs > 10%), presence of t(11; 14) versus not, multi-organ involvement (>1 vs 1; heart, liver, kidney, gastrointestinal tract, autonomic neuropathy), incorporation of ASCT in initial therapy. In univariate analysis, t(11; 14), mayo stage, multi-organ involvement, and inclusion of ASCT as part of initial therapy were significantly associated with ETF12 and 24. In multivariate analysis, presence of t(11; 14) and non- incorporation of ASCT as part of initial therapy are significant predictors of ETF12 (p=0.008 and p=0.0015, respectively) and ETF24 (p<0.0001 and p=0.003, respectively) while mayo stage is predictive of ETF24 (p=0.002), but not ETF12. Conclusions: We demonstrate that pts with ETF are older with higher prevalence of cardiac, renal involvement and multi-organ involvement and higher proportion of patients with t (11; 14) or in Mayo stage (III and IV). Presence of t(11; 14) and non- incorporation of ASCT as part of initial therapy are significant predictors of ETF at 12 or 24 months.

PS-149
Elotuzumab in Combination with Pomalidomide and Corticosteroids for Relapsed or Refractory Multiple Myeloma.

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Introduction Elotuzumab is a humanised monoclonal antibody to SLAMF7, a cell surface receptor that belongs to the signalling-lymphocyte-activation-molecule (SLAM) family, found on multiple myeloma (MM) cells

and natural killer (NK) cells. Elotuzumab has shown promising results when combined with immunomodulatory drugs such as lenalidomide (Lonial et al, NEJM 2015) in relapsed/refractory multiple myeloma (RRMM). We aimed to evaluate the activity of elotuzumab in combination with pomalidomide, a novel drug combination that to our knowledge has no currently published data. Methods We retrospectively reviewed 12 patients with RRMM, treated with elotuzumab in combination with pomalidomide and corticosteroids between November 2015 and December 2016. Elotuzumab was administered IV at a dose of 10mg/kg weekly for the first 8 doses followed by fortnightly infusions, with pomalidomide 4mg PO daily (range 3-4mg). Corticosteroid therapy consisted of dexamethasone (10 patients) given IV or PO with doses ranging from 4 to 40mg weekly and hydrocortisone (2 patients) 100mg IV prior to elotuzumab infusions. Treatment continued until disease progression or unacceptable toxicity. Results The median age was 64 years (range 56-78) with a male predominance (66%). The median number of lines of prior therapy was 5 (range 3-8). All patients were refractory to alkylating agents as well as bortezomib and lenalidomide. Nine (75%) patients had previously received high dose melphalan with autologous stem cell transplantation. Paraprotein subtype included 8 IgG, 1 IgA, 1 lambda light chain, 1 kappa light chain and 1 non-secretory patient. 11 out of 12 (91.7%) patients were initially treated with pomalidomide alone. The median time on therapy prior to addition of elotuzumab was 13 weeks (range 1-32). By IMWG criteria, 3 patients achieved a PR with no complete responders (ORR 25%). Seven (58.3%) patients in the cohort achieved a clinical benefit consisting of 3 PR, 3 MR and 1 SD. Amongst patients achieving a clinical benefit the median PFS was 255 days (range 28-376). Median treatment duration with elotuzumab was 9 weeks (range 3-54). The rates of grade 3 or 4 haematology toxicity found in this cohort were anaemia (50%), thrombocytopenia (50%), lymphocytopenia (83.3%) and neutropenia (66.7%). These rates were not unexpected given this patient population. There were no treatment discontinuations or death attributed to drug toxicity. 6 patients have died, 4 from progressive myeloma and 2 from infection. Conclusions Elotuzumab in combination with pomalidomide and corticosteroids was a tolerable and active regimen in a population of heavily pre-treated patients with RRMM. Given the potential complementary immunomodulatory effects of this drug combination, further investigation earlier in the disease course is warranted.

PS-150
MULTIPLE MYELOMA STANDARD DOSE VERSUS FIXED DOSE- A COMPARATIVE STUDY IN TRANSPLANT INELIGIBLE PATIENTS

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AIM To assess the efficacy of weekly 1.3mg/m2 versus 2mg flat dose in multiple myeloma with Lenalidomide and low dose steroids. To compare the toxicity profile with respect to Varicella reactivation rate, thrombocytopenia, peripheral neuropathy. RELEVANCE There is no published pharmacological data to support the use of body surface area based dosing of bortezomib in myeloma METHODOLOGY This is a prospective observational single institutional study. 60 patients satisfying the inclusion criteria of Age < 80 years, diagnosed as a case of multiple myeloma according to the international myeloma diagnostic criteria and transplant ineligible were included in the study. Patients receiving fixed dose Bortezomib 2mg i/v once, Lenalidomide 10 mg D1 to D21 with Oral Dexamethasone 40 mg weekly (n=28) and those receiving Bortezomib 1.3 mg/m2 calculated dose with Lenalidomide 10mg and Oral Dexamethasone 40mg weekly(n=32) were observed prospectively for efficacy and toxicity. None of the patients received prophylactic

Acyclovir for Varicella Zoster. Response assessment was done every 6 monthly as per standard Myeloma working group and toxicity assessment as per NTC version 4. Survival analysis was statistically analysed using the Kaplan Meier curves. RESULTS Patient characteristics between the two arms were well balanced. There was 100 % objective response in both the arms with 21.8% of patients in the standard dosage arm(ARM A) and 23.3% in the fixed dose arm had complete response(ARM B).66.3 % and 63.3% of patients in ARM A and B respectively had very good partial response (VGPR) to treatment. Eventhough none of the patients received prophylactic Acyclovir only 2 out of the total 60 patients developed Zoster infection.Those 2 patients belonged to the ARM A (p=0.213). 21.4 % (6 out of 28) and 9.38%(3 out of 32) in ARM A and B respectively developed Grade 3/4 peripheral neuropathy(p=0.281). Grade 3/4 thrombocytopenia was higher in the ARM A with 21.4 % patients developing the same compared to only 6% in ARM B (p=0.13). Kaplan Meier estimates for survival at 2 years was 92.2% for ARM A and 91.9% for ARM B. DISCUSSION In our study the median age was 69 years with 80 percent of patients male(n=48). The CR and VGPR rates between both arms were similar, impressing the fact that fixed dose 2mg Bortezomib is as efficacious as standard dosing 1.3mg/m2. The toxicity profile of both arms were comparable with fixed dosage arm showing a lesser toxicity with respect to percentage incidence. Intravenous Bortezomib was associated with Grade 3/4 peripheral neuropathy in 9 out of the sixty patients. 2 year survival results were also similar with 92.2% and 91.9% in ARM A and B respectively. CONCLUSION Our study albeit with limitations was able to demonstrate that fixed dose 2 mg Bortezomib dosage is as efficacious and better tolerable when compared to 1.3mg/m2 Bortezomib in transplant ineligible multiple myeloma patients.

PS-151 (d)
Depth of Response and MRD with Daratumumab Plus Bortezomib and

Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in RRMM: CASTOR

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Introduction: Daratumumab is a human CD38 IgGκ monoclonal antibody that significantly prolongs progression-free survival (PFS) and improves overall response rates (ORR) when added to the established standard of care regimens. This study was performed to further evaluate the depth of responses achieved among study patients in CASTOR. Methods: All patients received ≥1 prior line of therapy and were administered 8 cycles (Q3W) of bortezomib 1.3 mg/m2 SC (Days 1, 4, 8, 11) and dexamethasone 20 mg PO (Days 1-2, 4-5, 8-9, and 11-12) ± daratumumab (16 mg/kg IV once weekly in Cycles 1-3, once every three weeks for Cycles 4-8, then once every 4 weeks until progression). Patients refractory to bortezomib were ineligible. High cytogenetic risk (determined using next generation sequencing) was defined as having any of t(4;14), t(14;16), or del17p abnormalities. Minimal residual disease (MRD) status was determined with bone marrow aspirates that were ficolled using next

generation sequencing (ClonoSEQ™) at 3 sensitivity thresholds (10–4 to 10–6), and was assessed in patients with suspected complete response (CR) and at 6- and 12-months after first study dose. PFS was the primary endpoint. Results: Median (range) number of prior lines of therapy was 2 (1-10). After median follow-up of 13.0 months, PFS was significantly prolonged with DVd vs Vd (median not reached vs 7.1 mo; HR, 0.33; 95% CI, 0.26-0.43; P<0.0001). Higher ORR was observed with DVd vs Vd (84% vs 63%; P<0.0001), with significantly higher rates of very good partial response or better (62% vs 29%; P<0.0001) and CR or better (26% vs 10%; P<0.0001), respectively. This translated to a higher proportion of patients achieving deeper responses with DVd vs Vd (MRD-negative rates: 18% vs 4% at 10–4; 10% vs 2% at 10–5; 4% vs 1% at 10–6; all P<0.01). Similar MRD-negative rates were observed in the 1 prior line subgroup. MRD negativity was reached earlier for patients receiving DVd vs Vd, and MRD-negative status was durable within these patients. MRD-negative patients demonstrated prolonged PFS compared with MRD-positive patients across all sensitivity thresholds. In high-risk patients, ORR (82% vs 62%; P=0.039) and MRD-negative rates (14% vs 0% at 10–5; P=0.0018) were significantly higher with DVd vs Vd, and no MRD-negative patients progressed. Similar findings were observed among standard-risk patients with regards to ORR (85% vs 64%; P=0.0003) and MRD-negative rates (12% vs 2% at 10–5; P=0.0011). Individual case studies of patients who achieved MRD negativity will be presented at the meeting. Conclusions: DVd induced MRD negativity in ≥3 times as many patients as Vd, with rapid and durable achievement of MRD negativity. MRD negativity was achieved in high-risk patients receiving DVd but not Vd. No MRD-negative, high-risk patients progressed during the study. MRD negativity was associated with prolonged PFS and may provide long-term clinical benefit.

PS-152
Autologous stem cell transplantation in elderly multiple myeloma patients

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Autologous stem cell transplantation (ASCT) is currently approved as a "gold standard" first line treatment for multiple myeloma (MM) patients (pts) under 65 years old but the procedure could also be considered feasible in fit elderly patients based on several retrospective studies. We retrospectively analyzed 25 consecutive MM pts aged 65 or older (median age 67, range 65-70) who underwent upfront ASCT at our institution from January 2012 to June 2016. The induction therapy was bortezomib-based (bortezomib in combination with dexamethasone, VD, in 7 or VD plus thalidomide in 18 pts) for a median of 4 cycles (range 3-6). Peripheral blood stem cells (PBSC) were collected after high-dose cyclophosphamide (3 g/sqm in 10 pts, 4 g/sqm in 15 pts) plus G-CSF, with plerixafor in 4 pts. Three pts also received lenalidomide and dexamethasone to improve the depth of response before ASCT. At the time of conditioning 4/25 pts were in partial response (PR), 14/25 in very good partial response (VGPR), 5/25 in complete response/stringent complete response (CR/sCR) and 2/25 in stable disease (SD). The conditioning regimen consisted of melphalan at 140 mg/sqm in 10 pts or 200 mg/sqm in 15 pts. A median number of 4.26 x10^6 CD34+ cells/Kg was transplanted (range 2.09-10.44). The most frequent complication was fever (5 pts) with gram negative bacteriemia documented in 3 of 5. Other complications were represented by one case of atrial fibrillation and one case of pneumonia. All 25 pts achieved neutrofils recovery after a median of 12 days (range 8-25) and platelets recovery after a median of 14 days (range 8-45) after transplant. No grade 3-4 toxicities were recorded. No trasplant-related mortality was recorded at 100 days post transplantation. Three months after ASCT, among 22 evaluable pts, 7/25 pts were in CR, 11/25 pts in VGPR and 4/25 pts in PR. One

patient underwent tandem ASCT. Three patients received lenalidomide maintenance after ASCT. After a median follow-up of 28 months (range 5-58) 13/25 pts experienced disease relapse. Nineteen of 25 were still alive. Median PFS and OS were 19 and 39 months. Our data support the use of ASCT as an effective and safe first-line treatment approach also in elderly MM pts. A careful patient selection is needed to reduce the toxicity of the procedure.

PS-153
Case Report: Deep Sustained Response to Daratumumab Associated with T-cell Expansion in a Patient with Heavily Treated Relapsed and Refractory Myeloma

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In September 2010, a 70 year old male presented with a plasmacytoma of the right 11th rib, 10% clonal plasma cells, negative 24 hour UPEP, 0.3 g/dL SPEP (IgA kappa) and a k/l ratio of 1.96. Initial treatment was local external radiotherapy. No active lesions were detected by PET-CT in January 2011. In October 2011, the patient was diagnosed with multiple myeloma (IgA kappa; ISS stage I) with 17p deletion in 7.5% of plasma cells and lytic bone lesions involving the axial and appendicular skeleton with osteopenia. Induction therapy of 1 cycle of lenalidomide (LEN)/dexamethasone (DEX) (minimal response) and 5 cycles of bortezomib (BORT), LEN-DEX (partial response [PR]) was given between December 2011 and June 2012 prior to ASCT in September 2012. The patient achieved a very good partial response (VGPR) and remained on maintenance therapy of BORT weekly (1.3 mg/m2) and 10 mg LEN daily on days 1 to 21 of each 4 week cycle until disease progression in March 2013. In April 2013, the

patient received oral pomalidomide 4 mg on days 1 to 21 of each 4 week cycle, BORT weekly (1.5 mg/m2) and DEX and achieved a PR prior to disease progression after 6 cycles. In October 2013, now triple refractory 2 years after diagnosis, he was enrolled in the SIRIUS study and received intravenous daratumumab (DARA) monotherapy (16 mg/kg) at the approved dosing schedule. No infusion-related reactions occurred. The patient achieved a PR after 28 days, a VGPR after 56 days, and a stringent complete response (sCR) in May 2014 (194 days after the first dose) which the patient continues to maintain. Minimal residual disease was assessed by flow cytometry in December 2015 and the patient was negative at the 10–4 threshold. T-cell repertoire is an informative biomarker that measures a patient's immune status, and response to immune modulation (Foreau et al, Blood 2016 128:378). The patient's baseline immune profile was assessed prior to the first DARA dose in the SIRIUS study. Baseline peripheral NK, B-, and T-cell levels were similar to other enrolled patients. However, the patient had elevated baseline regulatory T cell (Tregs) levels compared with other patients. In the SIRIUS study, most patients experienced T-cell expansion, driven primarily by CD8 T cells. An expansion of 800% from baseline to 3 months of the CD8 T-cell population in this patient was among the largest in the study, and was accompanied by a 67% decrease in Tregs. The patient also had the greatest increase in T-cell clonality over this period and continues to sustain this clonal T-cell expansion after 32 months. T-cell receptor sequencing also indicated a substantial and sustained increase in fraction of T cells. The patient's deep clinical response, and robust immune profile changes that have been maintained for over three years, support the proposed immunomodulatory mechanism of action of DARA.

PS-154
Dendritic cell vaccination combined with lenalidomide and programmed death-1 (PD-1) blockade has synergistically induced a marked tumor regression in a murine myeloma model

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Background: There is an emerging evidence that the maximal benefit of dendritic cell (DC)-based cancer immunotherapy may be achieved by combination with other therapies that act to immunomodulation and tumor microenvironment. In this study, we tried to obtain the best efficacy of immunotherapy using DC vaccination in combination with lenalidomide and PD-1 blockade in a murine myeloma model. Materials & Methods: After establishing myeloma-bearing mice, five treatment groups were designed to be a mimic protocol as like treatment in clinics as following: 1) PBS control, 2) DCs, 3) DCs + lenalidomide, 4) DCs + PD-1 blockade, and 5) DCs + lenalidomide + PD-1 blockade. After treatment, preclinical response and in vitro immunological responses were evaluated. Results: DCs combined with lenalidomide and PD-1 blockade showed the best tumor regression among the study groups. These anti-tumor effects have meaningfully related to the decrease of immuno-regulatory populations, such as myeloid-derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Treg) and the increase of effector immune cell populations, including CD4+ and CD8+ T cells, natural killer (NK) cells, and M1 macrophages, accompanied with the activation of cytotoxic T lymphocytes (CTLs) and NK cells in the splenocytes from the treated mice. Moreover, the level of immunosuppressive cytokines, such as TGF-beta and IL-10, was significantly reduced in tumor microenvironment. Conclusion: DC vaccination in combination with lenalidomide plus PD-1 blockade has synergistically induced a strong antitumor immunity by modulating tumor microenvironment in a murine myeloma model. This protocol will become a promising translational approach to improve the efficacy of immunotherapy in the field of MM.

PS-155
Effect of Treatment with Lenalidomide Plus Low-Dose Dexamethasone Until Progression on Health-Related Quality of Life Over Time in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

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Introduction/Background The FIRST trial established significant progression-free and overall survival benefits for transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide plus low-dose dexamethasone (Rd) until disease progression (Rd continuous) vs melphalan, prednisone, and thalidomide (Benboubker et al. N Engl J Med. 2014). Treatment (tx) with Rd also improved health-related quality of life (HRQoL) over the first 18 months (Delforge et al. Haematologica. 2015). HRQoL data were not collected past 18 months. This analysis examined the effect of Rd continuous on HRQoL beyond 18 months by identifying predictors of change in HRQoL scores using data collected from the FIRST trial. Patients and Methods Univariate linear mixed-effects regression analyses (n = 535) identified variables collected until progression as predictors of 7 preselected HRQoL domains of interest: global QoL; physical functioning, fatigue, and pain (EORTC QLQ-C30); disease symptoms and side effects of tx (EORTC QLQ-MY20); and health utility (EQ-5D). Variables with univariate $P < .1$ were combined into

multivariate models for each HRQoL domain; variables with P < .1 were retained for final models. Modeled HRQoL domain score changes were validated against observed score changes prior to 18 months and extended to extrapolate HRQoL changes from baseline based on observed predictor values beyond 18 months for pts still receiving Rd at 24, 30, 36, 42, and 48 months. Results Key time-varying determinants of final mixed models of HRQoL domains included 1) Eastern Cooperative Oncology Group performance status: all domains; 2) ongoing hospitalization: global QoL, fatigue, side effects of tx, and health utility; 3) serum albumin: global QoL, physical functioning, fatigue, pain, side effects of tx, and health utility; 4) red blood cell transfusion within 30 days: fatigue, pain, and disease symptoms; 5) ongoing adverse events: global QoL; 6) ongoing grade ≥ 3 pain: physical functioning, fatigue, pain, disease symptoms, side effects of tx, and health utility; 7) ongoing grade ≥ 2 fatigue: fatigue; and 8) ongoing grade 3/4 anemia: physical functioning and side effects of tx. All observed changes in HRQoL scores from baseline fell within the 95% confidence interval of the final predictive models, except month 1 of the global QoL and fatigue models and month 3 of the disease symptoms model. Improvements in HRQoL scores from baseline in the first 18 months of tx were maintained through 48 months of Rd therapy, with the exception of month 36 for the fatigue domain. Conclusion The gains in HRQoL over the first 18 months in Rd-treated pts with NDMM were maintained for pts who remained on tx up to 48 months. This analysis requires further research to better define the impact of Rd continuous therapy on HRQoL compared with fixed-duration therapy followed by a period of observation.

PS-156
Development of Bone-Targeted Bortezomib to Treat Multiple Myeloma

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Background: Bortezomib (Btz, marketed as VELCADE) is an FDA-approved drug for the treatment of patients with multiple myeloma (MM) both initially and during relapses and also for mantle cell lymphoma following relapse. However, serious side effects of Btz, including peripheral neuropathy and thrombocytopenia, limit its utility clinically or prevent administration of effective doses. Thus, there is a major unmet clinical need to develop methods to deliver Btz or other anti-myeloma drugs to bones, the major sites where MM cells reside, at effective concentrations, which have a much lower risk of systemic adverse effects. Here, we designed a bone targeted Btz (BP-Btz) by linking it to a Bisphosphonate (BP) residue with high affinity for bone, but with no antiresorptive activity, in order to eliminate any BP side effects and compared its efficacy and systemic side effects with non-bone targeted Btz in a mouse MM model. Methods. 3 set of experiments were performed. 1) 5TGM1-GFP mouse myeloma cells were treated with 2-8 nM of PBS (veh.), BP, Btz or BP-Btz for 24hrs. The living cell numbers were counted. 2) 6-wk-old female NIH-III nude mice (N=6-8/group) received 5TGM1-GFP myeloma cells via the tail vein and were immediately treated with veh., 0.5mg/kg Btz, or 1mg/kg BP-Btz (=same molar conc. Btz), 3x/w for 2 wks. Tumor burden (GFP distribution/intensity) was examined with an IVIS Spectrum in vivo imager and bone destruction (femoral bone volume) was assessed with a VivaCT40 μCT scanner 1 wk later. 3) WT C57/B6 mice (N=4/group) were treated with veh, Btz or BP-Btz daily for 3 wks. The number of thymus and blood cells was counted. Morphology of sympathetic nerve in dorsal root ganglia was examined by EM. Results: 1) BP-Btz had 1-fold increased efficacy over Btz to inhibit 5TGM1-GFP cell growth. 2) BP-Btz decreased tumor burden and bone loss more than Btz (GFP intensity: 2.2 ± 1.8 x108 vs. 0.7 ± 1.6; BV/TV: $11.8\pm3.1\%$ vs. 7.4 ± 2.1). 3) In thymus, Btz, but not BP-Btz, decreased thymus cell # (14 ± 4 x106 vs. 143 ± 17), CD3+ T cell # (4 ± 1x106 vs. 21 ± 8) and B220 B+ cell # (0.7 ± 0.2x106 vs. 2.8 ± 1). In the peripheral blood, Btz, but not BP-Btz, reduced platelet # (125 ± 17x103/μl vs. 231 ± 67), red blood cell #

(5±1x106/µl vs. 7±1) and white blood cell # (1.3±0.3x103/µl vs. 5.2±1.9). 3) Compared to veh.-treated mice, Btz, but not BP-Btz, reduced nerve myelin thickness (3.6±0.7 vs. 2.4±0.6 vs. 3.8±0.9) and myelinated axon diameter (2.1±0.6 vs. 1.3±0.2 vs. 2.4±0.7). Conclusion: BP-Btz more potently reduced MM-induced bone destruction with less systemic adverse effects than Btz. BP-Btz represents a novel therapeutic approach to deliver Btz to bone using much lower systemic yet still highly effective local concentrations on release of the drug at the bone surface, thus increasing its efficacy and reducing the risk of adverse effects.

POSTER DISPLAY - FRIDAY

(d) *denotes a poster discussion abstract.*

1. **Disease Biology and Related Disorders**

PS-157
Outcome of very young (≤ 40 years) patients with immunoglobulin light chain amyloidosis (AL): A case control study

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BACKGROUND Light-chain amyloidosis (AL) is a rare plasma-cell disorder characterized by deposition of insoluble fibrils composed of immunoglobulin. Clinically relevant data about very young patients (pts) with AL are scant. METHODS Medical records of pts with AL evaluated at Mayo Clinic, MN, from1995-2015 were analyzed. Disease characteristics and outcomes of young pts at the time of AL diagnosis (cases) were compared to a 2:1 matched cohort of pts (controls) with AL who were ≥65 years at diagnosis. Isolated free light chain AL was defined as presence of only monoclonal Kappa or Lambda light chain in the serum or urine immunofixation without heavy chain involvement. Upfront autologous stem cell transplantation (ASCT) was defined as transplantation within 6 months of diagnosis. Kaplan-Meier method used for time-to-event analyses. RESULTS Of 3433 pts with AL, 50 (1.5%) were ≤ 40 years of age at diagnosis (cases). The median time between onset of symptoms and definitive diagnosis was 0.4 years for cases and 1 year for controls (p<0.0001). Unusual clinical manifestations in younger cohort included spontaneous splenic rupture (2%) and erectile dysfunction (4%). Isolated light chain AL was more prevalent in younger cohort (50%) compared with controls (32%, p=0.04). Within the younger cohort, isolated light-chain AL was associated with a higher rate of cardiac involvement (74%) compared to patients without isolated light chain disease (43%), p=0.03. No such difference was observed in the older cohort. Median follow-up for cases and controls were 10.9 vs 9.9 years, respectively. In cases, 1 and 10-year overall survival (OS) from diagnosis was 73% and 51%, respectively while, in controls, 1 and 10-year OS was 62% and 15%, respectively, p<0.001. The estimated average years-of-life lost was 8.6 years over 20 years of follow-up in cases. Cardiac involvement by amyloid material was associated with worse OS in both cohorts; (cases, median 3.2 years with cardiac involvement vs NR in those without; p=0.003; controls: median OS was 1.1 years with cardiac involvement vs 4.8 years in those without; p=0.02). In cases and controls, 62% and 20% were eligible for upfront ASCT, respectively. In cases, the median OS was NR in pts who underwent upfront ASCT vs 4.0 years in pts who did not, p≤0.0001. For controls, the median OS was 9 years for pts who underwent upfront ASCT vs 1.6 years for pts who did not, p=0.26.

DISCUSSION AND CONCLUSIONS AL is infrequently encountered at the age of ≤40 years, but loss of productive years of life is substantial in this cohort. Cardiac involvement remains a primary determinant of prognosis, irrespective of age. Although over one-half of young pts are alive 10 years after the diagnosis (contrast ~15% ≥ 65 years), early mortality remains substantial irrespective of age. Nearly half of the patients in cases underwent upfront ASCT, an approach associated with a better outcome.

PS-158

Health-Related Quality of Life (HRQoL) of Patients (pts) With Newly Diagnosed Multiple Myeloma (NDMM) Receiving Any or Lenalidomide (LEN) Maintenance After Autologous Stem Cell Transplant (ASCT) in the Connect® MM Disease Registry

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Introduction: Several phase 3 trials demonstrated maintenance therapy after ASCT extended remission and in some cases overall survival for pts with MM. Few analyses discussing impact of post-ASCT maintenance on HRQoL have been published. Connect® MM is the first and largest multicenter, US-based, prospective, observational, cohort study to characterize treatment patterns and outcomes for pts with NDMM. This analysis evaluated HRQoL of pts who received Any maintenance therapy, LEN only, or No maintenance post-ASCT. Methods: Pts ≥ 18 y with NDMM within 60 days of diagnosis were eligible for enrollment. For this analysis, pts who completed induction therapy and first-line ASCT who may or may not have gone on to receive maintenance were included. HRQoL tools analyzed were the EQ-5D, Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) and the Brief Pain Inventory (BPI). HRQoL assessments were analyzed at study entry (study baseline); after induction therapy but prior to ASCT (pre-ASCT baseline); and quarterly from 100 days post-ASCT until the end of maintenance (maintenance groups) or until progressive disease, discontinuation, or death (all groups) (analytic period). SAS Proc Mixed with a random effects unstructured covariance matrix adjusting for confounders was used. Results: Between Sep 2009 and Dec 2011, 1493 pts enrolled in Cohort 1. Of 540 pts who received ASCT, 238 met criteria for Any maintenance, 167 for LEN-only, and 138 for No maintenance. Median age (range) was 60 y (24-78 y); 61% were male, and 85% were white. The majority were ECOG PS 0/1 (64%) and ISS stage I/II (56%). Median duration (range) of maintenance in the Any and LEN-only maintenance groups was 23.0 mo (0.8-50.4 mo) and 24.4 mo (0.6-50.4 mo), respectively. The median number (range) of EQ-5D forms completed per pt during the analytic period was 4.5 (1.0-16.0), 5.0 (1.0-15.0), and 5.0 (1.0-16.0) for Any, LEN-only, and No maintenance groups, respectively. Mean pre-ASCT baseline HRQoL scores for each measure were similar across the 3 groups, with ranges of 0.79 (all groups; EQ-5D), 117.7-119.7 (FACT-MM Total), and 3.87-3.95 (BPI). Estimated differences on change in HRQoL scores from

baseline (least-squares mean) showed no significance comparing Any vs No maintenance (difference, 0.005; 95% CI, −0.0185 to 0.0293) or LEN-only maintenance vs No maintenance (0.017; 95% CI, −0.009 to 0.042) for the EQ-5D Overall Index. Similarly, no significant differences were observed with the FACT-MM Total Score or the BPI. Conclusions: NDMM pts in the Connect® MM registry receiving Any or LEN-only maintenance therapy vs No maintenance after ASCT demonstrated non-significant differences in HRQoL scores for the EQ-5D Index, FACT-MM, and BPI. These results suggest no difference in HRQoL for those who received maintenance therapy, compared with those who did not despite the risks associated with continued active therapy.

PS-159
IS IT USEFUL THE FOLLOW UP OF MGUS?

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The incidence of monoclonal gammopathy of undetermined significance (MGUS). increases with age (1-3% in those over 70 years). The risk of global progression to malignant gammopathies (MG), especially multiple myeloma (MM), is 1% per year. It is thought nowadays that all cases with MM evolve from a previous MGUS and / or smouldering MM (SMM) OBJECTIVES To assess the incidence of preceding MGUS/ SMM for patients (pt) diagnosed as symptomatic MM (MMs) according to International Myeloma Working Group (IMWG) criteria at the time of diagnosis for every particular case. MATERIAL AND

METHODS Retrospective analysis of 198 pts with MMs in our centre between 2001 and 2016. Demographic and clinical-biological details are collected at the time of MMs diagnosis, existence of previous MGUS / SMM, and outcome during their follow-up. PATIENTS: Gender: female/male = 87/111 Age: global median 77 years (45-93). Myeloma subtype: IgG 109 pt, IgA 54 pt, IgD 3 pt, light chain 29 pt, IgA + IgG 2 pt, no secretor 1 pt. RESULTS 64 pt had history of MGUS (58 pt) or SMM (8 pt) (overall 33.3%). Of the 64, 30 pt (46.8%) were regularly reviewed in our outpatient Hematology clinic. Amongst those 30 pt, 18 of them (60%) were found to have progressed to overt MM during one of the outpatient hematology clinic. The remaining were diagnosed at the time of an acute admission due to complications from progression to MMs. Patients without previous evidence of MGUS/SMM were diagnosed with MMs due to disease related events, and transferred from different Hospital Services. DISCUSSION The MGUS follow up recommendations based upon clinical and biological risk factors for progression to MG show significant differences amongst groups. It is assumed that all MMs were preceded by a high risk MGUS and/or SMM. We analyze how many pt with MMs had a previous MGUS and how many MMs were diagnosed during an outpatient clinic or were transferred from other departments due to MM related events. With this, we aim to optimize the monitoring regime and improve the early diagnosis. The latest IMWG recommendations suggests that preemptively treating MGUS/SMM leads to better long-term response. CONCLUSIONS Most of the pts with MMs (67.7%) were not previously diagnosed with a MGUS/ SMM The follow-up in our clinic according to the Guidelines recomendations allow us to detect the progression to MMs in 60% of pt with MGUS. However, 40% of MGUS pt were diagnosed with MMs after MM complications. Therefore, our group considers that it would be helpful to perform a closer follow-up based on the new

techniques that establish the treatment indications such as more sensitive imaging tests (PET-CT, CT or MRI) or abnormal serum free light chain ratio. It is uncertain whether an earlier diagnosis and treatment of MGUS progression to MM might have an impact on these patient´s long-term outcome.

PS-160
High IKAROS expression in bone marrow environmental, but not in myeloma cells predicts for survival with lenalidomide-dexamethasone therapy in myeloma

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Background: Immunomodulatory drugs (IMiDs) are a cornerstone in the treatment of multiple myeloma (MM), but specific markers to predict outcome are still missing. Recent work pointed to a prognostic role for cereblon (CRBN) in IMiD treated patients. However, the presence of several CRBN splice variants and the lack of standardized reagents currently limits is use as a predictive marker in clinical routine. We therefore analyzed the expression levels of CRBN and 5 CRBN-IMiD target genes (IKZF1, IKZF3, IRF4, MCT-1, CD147) in total BM mononuclear cells (BM MNCs) of patients treated with lenalidomide and dexamethasone for their predictive value. Moreover, IKAROS was found to be enriched in stromal cell populations and we therefore investigated the prognostic relevance of IKAROS protein levels in distinct BM cell populations. Methods: Forty-four patients were included for the retrospective gene expression study of CRBN-IMiD target genes. In addition, 26 patients (16 patients from our gene expression cohort and 10 independent patients) with stored whole BM samples were included for the analysis of IKAROS protein expression by flow cytometry. All patients received lenalidomide (25mg/day on days 1-21) in combination with dexamethasone in a 28 day cycle. Results: Total BM MNC gene expression levels of CRBN (R=0.30, P=0.05), IKZF1 (R=0.31, P=0.04), IRF4 (R=0.38, P=0.01), MCT-1 (R=0.30, P=0.05) and CD147 (R=0.38, P=0.01), but not IKZF3 (R=-0.15, P=0.34), were significantly associated with response. CD147 (R=0.35, P=0.046) and MCT-1 (R=0.63, P<0.001) expression levels were significantly associated with age, but no further correlations were observed between IMiD target genes and clinical parameters or outcome. Interestingly, IKZF1 expression was elevated in BM environmental cells (CD3+ T cells, CD14+ monocytes, CD15+ neutrophils) compared to MM cells and thus selected for further investigation by multicolour flow cytometry. This revealed variable fractions of IKAROS-positive cells within the different cell subsets analyzed, ranging from a median percentage of 90.5% IKAROS+ cells in CD34+ cells to 48.3% IKAROS+ cells in monocytes. Importantly, high IKAROS expression in certain cell populations was linked to better clinical outcome. High IKAROS protein levels in total BM mononuclear cells (median OS 83.4 vs 32.2 months, P=0.02), CD19+ B cells (median OS 71.1 vs 32.2 months, P=0.05), CD3+CD8+ T cells (median OS 83.4 vs 19.0 months, P=0.008) as well as monocytes (median OS 53.9 vs 18.0 months, P=0.009) were associated with superior overall survival (OS). In contrast, IKAROS

protein expression in MM cells was not predictive for OS. Conclusion: Our data indicate that IKAROS expression in distinct environmental BM cells and not in myeloma cells predicts for longer survival with Len-dex therapy and therefore corroborate the central role of immune cell populations for the clinical activity of IMiDs.

PS-161

B₂-MICROGLOBULIN (β₂M) IN RENAL DISFUNCTION PATIENTS. EFFECT IN OVERALL SURVIVAL IN ISS-SUBGROUPS IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENTS

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INTRODUCTION β₂-microglobulin (β₂M) is included in the prognostic International Scoring System to stablish prognostic groups in NDMM patients. The first clinical application of β₂M was the monitoring of processes with renal dysfunction. Elderly patients have more incidence of renal disfunction due to common comorbidities like Diabetes Mellitus or arterial Hypertension. METHODS Retrospective analysis from our cohort of 346 patients from Jan-1998 to Jan-2016, regardless of the treatment received. Median Age at Diagnosis: 74 (39-100). Men 195. Compare different ISS subgroups and the influence of renal disfunction measured by 2 different methods: - Classical "B-subgroup" listed in Durie-Salmon categories (Creatinine > 2 mg/dL) - Creatinine Clearence using Cockroft-Gault formula (ClCr< 60

ml/min) CHARACTERISTICS OF PATIENTS ISS Subgroups: - ISS-I. n= 29 - ISS-II. n= 75 - ISS-III. n= 181 - ISS-missed. n= 60 Durie-Salmon Subgroups: - DS "A". n= 284 - DS "B". n= 62 Cockoft-Gault Formula - ClCr >60 ml/min. n= 175 - ClCr < 60 ml/min. n= 72 - ClCr missed. n= 99 RESULTS All the patients with DS "B" are ISS-III. 62 of 72 patients with ClCr<60 are ISS-III. The other 10 were included in ISS-II subgroup. Median Overall Survival (in months) for the cohort were: - ISS-I: 57m - ISS-II: 37m - ISS-II: 17m Median OS is influenced in subgroup ISS-III by renal disfunction - by Durie-Salmon "B": 25 m (Cr<2mg/dL) vs 8 m (Cr>2 mg/dL) (p.0007) - by ClCr: 35m (ClCr>60ml/min) vs 10 m (ClCr<60 ml/min) (p.008) There are no differences in ISS-II regardless of ClCr, probably due to few cases. CONCLUSIONS Renal impairment worsens poor prognostic of ISS-III. It is important to measure accurately the renal disfunction, using the different formula to calculate creatinine clearance. Overall Survival in ISS-III subgroup without kidney failure may be similar to ISS-II.

PS-162

A retrospective cohort study to evaluate the outcomes of Multiple Myeloma treated in a tertiary care centre from India

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Background Multiple myeloma is a disease of elderly with a median age of presentation 70

years and accounts for 1% of all cancers. One of the major advances in the management of newly diagnosed myeloma patients has been the introduction of novel drugs as part of front line therapy. Both VTD and VCD regimens are efficacious and well-tolerated regimens. The overall response rates range from 70%-90%. However, scenario is different in our country, given the delayed presentations, decreased compliance, socioeconomic factors and significant delay in diagnosis and initiation of chemotherapy. We evaluated the outcomes of patients of Myeloma treated at our centre. Methods We retrospectively analysed Myeloma patients who were treated with different regimens at Tata Memorial Centre from January 2013 till December 2014. Patients aged ≥18 years who were diagnosed as Myeloma were included in the analysis. The primary objective was the overall survival (OS), secondary objectives were response rates, progression free survival and toxicity profile. Descriptive statistics were summarized with median and range, survival outcomes were analysed with Kaplan-Meier method and impact of different ISS stage on survival was assessed using log rank test Results Conclusions A total of 185 patients (145 males) with a median age of 58 years were treated. 45, 50 and 87 patients belonged to ISS Stage I, II and III respectively. For 3 patients baseline staging was not available. Bony lesion and anemia were present in 164 patients and 89 patients. Hyperdiploidy was the most common cytogenetic abnormality detected in 57% of patients, followed by gain (1q) (27%). 10 (5.4%), 75 (40.5%) and 82 patients (44.2%) belonged to high, intermediate and standard risk, respectively. 18 patients were not risk stratified at baseline. VCD was the common initial regimen used in 132 (71.3%) patients. 30 patients (16.2%) were treated by lenalidomide and dexamethasone and CTD was given to 15 patients as first line regimen. Only 72.9 % patients were able to complete the planned first line regimen. Based on limited toxicity data, grade 3/4 anemia, neutropenia and thrombocytopenia were present in 7.56%, 2.7%

and 3.6% patients respectively. Grade 2 and 3 peripheral neuropathy was present in 16 (8.6%) patients and 6 (3.2%) patients respectively. After first line therapy, 16 patients were in CR (8.6%) and 49.7% were in VGPR, 17.8% in PR and 3.7% in SD and 9 patients progressed and for 28 patients, response evaluation was not available. The median PFS and OS for Stage I, II and III was 24 months, 17 months and 15 months respectively and 39 months, 26 months and 25 months respectively. After a median follow up of 30 months, 27 patients were lost to follow up and 26 patients died. Conclusion Median age of presentation is a decade earlier in Indian population. The overall response rates and survival data of our centre is inferior as compared to published data.

PS-163 (d)
Utility of the new versus old immunophenotypic markers in the flow cytometric immunophenotyping of multiple myeloma

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Introduction: Flow cytometric immunophenotyping (FCI) has become a powerful tool in the diagnosis, prognosis, and response-monitoring of multiple myeloma (MM). It is critical to correctly identify and quantitate clonal plasma cells (CPC) versus normal plasma cells (NPC) in the patient's

sample. Due to significacnt overlap of expression-pattern between CPC and NPC, the old markers are not adequate for the precise separation of CPC from NPC. In this study, we determined the utility new versus old markers for FCI in MM Methods: We investigated the expression-pattern of four new immunophenotypic markers (CD81, CD200, CD44 and CD49d) and eight old markers (CD19, CD20, CD27, CD28, CD38, CD45, CD56, CD117) in the CPC from bone marrow aspirates (BM) from 219 MM cases and NPC from 20 to 62 samples of uninvolved staggingBM. FCI was performed using 9-10 color antibody-panel on Navios flow-cytometer (Beckman Coulter, BC). Data was analyzed using Kaluza software-V1.3 (BC). Results: We studied 219 BM samples from MM patients (age, 31-83 years;M:F, 166:53) and 20-62 BM from non-plasma cell neoplasm patients (age, 32-68; M:F, 40:22). Details of expression-pattern with sensitivity/specificity/p-vlaue of all markers are described in Table-1 (below). Thus, CD81 was the most sensitive and CD49d was the most specific marker.Of the old markers, CD19 followed by CD27 and CD56 were the highly sensitive markers while CD20, CD28 and CD117 were the most specific markers. Conclusions:Amongst the new markers, CD81 and CD200 are highly useful markers in FCI of MM.Since CD49d showed uniformly strong expression in plasma cells, it is potentially useful as additional gating-marker. Of the old markers, CD19 and CD27 followed by CD56 and CD45 were the most useful markers in the FCI of MM. Table-.Sensitivity & specificity of immunophenotypic markers in detecting clonal plasma cells: Markers Strong (%) Sensitivity (%) Specificity (%) p-Value Old Markers CD45 2.7 76.0 56.5 <0.0001 CD20 0.0 22.0 100.0 0.0020 CD19 0.0 98.2 53.2 <0.0001 CD38 67.1 32.9 95.2 <0.0001 CD56 39.3 76.3 90.0 <0.0001 CD117 0.0 37.0 100.0 <0.0001 CD28 1.8 38.4 100.0 <0.0001 CD27 0.9 84.0 80.0 <0.0001 New Markers CD81 0.5 95.0 73.3 <0.0001 CD200 16.9 74.0 73.3 <0.0001 CD44 31.2 44.7

70.0 0.2420 CD49d 33.3 11.1 93.3 0.7420

PS-164 (d)
Increase in M2 macrophage polarization in multiple myeloma bone marrow is inhibited with the JAK2 inhibitor ruxolitinib which shows anti-MM effects

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The bone marrow (BM) microenvironment plays an important role in multiple myeloma (MM). The BM niche is composed of multiple cell types including macrophages. Macrophages polarize into pro-inflammatory macrophage-1 (M1) or alternative macrophage-2 (M2) states that promote tumor growth and metastasis. We evaluated the proportion of M2 in BM from MM pts either showing complete response (CR) or progressive disease (PD), the effects of MM cells on M1 and M2 differentiation, and the role of cytokines in M2 polarization in MMBM. We also evaluated the effects of the JAK2 inhibitor ruxolitinib (RUX) on M2 polarization, and expression of the CXCL-12 and Trib genes which are involved in monocyte function. In addition, we assessed the effects of RUX alone and in combination with lenalidomide (Len) or bortezomib (Bort) on tumor growth and macrophage polarization in vivo using a human MM xenograft model. The results of flow cytometric analysis showed the percentage of M2 (CD36+/ARG1+) in BM was significantly increased in MM pts with PD (n=25) compared to those in CR (n=10; P=0.005) whereas there was no difference in the percentage of M1 (CD86+/iNOS+) in BM derived from MM pts with PD compared to those in CR. The proportion of M2 was also markedly increased

in BM biopsies or mononuclear cells (MCs) from MM pts with PD compared to those in CR using IFC staining. CXCL-12 and Trib1 gene mRNA levels were higher among pts with PD compared to those in CR. We co-cultured U266 MM cells or fresh MM BMMCs with purified healthy human monocytes for one week. The percentage of M2 markedly increased and the proportion of M1 cells decreased. We investigated the effects of the JAK2 inhibitor RUX on M2 differentiation induced with MM tumor cells. After exposure to RUX, the percentage of M2 cells decreased when the monocytes were co-cultured with MM tumor cells. Monocyte Trib1 gene expression treated with RUX was also reduced compared with untreated cells. Using our human MM xenograft model LAGκ-2, RUX (1.5mg/kg) reduced tumor growth and decreased the proportion of M2 in the tumor tissue of MM tumor-bearing SCID mice. The combination of RUX with Len markedly reduced tumor volume in LAGκ-2. We also further evaluated RUX in combination with Bort and the effects on M2 polarization in the MM xenograft model. The results showed Bort alone increased M2 polarization but the combination of RUX with Bort markedly reduced M2 formation. MM cells induce monocytes to become M2 through increasing Trib1 gene expression. M2 promote tumor cell proliferation by increasing cytokines such as CXCL12 in MMBM. This study demonstrates that the JAK2 inhibitor RUX inhibits both M2 polarization in MM, and reduces tumor growth in SCID mice bearing human MM. The results suggest that RUX inhibitor alone or combination with or Len or Bort may be effective for treating MM pts.

PS-165 (d)
Targeted sequencing of circulating cell-free DNA in multiple myeloma allows analysis of somatic mutations, copy number aberrations, and translocations

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Background: Multiple myeloma (MM) is characterized by frequent genetic abnormalities such as copy number aberrations, immunoglobulin heavy chain (IGH) translocations, and recurrently mutated genes that may be exploited by targeted therapies. Many of these genetic changes have been linked to high-risk disease and their analysis has been used for patient stratification on clinical trials, monitoring of disease response to targeted therapies, and routine clinical management of MM patients. Currently, MM genetic profiling requires genetic material obtained from bone marrow (BM) aspirates, a painful procedure that poses an obstacle to enrolment and retention of patients in clinical trials. This study aims to develop a non-invasive method for myeloma genetic profiling by targeted deep sequencing of circulating cell-free DNA (cfDNA). Methods: In our pilot study, we developed and validated a Liquid Biopsy Sequencing (LB-Seq) method for hybrid capture and sequencing of all coding exons of KRAS, NRAS, BRAF, PIK3CA, and EGFR (18 kb) in 64 cfDNA specimens from 53 myeloma patients to >20,000X mean target coverage. We then scaled this method for concurrent analysis of 200-kb MM-specific target region including all exons of 38 prognostic or therapeutically relevant genes (e.g., KRAS, NRAS, BRAF, TP53, ATM, ATR, CCND1, ZFHX4, FGFR3, DIS3, PTEN, IRF4, NFkB pathway genes and others), a custom probe set for detection of IGH translocations, and SNP-based copy number analysis on chromosomes 1 and 17. The new panel analysis utilized molecular barcoding and has been tested

using 27 cfDNA specimens from 13 patients, including 2-6 serial plasma samples in 5 patients. Results: From 48 cfDNA specimens with matched BM sequencing data, LB-Seq detected 49/51 likely somatic mutations (96% sensitivity) with allele fractions as low as 0.25% in cfDNA and subclonal hierarchies reflecting BM tumor profiling. Four additional mutations were found in cfDNA that were likely missed by BM testing, based on droplet digital PCR validation and consistency between serial cfDNA specimens (98-100% specificity). Using a similar approach, we then tested the expanded MM-specific panel. LB-Seq enabled detection and tracking of clonal and subclonal somatic point mutations in multiple genes (e.g., KRAS, NRAS, TP53, ATR, TRAF2, TRAF3), copy number changes (del(17p), gain(1q)), and tumor-specific V(D)J rearrangements. Further testing of the expanded MM panel is ongoing. Conclusions: Genetic profiling of MM through targeted deep sequencing of cfDNA reflects genetic diversity of MM and is a high fidelity adjunct to genetic profiling of BM tumor DNA. The expanded MM panel developed in this study can enable longitudinal tracking of genetic evolution of MM tumors, monitoring of molecular response to targeted therapies, earlier detection of disease progression and secondary resistance mutations, and subclonality analysis using blood-based testing.

PS-166 (d)
Prognostic implication of somatic mutations by next generation sequencing: an analysis from the MMRF CoMMpass study in newly diagnosed multiple myeloma patients.

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Introduction: Next-generation sequencing is becoming an attractive approach to characterize multiple myeloma (MM) genomic profiles. However, the clinical relevance and contribution to risk assessment of such approaches is unknown. The Multiple Myeloma Research Foundation (MMRF) CoMMpass trial (NCT01454297) has collected data from newly-diagnosed MM patients enrolled worldwide. Comprehensive analysis of somatic mutations of MM cells could reveal disease features with prognostic value not detectable with traditional approaches. Methods and materials: CD138+ purified MM specimens from bone marrow aspirates and peripheral blood cells were collected at diagnosis. Whole exome libraries from both tumor and constitutional DNA samples were created. Somatic single nucleotide variants (SNV) were identified, only nonsynonymous SNV were included in the analysis. We evaluated the impact on progression free survival (PFS) of recurrently mutated genes in a multivariable Cox model. A backward selection based on the Akaike Information Criterion (AIC) was used to identify the final Cox model used to create a scoring system. Results: 517 patients with baseline somatic mutation data were included in the analysis. Median age at diagnosis was 64 years (range 27-93), all patients received standard of care agents as first line treatment, 236 (45.6%) received autologous stem cell

transplantation (ASCT). The most recurrent mutated genes were KRAS (25%) and NRAS (19.5%). Based on the impact on PFS of recurrently mutated genes, we created a scoring system determined by the mutational status of 9 genes identified in a nonbiased manner. Three groups were identified: group I (score 0-2, 17%); group II (score=3, 51%), and group III (score >3, 32%). After a median follow-up of 371 days, the 18-month PFS rate was 93% for group I, 85% for group II, and 67% for group III. The hazard ratio was 2.34 (p=0.112) for group II versus group I, and 5.96 (p<0.001) for group III versus I. The prognostic trend of the score was confirmed in different patient subgroups including ASCT/no ASCT, standard/high risk cytogenetic profile, ISS I, II, or III. Of note, 23.3% of patients in group I had an ISS III and 30.4% of patients in group III had an ISS I. Conclusion: The use of a prognostic model based on the mutational status of 9 recurrently mutated genes could improve risk assessment of newly-diagnosed MM patients. Longer follow-up and validation in independent cohorts are needed to confirm our findings.

PS-167
Easy to Use Integrated Software for Detection and Isotyping of Monoclonal Gammopathies via MALDI Mass Spectrometry

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Background: Monoclonal gammopathies are centrally characterized by an abnormal expansion of clonal plasma cells in bone marrow, which results in secretion of an over abundant monoclonal protein (M-protein) into serum. For the past 50 years, electrophoretic separation of serum and urine proteins has been the backbone for detecting and monitoring M-protein. We recently developed a MALDI mass spectrometry-based assay, called Mass-Fix, for detecting M-proteins, encountered in a clinical laboratory, in an automatable, cost effective, and sensitive fashion [1]. Objective: The goal of this study is to develop an integrated software environment that automates the steps involved in performing the Mass-Fix assay as well as allowing clinical pathologists to interpret the results of the assay in an effective manner. Methods: Laboratory and software requirements for Mass-Fix assay were gathered using routine business requirement analytics. The software was developed using Microsoft C# programming language and Microsoft SQL database. Software development was carried out using an agile methodology. Results: The Mass-Fix application was designed as a highly automated, client-server based model. In this model, a set of automated computer services were designed to run on a liquid handler, which takes in a set of 64 samples and prepares them for stamping on a set of 4 MALDI target plates. The user starts this process by pushing the samples and reagent plates into the handler and starting a pre-programmed protocol. While the liquid handler is processing samples, the liquid handler service automatically captures the patient metadata and quality control metadata and uploads them into a central database. Next, the user moves the processed samples on to a Mosquito automated spotter for them to be arrayed on set of 4 MALDI target plates. Metadata about the sample location on each MALDI target plate is automatically captured, via a single barcode scanning per plate, and stored in the database. The user runs a pre-programmed spotting program. Next, the user loads the spotted MALDI plates on a Bruker MicroFlex mass spectrometer and a pre-programmed data acquisition method is started. While the instrument is acquiring the data, another automated service loads the collected spectra for each patient into the database. Finally, a clinical laboratory technician reviews

each patient record (along with QC data and associated lab test results) in an integrated graphical user interface to determine whether the patient has an M-protein, and if so, of what isotype. The results are automatically sent to the laboratory result reporting system. The software was tested with 4 runs (each containing 64 samples) in a clinical laboratory. Conclusions: We have automated the Mass-Fix assay and developed an integrated software environment for ease of use. [1] Mills JR et al; Clin Chem 2016 Oct; 62 (10):1334-44;

PS-168
Low-pass sequencing of plasma cell DNA and of ccfDNA for the detection of copy number aberrations and early response monitoring in multiple myeloma

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Cytogenetic abnormalities are powerful prognostic indicators in multiple myeloma (MM). Currently, the technique of choice for the detection of those chromosomal aberrations in bone marrow plasma cells is FISH, either or not in combination with conventional cytogenetics or array-CGH. Next generation sequencing (NGS) technologies offer new perspectives for the diagnostic work-up of malignant disorders. In this study, we compared low-pass sequencing with array-CGH for the detection of somatic copy number aberrations (CNAs) in MM. Secondly, we explored whether sequencing of circulating cell-free DNA (ccfDNA) can be used to monitor early response. Method: we obtained

bone marrow aspirates from 8 cases with MM. DNA extracted from plasma cells purified by CD138-selection was subjected to array-CGH (n=8) and low-pass sequencing (n=4). Data were analyzed using the Cytosure Interpret Software and our in-house pipeline respectively. Paired samples of ccfDNA obtained at diagnosis and at early time points after therapy initiation, were analyzed by low-pass sequencing. Results: array-CGH on DNA from purified plasma cells from 8 cases yielded 1 normal and 7 abnormal results. DNA from 4 of the abnormal cases was analyzed by low-pass sequencing, which yielded identical CNA patterns. In 5 of the 8 paired ccfDNA samples, sequencing of ccfDNA showed a genomic representation profile compatible with array-CGH. The 3 remaining cases had normal ccfDNA profiles despite abnormalities in array-CGH. This is probably due to a lower disease burden, as these cases had lower plasma cell counts and less active disease, not requiring treatment. Four patients with an aberrant ccfDNA profile at diagnosis were treated during the course of this study. The ccfDNA profiles of 3 of these patients returned to normal within 3 to 8 weeks after treatment initiation. The fourth patient is clinically not responding well, consistent with persistence of the abnormal ccfDNA profile under treatment. Conclusion: this proof-of-principle study indicates that low-pass sequencing can truthfully reveal CNAs in MM, and should be explored further as a novel and cost-efficient alternative for array-CGH in the diagnostic work-up of MM. In addition, we provide evidence that ccfDNA from patients with MM contains circulating tumor DNA. This can be developed as a novel tool for the measurement of disease burden at diagnosis and the assessment of early disease response in a dynamic fashion.

PS-169
Multiple myeloma can be accurately diagnosed in acute kidney injury patients using a rapid serum free light chain test

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Background: Acute kidney injury (AKI) is common in patients with myeloma (MM). Whether serum free light chain (sFLC) measurements can distinguish between myeloma and other causes of AKI requires confirmation to guide early treatment. A rapid and portable sFLC test (Seralite®) has recently become available and could reduce delays in obtaining sFLC results and accelerate diagnosis in patients with unexplained AKI. This study evaluated the accuracy of Seralite® to identify MM as the cause of AKI. Method: sFLCs were retrospectively analysed in patients with AKI stage 3 as per KDIGO Clinical Practice Guidelines (serum creatinine ≥ 354 μmol/L or those on dialysis treatment) (n = 99); 45/99 patients were newly diagnosed with MM. Serum samples from healthy donors (n = 91) were also analysed for sFLCs for comparison with patient results. Results: The Seralite® κ:λ FLC ratio accurately diagnosed all MM patients in the presence of AKI: a range of 0.14–2.02 returned 100% sensitivity and 100% specificity for identifying all non-myeloma related AKI patients. The sFLC difference (dFLC) also demonstrated high sensitivity (91%) and specificity (100%), with an optimal cut-off of 399 mg/L to distinguish between myeloma and non-myeloma AKI patients. We propose a pathway of patient screening and stratification in unexplained AKI for use of Seralite® in clinical practice, with a κ:λ ratio range of 0.14–2.02 and dFLC 400 mg/L as decision points. Conclusion: Seralite® accurately differentiates between AKI due to MM and AKI due to other

causes. This rapid test can sensitively screen for MM in patients with AKI and help inform early treatment intervention.

PS-170
Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests

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Background: Free light chain (FLC) quantitation is vital for diagnosis and monitoring of light chain only (LCO) myeloma. The recommended method of measuring response is in urine (uFLC) and whilst introduction of measurement in serum (sFLC) indicates it a more sensitive measure of disease activity, it requires further validation. This study aims to guide integration of quantitative serum FLC (sFLC) tests into clinical practice, including a new rapid test (Seralite®). Methods: Analysis of blood and urine from 5573 newly diagnosed myeloma trial patients provided 576 light chain only (LCO) and 60 non-secretory (NS) cases. Serum was tested by Freelite® and Seralite® at diagnosis, maximum response to therapy and relapse. Results: 20% of LCO patients had urine FLC levels below that recommended for measuring response but >97% of these had adequate sFLC levels (oligosecretory). The recommended Freelite® level of FLC >100mg/L for measuring response was confirmed and equivalent level of FLC difference (dFLC) >20mg/L identified for Seralite®. By both methods, ≥ 38% of NS patients had measurable disease and could be reclassified as oligosecretory myeloma. In

individuals sFLC levels varied between tests, generally higher FLC levels were observed on Freelite® at all 3 time points. However, good clinical concordance was observed at diagnosis and in response to therapy. Relapse was identified using a FLC increase >200mg/L on Freelite® and found 100% concordance with a corresponding Seralite® increase of dFLC >30mg/L. Conclusion: Both Freelite® and Seralite® sensitively diagnose and monitor oligosecretory and LCO myeloma. The rapid nature of Seralite® could fast-track FLC screening and monitoring.

PS-171
Overview of multiple myeloma in Rwanda

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ABSTRACT Overview of multiple myeloma in Rwanda. Authors Fabien Ntaganda, Diogene sebahire, Alleluia jean Marie Vianney Institutions: Rwanda Military Hospital / King Faisal Hospital Purpose Multiple myeloma is multifocal plasma cell neoplasm associated with monoclonal protein on serum/urine electrophoresis. The diagnosis involves bone marrow biopsy, special stains; immunofixation and cytogenetics not available in the majority of African hospitals. The treatment of multiple myeloma is not affordable to the majority of patient as a consequence many of them die at early age result of limited access to chemotherapy. Patients and Methods Since 2011 Thirty three patients have been seen in hematology clinic since November 2011 to now. The pathology work up for multiple myeloma patients involves: Bone marrow biopsy was performed systematically to all patients and provide the disease burden in term of plasma cells. Serum protein electrophoresis and immunofixation were also done systematically to all patients to determine the M protein and the light chain. Imaging studies including skeletal survey, CT scan were also performed to the majority of the patients. Cytogenetic studies could not be performed locally. Full blood counts, Renal function. In term of therapeutic management, few parturient benefited from bone marrow transplantation abroad. Results Thirty three patients were seen in hematology clinic since November 2011 to now. The median age is 44.6 years, range from 40 to 87, with an early age presentation in our population. The majority of the patients (61%) presented at the clinic at late stage with pathological fracture. Immaging shows extensive lytic lesion in the majority of patient on simple X Ray. More than 70% of our patient presented with high plasma cell burden with more than 40% of plasma cell. The immunofixation shows IgG kappa as the predominant form. One patient presented at the hospital with isolated thrombocytopenia and gum bleeding. Anemia is the hallmark of the disease with a hemoglobin of less than 9g/dl in the majority of patient. High level of serum calcium was not observed in our patients. Only 6 patients post bone marrow transplant are still alive. The rest of patient died in period of less than a year. Conclusion This overview brings a light on the practice of pathology in Rwanda. There is a lot to improve in terms of early diagnosis. Contrary to European countries myeloma present at very early age in our population compare to western data. Further researches should be done to determine risk factors in black population compare to the Caucasian population. Autologus stem cell transplantation improve the overall survival of myeloma patients, hence access to the therapy should be a topic of discussion in resource limited countries.

PS-172
Newly diagnosed multiple myeloma is associated with hypercoagulablity and high risk of VTE. The ROADMAP study

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Background: Venous thromboembolism (VTE) is a common complication of patients diagnosed with multiple myeloma (NDMM). Incidence ranges between 8-22 per 100 person-years. Routine pharmacological thromboprophylaxis is not recommended. Elaboration of a risk assessment model (RAM), which includes biomarkers of hypercoagulability, could lead to better identification of MM patients eligible for pharmacological thromboprophylaxis. Aim: To explore the relationship of MM with cellular and plasma hypercoagulability aiming to identify relevant biomarkers for use in combination with clinical factors in a RAM for VTE. Materials and Methods: From July 2014 to June 2016, 103 patients with NDMM were recruited. Controls consisted of 30 healthy age & sex-matched individuals. At inclusions, 3 and 6 months patients were interviewed, lower limb echodoppler was performed and blood samples obtained. Biomarkers measured include Thrombin generation (TGT), P-Selectin, heparanase plasma levels, procoagulant phospholipid clotting time (PPL-ct), Factor VIIa, D-Dimers (DDi), Tissue Factor activity (TFa), fibrin monomers (FM), antithrombin (AT), Factor Va and thrombomodulin (TM). The primary end-point was the occurrence of any symptomatic and objectively confirmed VTE. Results: Median age was 66.5 years, median time to follow up 11.5 months and mortality rate 15.5%. The VTE rate was 8.7% (n=9, median time of event since diagnosis 3 months). At baseline, compared to controls, TFa levels were higher in NDMM patients without a corresponding increase of FVIIa. D-Di levels were also higher indicating either increased

sustained in vivo thrombin generation or increased fibrinolysis. The shorter PPL-ct points to higher concentrations of procoagulant microparticles in plasma. The lower levels of P-selectin in NDMM patients are probably associated with an "exhausted platelet" status. Initiation and propagation phases of thrombin generation were attenuated, peak and endogenous thrombin potential were decreased indicating a down-regulation of the thrombin generation process. Higher heparanase levels point to increased endoglycosidase activity and depolymerisation against heparan sulfate. Biomarker levels for 64 patients at 3 months (t1) were compared to baseline (t0). At t1 D-dimer and TFa levels were lower, indicating some degree of cellular hypercoagulability reversal with therapy. AT and TM levels increased at t1 versus t0. Finally thrombin generation at t1 was attenuated further. Conclusions: Patients with NDMM are at a high risk of developing VTE and show biological signs of cellular hypercoagulability. A significant fraction, but not all, of the patients have signs of plasma hypercoagulability. The high inter-individual variability of TG underlines the heterogeneity of blood coagulation alterations in NDMM patients. Prospective data will allow validation of the clinical significance of these findings.

PS-173
Organ Biomarker Responses in Patients With Light Chain Amyloidosis Treated With NEOD001 Are Independent of Previous Hematologic Response

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Introduction: In amyloid light chain (AL) amyloidosis, misfolded light chain (LC) accumulates in tissue, resulting in organ dysfunction. Current AL amyloidosis therapies limit LC production, but ~75% of patients have persistent organ dysfunction. NEOD001, an investigational monoclonal antibody that targets misfolded LC and is thought to neutralize circulating LC aggregates and to clear insoluble deposits, was shown to be safe, well tolerated, and associated with cardiac, renal, and peripheral neuropathy responses in a phase 1/2 clinical trial. Here we analyzed the association between organ response and depth and time since last plasma cell–directed (PCD) treatment. Methods: Inclusion criteria for this trial were that patients complete ≥1 PCD treatment before enrollment, attain partial hematologic response (HR) or better to any previous therapy, and have persistent organ dysfunction. NEOD001 was administered intravenously every 28 days. During the dose-escalation phase, 27 patients received NEOD001 at 0.5, 1, 2, 4, 8, 16, or 24 mg/kg in a 3+3 study design. Another 42 patients with renal, cardiac, or nerve involvement were enrolled and treated (24 mg/kg) in the expansion phase. We assessed cardiac and renal responses based on consensus criteria. Relationship of previous HR to NEOD001 cardiac or renal responses was examined. Results: The study (n=69) included 36 cardiac-evaluable patients and 36 renal-evaluable patients. Median time since diagnosis was 2.9 (range, 0.4-16.0) years, and 45% of patients had undergone ≥3 previous PCD regimens. Median time since last PCD treatment to the start of NEOD001 intervention was 5.8 (range, 0.6-85.8) months. Best response rate indicating organ response was observed in 53%

of cardiac-evaluable patients (n=19/36) and 64% of renal-evaluable patients (n=23/36). Time from patients' best HR to previous PCD treatment did not impact the NEOD001 organ response rate (cardiac/renal: 35.6/30.6 [responders] vs 36.6/32.5 [stable] months; P>0.05). Depth of patients' best HR also did not impact the NEOD001 organ response (cardiac/renal: 47.1/68.8% [CR], 66.7/63.6% [VGPR], 42.9/62.5% [PR]; P>0.05). Similarly, time or depth of patients' last HR did not impact the NEOD001 organ response rate (P>0.05). Patients with NEOD001 organ responses were no more likely to have had their last PCD therapy <6 vs ≥6 months from their first NEOD001 dose. Previous treatment type had no impact on the NEOD001 organ response rate (cardiac/renal: 55.6/61.1% [stem cell transplantation], 52.0/68.8% [bortezomib-based therapy], 50.0/57.1% [other chemotherapy]; P>0.05). Conclusions: Organ responses in patients treated with monthly NEOD001 infusions were independent of time since previous chemotherapy, depth of hematologic response, or predominant type of PCD treatment.

PS-174
EFFECT OF IMPROVEMENTS OF SURVIVAL, POPULATION AGING AND IMWG´14 CRITERIA ON INCIDENCE AND PREVALENCE OF MULTIPLE MYELOMA

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INTRODUCTION There are some variables that can modify Multiple Myeloma incidence of New Diagnosed (NDMM) and prevalence over the time: Past decade shows a new demographic data in our society: the increment of expectancy of life and an excellent performance status. In the last years we have assisted to an amazing improvement in the management and expectancy of life of Multiple Myeloma (MM) patients. Recent changes in criteria recommendation by IMWG´14 to begin treatment in NDMM patients can increment its incidence. New expensive but very effective and well tolerated antimyeloma (antiMM) agents are in the center of attention of Hematologic and Public Healthcare Systems. There are data of improvement of survival that can increment of prevalence. OBJECTIVES We have analysed our data base and calculate incidence by sex, age and three 5-years periods of time at diagnosis and obtain tendencies to get ready for next decade of ageing people with best antimyeloma agents. We have analysed prevalence of MM patients on last 7 years with cutoff date on 1st of November (2010 to 2016) MATERIAL We retrospectively analysed the incidence of patients with new diagnostic of Multiple Myeloma (NDMM) from 1998 to 2012. Then we divide the cohort in several groups: sex and age at diagnosis (3 groups: <65, 66-75 and 75y) and in four 5-year (quinquennium) period of time (1998-2002, 2003-07, 2008-12, 2013-NOV2016). We have calculated the incidence per 100000 inhab/year using census data of our Local Registry of Tumours of our Public Health Area. Characteristics of patients: n= 346. M/F: 206/140. Median age at diagnosis: 74 years (Range: 39-100). RESULTS A) INCIDENCE RATES In the past IMW (Roma-14#PO197) we reported incidence rates form 1998 to 2012. We observed a constant increase of Annual Average of incidence from 4.57 cases /100000 inhabitants/ year from the 1st period to 6.15 in the last. Adjusted by Age Incidence also

increase from 14 to 18.5 cases in the O65 group From 2013 to Nov-2016 global and adjusted by age incidence remains similar to last years data with 80 new cases in the 4 year-period (5,9 cases for global population and 17,2 cases for over65 population). After IMWG´14 criteria to begin treatment in NDMM the incidence was similar to the last 7 years (2008-12 period plus 2013-14) Incidence with 37 NDMM cases (25 O65y group). B) PREVALENCE RATES (PrevR) - 2010. 74 patients alive. PrevR: 21.25 /100000 inhabit. - 2012. 77 pats alive. PrevR: 22.2 /100000 inhabit. - 2014. 84 pats alive. PrevR: 24.4/100000 inhabit. - 2016. 103 pats alive. PrevR: 30.3 / 100000 inhabit. CONCLUSIONS Although we don´t observe substantial changes on incidence rates of NDMM, we have noted an important rise on prevalence rates of more than 40% from 2010 to 2016 (21.2 to 30.3 pats alive /100000 inhabit.) Several new antiMM drugs are available in the therapeutic arsenal and probably increases the prevalence rates.

PS-175
Involvement of a chondroitin sulfate proteolgycan and its correlation with microRNA in bone marrow microenvironment of Multiple Myeloma

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ABSTRACT Background Multiple Myeloma (MM) is the second most common hematological malignancy characterized by the uncontrolled proliferation and accretion of abnormal plasma cells in the bone marrow. The growth of these myeloma cells is facilitated by

the bone marrow niche consisting of numerous proteins, proteoglycans, cytokines and growth factors. One of the chondroitin sulfate proteoglycan, i.e., Versican (VCAN) has gained consideration in the context of solid tumors where in it has been shown to promote tumor progression. The importance of VCAN has been considered to identify its involvement in association with MM. The regulation of VCAN could be achieved by non-coding RNAs, i.e., microRNAs whose relative expression has also been assessed. Materials and Methods 30 newly diagnosed MM patients and 20 controls were recruited. The bone marrow aspirate was collected from the study subjects followed by isolation of Bone Marrow Mononuclear Cells (BMMNCs). In a representative sample population (n=10), Bone Marrow Stromal Cells (BMSCs) was harvested from the BMMNCs by primary culture. RNA was isolated from both BMSCs and BMMNCs to investigate the relative mRNA expression of VCAN and its four isoforms (V0, V1, V2 & V3) along with the relative microRNA expression of miR-144, miR-199a3p and miR-203. The spearman correlation analysis was performed to determine the interrelationship, if any, between VCAN and microRNA. Results The relative mRNA expression of VCAN and its isoforms (V0 and V1) were found to be significantly higher (p<0.01) in MM patients as compared to controls in both BMMNCs and BMSCs with higher expression in BMSCs in comparison to BMMNCs. The relative microRNA expression of miR-144, miR-199a3p and miR-203 were significantly reduced (p<0.05) in patients in both BMMNCs and BMSCs with BMSCs having lower expression than the levels in BMMNCs. Upon spearman correlation analysis, microRNA levels were found to have negative correlation with VCAN and its isoforms in both BMMNCs and BMSCs signifying the inverse relation in their expression. Conclusion Augmented levels of VCAN and its isoforms in the bone marrow of patients especially in BMSCs imply their involvement in the bone marrow microenvironment of MM which could

be exploited as a therapeutic target for the treatment of the malignancy. The negative correlation of microRNA expression indicates the plausible involvement of these microRNAs in regulation of VCAN in MM. Thus, targeting VCAN using microRNAs could be established as the functional therapeutic approach in MM.

PS-176
Stain Color Normalization and Segmentation of Plasma Cells in Microscopic Images as a Prelude to Development of Computer Assisted Automated Disease Diagnostic Tool in Multiple Myeloma

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Background: Normalization and segmentation of cells is a precursor to cell analysis required for developing any computer assisted automated disease diagnostic tool. In this work, we address stain color normalization and cell segmentation from microscopic images stained with Jenner-Giemsa stain for multiple myeloma (MM). Materials & Methods: Images were captured from the slides of patients with MM and stained using Jenner-Giemsa stain. The proposed method of stain normalization carried out white balancing for illumination correction, stain vector correction, and stain quantity correction. Stain vector correction deals with errors caused due to variations in the stain chemical over time and batches. This was achieved via singular value decomposition (SVD) method. Here, a given RGB) image was first converted to the Optical Density (OD) space and reshaped to a 3xN matrix (with N no. of pixels and Red, Green, and Blue channels). SVD of this matrix is computed and all singular vectors of the input query image are aligned with the stain basis

vectors of the reference image. Correspondingly, all intensity values are appropriately rotated in the OD space. Lastly, stain quantity correction is achieved via histogram percentile matching. The cell segmentation is carried out using modified multiphase level set formulation with three stages. In stage-1, intensity probability density functions (pdfs) of plasma cell (PC) nucleus, PC cytoplasm, unstained cells, and background are modeled in RGB, HSV, and Lab color spaces, and unstained cells are removed. In stage-2, regularization terms are added based on the pdfs to the multiphase level set formulation. In stage-3, watershed along with circle Hough transform are applied to segment cell clusters. To reduce false positives, Gaussian mixture modeling is used to filter out unwanted cells. Results: We tested our stain color normalization method on many MM images with one image as the reference. Both qualitative and quantitative results demonstrate that the proposed method efficiently normalizes stain color variations. The segmentation pipeline is tested on 50 MM images consisting of 165 single/isolated cells and 21 clusters. Our proposed method segmented 141 single cells and 16 clusters successfully, and had only one false positive cell. Compared to the other methods of intensity thresholding and conventional multiphase level set, the proposed pipeline is robust and provides greatly improved results. Conclusion: This work presents a method to normalize variations in stain color of MM images stained with Jenner-Giemsa stain and a 3-stage pipeline for efficient cell segmentation. The proposed methods lead to effective stain normalization and segmentation of plasma cells from microscopic images of multiple Myeloma. This is a step forward for the development of computer assisted automated analysis of microscopic images of MM.

PS-177
Immunophenotyping Patterns of Plasma cells in Plasma Cell Proliferative Disorders

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Presence of normal plasma cells (PC) and preserved B-cell compartment in the bone marrow of patients with plasma cell proliferative disorders (PCPDs) is associated with better outcome as it is reflective of normal functionality of the immune system. In this study, flow cytometric immunophenotyping was carried out on the bone marrow aspirates collected from 165 patients with PCPDs (Multiple myeloma - 130; MGUS-10; Plasmacytoma, POEMS & Amyloidosis- 5 each) & 10 patients with Hodgkin's disease (HD) to study the immunophenotype of normal and malignant PC followed by assessment of their presence/absence in the samples of PCPDs. All the samples were processed within 12-hours of collection using the Euroflow bulk lysis protocol and stained with two-tube 8-color panel comprising of CD38, CD138, CD45, CD117, CD19, CD56, CD27, CD81, Cy-Kappa, Cy-Lambda, acquired on Gallios flow cytometer (Beckman Coulter, USA) and analyzed using Kaluza software. The adequacy of the bone marrow aspirate was assessed based on the presence of myeloid and lymphoid progenitors on flow cytometric immunophenotyping. A minimum of 1.5 million events were acquired in all tubes. The PC were gated using sequential gating strategy and the immunophenotype of PC observed in HD samples were considered representative of normal PC. The PC in HD samples comprised chiefly of two cell populations: CD19+CD56- and CD19+CD56+ polyclonal PC with variable expression of CD27 and CD81 but very dim to negative expression of CD117. In multiple myeloma (MM) samples, the PC were predominantly CD19-CD56+ in newly diagnosed cases, a mix of CD19-CD56+ and CD19+CD56+ in relapsed and progressive

disease whereas CD19+CD56+ cluster predominated in cases with responses of partial response or better. Similarly, in PCPD other than MM, the predominant population consisted of CD19+CD56+ polyclonal PC and a minor population of CD19-CD56+ which was discernible in all cases. In addition, the MM patients on chemotherapy and those with PCPD, showed presence of CD19+CD56- polyclonal PC. The expression of CD27 and CD81 was variable and was not found to be useful in delineating normal and malignant PC. Due to short follow-up duration of the study (median duration of 9 months), the prognostic impact of the percentages of normal and malignant PC in PCPD could not be established. Overall, CD19, CD56 along with Cy-Kappa, Cy-Lambda and PC gating markers were most useful in delineating normal and malignant PC

PS-178

Targeting ongoing DNA damage in multiple myeloma. Effects of different inhibitors of the DNA damage response on plasma cell survival

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Human myeloma cell lines (HMCLs) and a subset of myeloma patients with poor prognosis have recently been shown to exhibit high levels of replication stress (RS), leading to DNA damage. Here, we confirmed the presence of DNA double strand breaks (DSBs) in several HMCLs by measuring gamma-H2AX and Rad51 foci, and analyzed the effect of different inhibitors of the DNA damage response (DDR) on MM cell survival. Inhibition of ATR, the major kinase mediating response to RS, using the specific inhibitor VE-821 induced higher cell death in HMCLs and primary cells than in control lymphoblastoid cells and U266, a cell line which exhibited low DNA damage. Interestingly, the absence of ATR was found partially compensated by ATM, since chemical inhibition of both kinases using VE-821 and KU-55933 increased cell death of MM cells with DNA damage. Using a reporter repair substrate that we integrated in the DNA of HMCLs we found that ATM and ATR were involved in DSB repair by homologous recombination (HR), and inhibition of both kinases resulted in a stronger inhibitory effect. Cell death induced by the combination of ATM and ATR inhibitors seemed to be associated with the role of these proteins in HR, since when we abolished HR using the MRE11 inhibitor mirin, or the RAD51 inhibitor B02, cell survival of HMCLs exhibiting DNA damage was severely reduced. On the contrary, inhibition of the other route involved in DSB repair, non-homologous end joining (NHEJ), using the DNA-PK inhibitor NU7441 did not affect MM cell viability. Interestingly, we found that NHEJ inhibition did not increase cell death when HR was simultaneously inhibited with B02, but it clearly enhanced cell death when HR was inhibited with mirin, that interferes with recombination before DNA resection takes place. Taken together, our results demonstrate for the first time that MM cells with ongoing DNA damage rely on an intact HR pathway, providing a therapeutic window. In addition, we show that inhibition of HR after the initial step of end resection might be more appropriate to induce MM cell death since it prevents the occurrence of a compensatory NHEJ repair mechanism. These preclinical observations provide the rationale for its clinical evaluation.

PS-179

The Impact of Maintenance Lenalidomide and Depth of Response on the Mutational Status of the Myeloma Clone from Presentation to Relapse

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The use of lenalidomide (len) maintenance has been associated with improved outcomes in both transplant eligible (TE) and non-eligible (TNE) newly diagnosed myeloma patients (NDMM). Despite this an understanding of the impact of maintenance on MM clonal architecture and mutational load has not been assessed. Applying constant treatment pressure may halt cancer cell division, slowing genetic and clonal evolution. We addressed this hypothesis by performing whole exome sequencing (WES) on 70 paired presentation/relapse samples, comparing those who received maintenance len and those being actively observed. We have undertaken a nested case control analysis using patients enrolled to the NCRI Myeloma XI trial for NDMM patients who had completed induction +/- ASCT and been randomised to maintenance with len or observation. WES was performed to a median depth of 125x on 70 presentation/relapse pairs. Of the 70 patients included, 35 (50%) received len maintenance and 35 (50%) observation, with a median age of 66 and 69 respectively. Twenty nine (41%) patients had undergone ASCT. The median time to relapse following maintenance randomisation was 10 months for the len group and 11 months for the observation group. Sixty one patients (87%) achieved a ≥VGPR as their best response prior to relapse. At presentation the median number non-silent mutations was comparable in both the len maintenance and observation groups (37 vs 34, p=0.75). At relapse the median number of mutations in the len group was 34 vs 44 in the observation group (p=0.22). The number of mutations at presentation and relapse for the whole cohort (n=70) was 37 vs 41 respectively (p=0.25). In patients who achieved a CR (n=33, 47%) the number of mutations at presentation was 33 vs 41 at relapse (p=0.05). The mutational load in patients who achieved<="" div="">

PS-180
Absolute lymphocyte count and ratio of absolute lymphocyte count/absolute monocyte count (ALC/AMC) provides a readily available prognostic indicator in multiple myeloma

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Introduction: Multiple myeloma (MM) is a malignant neoplasm of plasma cells with median duration of survival less than five years. However, there is considerable variability from one patient to another. Many clinical and laboratory parameters are being used for prognostication in MM. Recently, absolute lymphocyte count (ALC), absolute monocyte count (AMC) and ALC/AMC ratio in peripheral blood has been reported to be an independent prognostic factor in multiple myeloma (MM). Methods: One hundred and forty-one cases of MM diagnosed in TMH from 2004 to 2013 were studied for ALC and ALC/AMC ratio in peripheral blood at diagnosis. CBC was performed on LH750 and ADVIA2120i. The

results were further correlated with other laboratory and clinical prognostic factors. Statistical analysis was performed by using SPSSv16. Results: On univariate analysis, low ALC (<1,400 cells/μL) and low ALC/AMC ratio (<2.9) were significantly associated with poor overall survival (OS) (p=0.04 and p<0.01, respectively) but not with progression free survival (PFS) (p= .838, and p=.925, respectively). Low ALC/AMC ratio (<2.9) was also found to be associated with other poor prognostic factors such as low hemoglobin level (p=.02), high β2-microglobulin (p=0.002) and high risk cytogenetics (p=0.008). Similarly, low ALC (<1,400 cells/μL) was significant association with high risk cytogenetics (p=0.002). Conclusions: Absolute lymphocyte count and ratio of absolute lymphocyte count/absolute monocyte count (ALC/AMC) provides a readily available and reliable prognostic indicator in multiple myeloma.

PS-181
Phenotypic analyses of NK cells in patients with multiple myeloma

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Introduction In the field of oncology, the exploitation of host immune function is critical for the development of the novel cancer therapy. The recent advance of immunotherapy using monoclonal antibodies for multiple myeloma shows a promising therapeutic effect. NK cells play an important role in the anti-myeloma immune response, and the investigation of NK cell function provides us a beneficial information. We performed phenotypic analyses of NK cells in patients with multiple myeloma. Methods Peripheral blood samples were obtained from 29 multiple myeloma patients (10

newly diagnosed cases of myeloma, 8 relapsed, and 11 in complete or partial remission), and 9 healthy volunteers. NK cells were identified as a fraction of CD3 negative and CD56 positive, and NKp46 was further used for NK cell identification in CD56 positive myeloma cell-containing samples. The phenotype of NK cells was characterized by the expression of SALMF7, NKG2D, FcgammaRIII, PD-1, and CD56bright or dim. Results At the diagnosis of multiple myeloma, the number of NK cells was significantly low in comparison to that of patients in remission (p=0.035) and relapse (p=0.029). The expression of SLAMF7 did not differ between disease statuses. Regarding immune checkpoint molecule, the expression of PD-1 on the NK cells of myeloma patients was significantly increased in comparison with that of healthy donors (p=0.033). Notably, the expression of FcgammaRIII, which is a key player in a mechanism of antigen-dependent cytotoxicity, was significantly suppressed in the NK cells of myeloma patients (p=0.001). Furthermore, the significant increases in the total number of NK cells (p=0.0004) and in CD56dim NK cell fraction (p=0.0013) were observed in patients who were treated with immunomodulatory drugs (IMiDs). Conclusion The phenotypic analyses suggested that the anti-tumor function of NK cells may be suppressed in myeloma patients. However IMiDs may increase the activated NK cells. Further investigation is warranted.

PS-182
Characterizing the amyloidogenic protein in patients progressing to light chain amyloidosis from asymptomatic precursor states using mass spectrometry

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Background: In AL amyloidosis (AL) clonal, misfolded light chains (LC) deposit in organs. Our group has developed a mass spectrometry (MS) method that can identify circulating monoclonal proteins, based on their unique molecular mass signatures.Given the propensity for patients with AL to have MS patterns consistent with post-translational modifications (PTMs), we hypothesized that these changes are present long before the diagnosis of AL and can serve as a predictor for AL in patients with an asymptomatic plasma cell dyscrasia (aPCD). Methods:We included 64 patients with AL who had a preceding aPCD and who had stored serum samples at both time-points.The mass/charge (m/z) of monoclonal LC peaks (P) was noted for each sample.Presence of a PTM was defined as the presence of ≥ 1 "heavy" Ps at a particular charge state.A P was considered heavy if its m/z exceeded the right sided 95% C.I. of the m/z distribution of the respective normal LC.We used 9 patients with relapsed multiple myeloma (MM) without AL as controls.Results: Prior aPCDs were MGUS (N=33), smoldering myeloma (n=9) and MM (N=1).In 21 patients aPCD was not further classified with a bone marrow biopsy.The median interval between aPCD and AL diagnosis was 77 months.At aPCD diagnosis, 42 patients had a single, typical P and 21 patients (33%) had PTMS: 13 patients had a single heavy P; 5 patients had 2 P (only one of which was heavy); and 3 patients had 2 heavy peaks.No PTMs were noted in our MM controls.The m/z of all typical and heavy P observed at aPCD remained unchanged for 63 patients as they transitioned to AL, which suggests no new PTMs occurred with the exception of one patient, who had a single PTM at aPCD diagnosis, but developed 2 additional heavy P appearing at +1232 and +1392 Dalton at AL diagnosis, suggestive of new PTMs.In all but 3 aPCD, the typical P was more abundant relative to heavy P.Heavy P abundance increased in 6 patients as they transitioned from the aPCD to the AL state and exceeded that of the typical P in 3 patients, suggestive of

increasing abundance of existing PTMs in these cases.Finally, we consistently noted a secondary P at +160 Daltons, which did not qualify as a PTM based on our definition.This was present in 60 patients in the aPCD state; 62 in the AL state; and in all control patients with MM.However, whereas in MM the median ratio for this peak relative to the typical peak was 0.4, in the aPCD samples it was 0.8 (p=0.0006), and in 10 patients, the intensity of this peak exceeded that of the typical P, a phenomenon never observed in MM.Finally, in 3 cases it surpassed the intensity of the typical P during aPCD to AL transition.Conclusions: Pre-existing PTMs are present in 1/3 of AL patients and not in MM and can be used to identify patients at risk for AL. New PTMs are uncommon, but the relative abundance can change over time.More work to clarify the nature of the mysterious +160 Dalton peak is ongoing.

PS-183
Hyperammonemic encephalopathy as initial presentation of Multiple Myeloma

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Background. Impairment of consciousness is frequently observed in Multiple Myeloma (MM), often due to hypercalcemia, hyperviscosity, sepsis or drug effect. Hyperammonemic encephalopathy (HE) with normal liver function and urea metabolism has been previously reported as a rare manifestation of relapsed/refractory MM and is associated with high mortality rate. We report a case characterized by hyperammonemic encephalopathy as initial presentation of Multiple Myeloma and a survey of ammonium concentration in a series of newly diagnosed MM (NDMM). Patients and results. A 77 years-old woman came to the attention of the Neurologists for rapid cognitive impairment with somnolence evolving within few hours in comatose state. Laboratory findings showed pancytopenia, serum IgGκ monoclonal component (IgG=24.3 g/L, sFLCκ=1700 mg/L and κ/λ= 1232, Bence-Jones=200 mg/24 h), normal blood levels of liver and renal function tests, sodium, calcium, glucose, TSH, vitamin B12 and folate. Despite normal liver function and urea metabolism, blood ammonia level was 68 μmol/L (n.v. 11-35). A bone marrow biopsy confirmed the suspicion of MM and a diagnosis of hyperammonemic encephalopathy (HE) was made. After a brief course of intravenous dexamethasone the patient showed improvement of vigilance along with normalization of ammonia level. Therefore, she underwent bortezomib-dexamethasone based therapy obtaining a rapid hematological response, persistently normal serum ammonia levels and normal neurological examination, suggesting that HE was related to MM. We performed a survey of patients with NDMM in the last 12 months (37 patients). We found unexplained hyperammonemia without encephalopathy (mean value 60; range 44-79) in 4 other newly diagnosed MM without other metabolic disorders. All patients presented high risk disease with aggressive clinical presentation. A decrease of ammonia levels until normalization after adequate MM therapy was reported in all patients after therapy. Conclusions. To our knowledge, the above quoted case is the third case in literature of hyperammonemic encephalopathy as presenting feature of MM. Pathophysiology of increased serum level of ammonia in MM is not clear. However, it is known that MM cells produce an excess of ammonia from extracellular glutamine and plasma cells show features of glutamine addiction. Therefore, the inhibition of glutamine uptake could represent a potential new therapeutic strategy. Should be confirmed by prospective trials, our data might suggest the potential relevance of measurement of blood ammonia levels in newly diagnosed MM patients, independently from the presence of neurologic signs, as a marker of an aggressive disease.

PS-184
SUBCUTANEOUS BORTEZOMIB IN OLDER MULTIPLE MYELOMA PATIENTS (> 75 y/o)

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INTRODUCTION: Formulation and administration of subcutaneous Bortezomib (SC-BTZ) has lead to a really important change in Multiple Myeloma's patients management getting to achieve a optimum dose cadence and accumulation without large adverse events, dose reductions or discontinuations, improving this way response rates in comparison with intravenous (i.v.) formulation. PATIENTS AND METHODS: Data were analysed from medical records. This is a descriptive retrospective study

about SC-BTZ tolerance and way of administration in older patients (75 y/o or more). One hundred eleven patients were treated with SC-BTZ in our department, 36 (32.4%) were 75 or older. Median age at treatment beginning was 79.5 y/o (75-87), 21 were males an 15 females, 30 got treatment as a first line therapy and 6 of them as second o subsequent lines. In most of the curses (220/288) was administered a weekly based regiment Therapy schemes used were: VMP: 20; VEL-DEX/PRED: 16. Overall response rate (>PR) was 72% (26/36), 4 patients progressed and 6 got an stable disease/minimal response. Median number of curses received by patients was 8 (6-11). Thirty of 36 patients got the whole scheme therapy which was planned at the beginning. Twenty five of them got 100% of the prescribed curses of treatment. We had to discontinue treatment in 7 patients: 4 due to progression, 3 due to other causes (1 of them because G3 toxicity, other because his own decision and the last one because not related death). Dose was decreased in 5 patients, 3 due to neuropathy, 1 because liver dysfunction and other 1 because his own decision. Grade 3 Neuropathy rate was 2.7% (1/36) an Grade1-2 8.3% (3/36). No discrepancy with 66-75 y/o patient group treated with similar curses o treatment was found. CONCLUSIONS: SC-BTZ offers an excellent security and tolerance outline in this particular group of patients. Overall neuropathy rate is similar in >75 y/o group, G3 toxicity is practically non-existent within weekly based regiment. No serious adverse event was shown in this patient group.

PS-185
Polyclonal immunoglobulin recovery is enhanced after autologous stem cell transplant and associates with improved clinical outcomes in multiple myeloma patients

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Background: Uninvolved immunoglobulin suppression as determined by heavy+light chain measurements (HLC-pair suppression, e.g. IgGκ levels below normal in an IgGλ patient) is a common finding in multiple myeloma (MM). HLC-pair suppression following treatment has been associated with poor prognosis; however how myeloma therapies affect immunoglobulin suppression and recovery is poorly understood. Here we studied the characteristics and clinical impact of HLC-pair suppression in a population of newly diagnosed MM patients treated with novel agents ± ASCT (autologous stem cell transplant). Methods: The study included intact immunoglobulin MM patients from the IFM2009 clinical trial. Patients were treated with RVDx3+ASCT+RVDx2 (transplant arm) or RVDx8 (non-transplant arm), followed by 12 months lenalidomide maintenance. Sera was analysed for HLC levels using Hevylite immunoassays (The Binding Site). Treatment arms were compared for HLC-pair suppression at the end of induction (transplant arm n=212; non-transplant n=208) and before maintenance (transplant arm n=255; non-transplant n=252). HLC-pair suppression was defined as uninvolved HLC levels below the published normal ranges (IgGκ<3.84, IgGλ<1.91, IgAκ<0.57 and IgAλ<0.44 g/L), and severe suppression as greater than 50% reduction below these levels. Results: After induction therapy and before randomisation, the proportion of patients with HLC-pair suppression was similar between transplant and non-transplant arms (66% v 73%, respectively;

p=0.109); and levels of suppression were severe and comparable between the two groups (median HLC-pair suppression: 71% v 69%, respectively, p=0.533). By contrast, prior to maintenance therapy fewer patients were suppressed (26% v 49%; p<0.001), and levels of suppression were moderate (median HLC-pair suppression: 42% v 58%; p=0.036) in the transplant compared to non-transplant arm, respectively. At this time, HLC-pair suppression in non-transplant patients associated with shorter PFS (median PFS 726 v 1296 days, p<0.001); possibly reflecting their deeper degree of immunoglobulin suppression. Conclusions: Autologous stem cell transplantation in the era of novel agents positively impacts polyclonal immunoglobulin recovery as measured by uninvolved HLC levels, suggesting better repopulation of the normal plasma cell bone marrow pool. By contrast in a significant proportion of non-transplant patients, median suppression remains severe, possibly reflecting an inability to achieve normal immune function in these patients which may impact clinical outcomes.

PS-186 (d)

Glycosylation of immunoglobulin light chains is associated with amyloidosis

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INTRODUCTION: In light chain amyloidosis (AL), the deposition of immunoglobulin light-chains (LCs) in a fibrillary form could cause irreversible organ damage of the affected organs. The primary structure of LC, including sequence and post-translational modifications (PTM), is thought to be important for the amyloidogenicity of LC. Our group and others have reported that κ and λ exist as monomers and dimers and that glycosylated and cysteinylated forms of the LCs exist in patients with AL. Our group has used high resolution microflow liquid chromatography-ESI-Q-TOF MS (a.k.a. miRAMM) to monitor these PTM's in LCs from a population of clonal plasma cells. The aim of this study was to evaluate the performance of high-throughput/low resolution MALDI-TOF MS (MASS-FIX) as compared to high resolution/low-throughput microflowLC-ESI-Q-TOF MS to identify LC glycosylation in patients with a plasma cell dyscrasia. MATERIAL & METHODS: Matched serum and urine of 233 patients with a monoclonal protein identified by MASS-FIX or IFE were studied. Intact LCs were identified as having a PTM if mass peaks were observed above the normal mass/charge (m/z) range for monoclonal LCs. Samples with an indication for glycosylated LCs by MASS-FIX were reanalyzed by microLC-ESI-Q-TOF MS on a SCIEX TripleTOF 5600 mass spectrometer. Glycosylated LCs were identified by their increased molecular mass and the presence of multiple peaks associated with different glycoforms each separated by the molecular mass of one or more monomers of either pentose (132 Da), deoxyhexose (146 Da), hexose (162 Da), hexosamine (191 Da), N-acetylhexosamine (203 Da), or N-acetylneuraminic acid (291 Da). RESULTS: On MASS-FIX, the mass spectra of 51 patients' paired serum and urine samples had LCs with a spectral pattern consistent with PTM, and their diagnoses follow: 32/62 AL pts (52%); 7/89 (8%) MM pts; and 12/70 (17%) MGUS . Upon analysis of these 51 MASS-FIX atypical patterned patients by high resolution microLC-ESI-Q-TOF MS, 32 patients had spectra of their serum c/w glycosylated LCs: 22/32 AL pts; 4/7 MM pts; and 6/12 MGUS, including 1 LC-MGUS suspected to be AL and 1 patient with ALECT2 with a coexistent LC-MGUS. Analysis of their urine showed that (22/51) patients had glycosylated LC; importantly, the molecular

masses of the LCs in urine matched the molecular masses in serum. DISCUSSION & CONCLUSIONS: We have demonstrated that a higher percentage of patients with AL amyloidosis have atypical spectra c/w PTM of their LC by MASS-FIX. Upon high-resolution MS, the majority of these atypical patterns were consistent with glycosylation. These data suggest that these techniques may increase our ability to identify patients with and/or at risk for AL, but further study will be required.

PS-187
Prevalence of ocular disorders in multiple myeloma

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Background: OS of multiple myeloma (MM) patients (pts) has increased due to the availability of new drugs. However, since MM is an incurable disease, pts are exposed to repeated lines of therapy with different agents. It is increasingly important to monitor the long-term side-effects of treatments. In the present study we focused on ocular disorders. Aims: assessing the prevalence of ocular disorders in MM treated pts. Methods: 87 symptomatic MM pts were enrolled in a prospective protocol consisting in a complete ophtalmologic evaluation. Best corrected visual acuity (BCVA) was assessed; lens opacities were classified according to the LOCS III score; intraocular pressure was measured and was considered pathological if >21mmHg; Schirmer test was pathological if <15mm. Binary logistic regression analysis (univariate and multivariate) were conducted to relate ocular disorders to age, comorbidities (diabetes, hypertension, smoking, autoimmunity) and common MM variables. Results: Median age was 63 yrs. Median cumulative dose of dexamethasone was 1600mg (range 80-8480). Inadequate visual acuity was found in 35/71 pts (49%); severe visual loss (< 20/40) was found in 13/71 pts (15%) 10 of which had pre-existing ocular history of lazy eye, myopia, pseudophakia, vitrectomy, retinitis pigmentosa and trauma. No relation was found with cumulative steroid dose, duration or type of treatment. Instead, in multivariate analysis age and history of hypertension resulted to be independent risk factors for visual impairment, (age OR:4.6 p0.004; hypertension OR: 2.8 p=0.05). Retinal disorders (11%) were correlated to age and hypertension in multivariate analysis. Fifty percent of pts (44/87) had lens opacities of any grade: cataract was observed in 6/87 pts (7%), and in all cases was posterior subcapsular cataract LOCS III ≥2; moderate lens opacities were observed in 32% pts (28/87), while 23% showed nuclear or concomitant nuclear/cortical opacities (LOCS III 2-3) and 9% posterior subcapsular opacities (LOCS III 1). Lens opacities related with age >63 years (OR: 4.0 p=0.009) and time from diagnosis >37 months (OR: 2.6 p=0.05) in multivariate analysis. No association was found with cumulative steroid dose or other drugs exposure. Inadequate tears production was observed in 52% pts (45/87). Conclusion: Our study shows a high prevalence of visual impairment and early lens opacities in MM pts. We observed a higher prevalence of posterior subcapsular cataract compared to other cataract subtypes. Retinal disorders were relatively frequent, correlating to age and hypertension. A high prevalence of inadequate tear production was observed, as well. Interestingly, no significant increase in intraocular pressure was noticed, possibly because of chronic but pulse administration of steroids. Pts with hypertension show an increased risk of retinal disorders. We recommend an adequate ophthalmologist

follow-up in treated MM pts

PS-188
Maturing data from the Australia and New Zealand Myeloma and Related Diseases Registry

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Background: Multiple myeloma (MM) is associated with a high community burden of disease. The Australia and New Zealand (ANZ) Myeloma and Related Diseases Registry was established in 2012 to explore epidemiology, practice variation in diagnosis and management, and clinical outcomes. Methods: All patients registered from 21 Jan 2013 to 31 Oct 2016 were included. Patient baseline characteristics, diagnosis, therapy and outcomes were assessed. Time to survival and disease progression were estimated using survival analysis. Results: In total, 1329 patients were registered. Fewer than10 patients have opted off the registry since its inception. Of 1189 pts with diagnosis, 819 patients (69%) had MM and 59% of patients with gender were male (772/1299). Mean age at diagnosis was 66y, with 35% over 70y. Of all MM patients 34% were high risk (based on FISH, ISS, LDH, cytogenetics), and CRAB was identified in 67%: 446 had bone lesions, 188 had anaemia and 68 renal impairment. Of 529 patients with ECOG status recorded, 23% were $\geq$ grade 2, and 31% of patients with ISS available had ISS=3. Of 738 patients with MM and bone marrow biopsy information, 612 had flow cytometry data (not performed in 328, 54%); 557 had cytogenetics data (not performed in 238, 41%); 579 had FISH data (not performed in 207, 36%). Findings reflect local access to treatments and tests. First-line chemotherapy data were available for 678 patients: 87% received bortezomib-based therapy, 11% received an immunomodulatory drug; 6 received both. First-line response data were available for 489 patients; ORR ($\geq$PR) was 84%; response rate for patients on bortezomib was 88%. Only 49 MM patients (6%) were noted as clinical trial participants. Of 430 MM patients $\leq$70y with follow-up data, autologous stem cell transplant (ASCT) had been performed in 299 (70%). Only 6 patients >70y had ASCT. In 65% of 191 cases where ASCT was not planned, the rationale was age. Bortezomib-based first-line chemotherapy was used in 83% of 199 patients not for ASCT with available therapy data. Second-line chemotherapy data were available for 213 patients: 36% received bortezomib-based therapy, 69% received an immunomodulatory

drug; 16% received both. Second-line response data were available for 142 patients; overall response rate (≥PR) was 65%. Bortezomib RR was 81%. Median time to disease progression was 29.5 months. Median overall survival for the cohort was not reached. Median times from diagnosis to treatment and ASCT were 20.5 days (9-36) and 6.4 months (5.2-8.1) respectively. Conclusion: 'Real world' myeloma data are scarce internationally and in ANZ. Most patients are treated with bortezomib-based first-line therapy and immunomodulatory drugs for second-line therapy. Few patients were enrolled in clinical trials. Maturing registry data can describe the epidemiology, treatment, and outcomes in MM and help inform future clinical management and research.

PS-189
Ten year data of multiple myeloma patients treated at a tertiary care centre in western India

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Background: Multiple myeloma is a plasma cell disorder accounting for approximately 12% of all hematological malignancies. It is second most common hematological malignancy and is characterized by clonal proliferation of plasma cells in either bone marrow or focally, M-protein in serum and/or urine, bony lytic lesions and renal impairment. The disease spans a clinical spectrum from asymptomatic to aggressive forms due to deposition of abnormal immunoglobulin chains in tissues. Although vast data is available in literature, Indian data is not readily available to assess disease burden and its management issues. We retrospectively analyzed myriad clinical features of multiple myeloma patients, their types and stages and their response to various types of chemotherapies available in our tertiary care centre. Aim of study: • A retrospective observational study to evaluate clinical profile and management of multiple myeloma patients presented to a tertiary care centre in western India Objectives: 1) To study demographic data of multiple myeloma patients and assess their various clinical and laboratory parameters 2) To assess types of multiple myeloma patients at our centre 3) To evaluate response to various chemotherapy protocols 4) To check drug toxicity in multiple myeloma patients on treatment Results: Total 131 patients were eligible for retrospective evaluation who presented to our centre from year 2007 to 2016. Departmental proformas and records of these patients were analyzed. As it is retrospective analysis, data of few patients was incomplete. Out of these patients, 79 were males and 59 were females. Median age was 58 years (Range 29 to 79 years). Bony pains was the most common symptom (59.5%) followed by constitutional symptoms (57.2%), anemic symptoms (35.1%). On investigations, 74.8% patients had Hb < 10 gm% while thrombocytopenia was noted in 10.7% patients. On presentation, 56.5% patients had high creatinine while 30.9% had high calcium levels. 58.8% patients had elevated beta 2 microglobuline (>5.5 ng/ml). As per ISS staging, 7.6% (7/92), 20.6% (19/92) and 75% (69/92) patients were in stage I, II and III at presentation respectively. 72.8% had lytic lesions evident either on xray or MRI. IgG kappa was most common type of myeloma (40.5%) followed by IgA lambda (13.7%) and IgG lambda (12.2%). 17.6% patients had light chain myeloma out of which 60% had kappa light chain while 40% had lambda light chain only. 8.4% patients had none of these monoclonal proteins seen. Out of all patients, 94% received at least some form of chemotherapy. 27% (36/131) patients were lost to follow up after incomplete first line therapy. 35.9% received CyBorD (cyclophosphamide + bortezomib + dexamethesone) protocol while 19.4 % received MPT (melphalan +

prednisolone + thalidomide) regimen. 8 patients

PS-190
POEMS syndrome: a Clinical experience of 48 patients and comparative analysis of consolidation ASCT versus non-ASCT cohorts.

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INTRODUCTION: We here present the updated report of clinical features and treatment outcome of 48 cases seen over a period of 23 years. We have also compared the data of 9 patients who underwent Autologous stem cell transplant (ASCT) with the remaining. PATIENTS AND METHODS: Between January 1993 and November 2016, 48 patients were diagnosed to have POEMS syndrome using Mayo clinic criteria (2011). Major criteria was optional as we do not routinely do VEGF assay. RESULTS: Patients' median age was 45 years (Range 25-70 years). The male: female ratio was 3.8: 1. Polyneuropathy and monoclonal plasmacytosis were present in all. Endocrinopathy was present in 60% of patients with hypogonadism (23%), adrenal axis disorders(23%) and hypothyroidism in 55% of patients.10 patients had Castleman's disease(hyaline vascular). Effusions were noted in 45% patients. Osteosclerotic bone lesions were present in 72% patients. ASCT: Nine patients underwent a consolidation ASCT after a median of 4 cycles of induction; Bortezomib and Dexa was the most common regimen. Post induction 6 patients achieved complete haematological response (CRH), two had partial (PRH) while there was clinical improvement in 7 of 9 patients. Median interval from diagnosis to ASCT was 12.2 months (range=4.9-26.9 months). Median melphalan dose was 140 mg/m2.Two patients had Engraftment syndrome. Post- transplant all 9 had CRH and clinical improvement.Modified Rankin Score (mRS) was used to assess the improvement in disability after treatment. Median baseline score among these 9 patients was 4 that improved to 3 after induction and remained at 3 after ASCT. The rest 39 patients were treated with chemotherapy followed by maintenance. Single regimen was used in 27 and two lines were used in 12. Melphalan +Prednisolone was the most common regimen (n=23) followed by Bortezomib+Dexa (9) and Lenalidomide +Dexa (2). Nine patients continued maintenance. At last follow up, CRH was detected in 10 and PRH in 12 patients. Clinically improvement (CR+PR) was noted in 21 and stable disease was seen in 10. Median mRS improved from 4 to 3 during this period. The hematological response at last assessment was significantly better in the transplant group as compared to non transplant (p=0.045). At a median follow up of 66 months (range 41- 90 months), the median overall survival was not reached. CONCLUSION: Clinical features of POEMS in this part of the world are similar to those reported from larger studies. ASCT in consolidation rather than upfront is a feasible option with better haematological responses and good clinical outcomes.

PS-191
Neoplastic plasma cells generate an inflammatory environment within bone marrow and markedly alter the distribution of T cells between lymphoid compartments

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Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) are characterised by the accumulation of malignant plasma cells within bone marrow and lead to a range of abnormalities in the peripheral blood T cell repertoire. We investigated the level of inflammatory chemokines within the bone marrow and blood of patients with MGUS and MM and related this to the pattern of chemokine receptor expression on T cells in both compartments. The expression of a wide range of chemokine ligands for CXCR3 and CCR4 was markedly increased within the bone marrow of patients with MGUS and MM compared to healthy donors. The most marked effects were seen for CCL4 and CXCL9 which were increased by 4 and 6 fold respectively in the bone marrow of patients with myeloma. The expression of CXCR3 and CCR4, the major TH1 and TH2-associated chemokine receptors, was increased substantially on T cells within the bone marrow of patients whereas the percentage of CXCR3-expressing T cells within blood was correspondingly decreased. The presence of even small numbers of neoplastic plasma cells can therefore generate an inflammatory chemokine tumour microenvironment. This leads to the recruitment and retention of specific T cell subsets and is likely to underlie many of the features regarding the nature of the peripheral T cell repertoire in these patients. This local inflammatory reaction may represent a tumour-specific immune response or may itself play an important role in tumour progression and as such may offers a potential novel target for therapeutic intervention.

PS-192
Plasmacytomas in multiple myeloma: 45-years experience from a single institution.

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INTRODUCTION: Plasmacytomas (Ps) are frequent in patients with multiple myeloma (MM) and are considered to be associated with poor prognosis. There are two types of Ps: 1) paraskeletal plasmacytomas (PPs) consisting of soft-tissue masses arising from focal bone lesions and 2) extramedullary plasmacytomas (EMPs) consisting of soft-tissue masses with no contact with bone. However, the outcome of patients who develop Ps at diagnoses or at relapse as well as the outcome of the two types of Ps is not well established. AIM: To analyze the incidence, characteristics and outcome of patients with MM and Ps treated at our institution between 1970-2014 as well as the outcome of these patients before (period 1: 1970-1999) and after (period 2: 2000-2014) the introduction of novel drugs. PATIENTS: A total of 1.116 multiple myeloma patients (548 males, 568 females) were diagnosed and treated at our institution from January 1970 to December 2014. RESULTS: Overall, 220 patients (19.7%) had Ps at diagnoses (17.1% PPs and 2.6% EMPs). The incidence of PPs in period 1 was 12.9% versus 21.6% in period 2 (p<0.0001) while the incidence of EMPs remained unchanged over the years (2.5% versus 2.6% in periods 1 and 2, respectively). The median OS of patients with PPs was 3.5 years (2.1 years in period 1 and 5.2 years in period 2) while the median OS of patients with EMPs was 1.8 years (1.3 years in period 1 and 3.9 years in period 2) being the diference in OS statistically significant between patients with PPs and EMPs (p=0.03). The OS of patients without Ps was 3.4 years (2.6 years in period 1 and 4.8 years in period 2) which was similar to the OS of patients with PPs (p=0.5) and significantly longer than that

observed in patients with EMPs (p=0.03). The overall incidence of Ps at relapse was 21.6% (15% PPs and 6.6% EMPs). 43% of patients with Ps at diagnoses developed Ps at first or subsequent relapses versus 14.6% of patients without Ps at diagnoses (p<0.0001). The OS from the time of relapse with Ps was significantly longer in those who relapsed with PPs compared with patients who developed EMPs (median 11.4 versus 10.4 months, p=0.03). Thus, in period 1 the OS for patients relapsing with PPs or EMPs was 7.5 and 8.7 months, respectively (p=0.1) while in period 2 the OS was 20.8 and 14.5 months for patients relapsing with PPs and EMPs, respectively (p=0.08) CONCLUSIONS: EMPs are more frequent at relapse that at diagnoses (2.6% versus 6.6%) while the incidence of PPs is similar at diagnosis and at relapse (17.1% versus 15%). The development of Ps at relapse is significantly higher in patients who had Ps at diagnoses (43% versus 14.6%). Patients with PPs at diagnosis had similar survival than those without Ps while patients with EMPs had poorer outcome than those with PPs or patients with no soft-tissue involvement, both at diagnosis and at relapse.

PS-193
Transcriptional programs associated with extra-medullary tumor progression in multiple myeloma

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Multiple myeloma is an incurable cancer of plasma cells. A subset of patients acquires treatment resistance and succumbs to rapid progression. Genetic heterogeneity is suspected as a main culprit for the development of or bona fide treatment resistance. Genetic heterogeneity could be assessed by inferring sub-clonal populations from whole exome or genome sequencing of the bulk tumors or by direct detection of somatic mutations in single tumor cell DNAs. However, the DNA analysis alone cannot solve how the mutational heterogeneity contributes to the pathology or treatment resistance. In this study we explored single cell RNA sequencing to assess alterations in both genome and transcriptome upon disease progression. The results demonstrate that myeloma cells with distinctive copy number alterations in each patient, share common transcriptional signatures in the bone marrow. Myeloma cells in the extramedullary sites engage into differential transcriptional programs primarily influencing the interaction between myeloma cells and the microenvironment. Based on the results we propose diverse transcriptional programs associated with extramedullary disease progression in multiple myeloma.

PS-194
Defining clonal plasticity using whole exome sequencing in single cells in an index case of amp1q21 multiple myeloma

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Introduction Genomic-wide analysis of multiple myeloma (MM) reveals subclonal evolution as a major mechanism in disease evolution and progression, and interrogation of the entire

functional genome at the single cell (SC) level is essential to fully map intraclonal variation (ICV) and competition as the driver mechanism. To progress this, we have sought to establish whole exome sequencing (WES) in SCs in MM, initially in an index case of amp1q21 MM. Methods CD138+ tumour cells and CD3+ T-cells were isolated from a presentation case of amp1q21 MM. Single MM and T cells were isolated for single cell WES. Whole genome amplification was performed using Qiagen REPLI-g Mini kit, and exome capture was performed using Agilent SureSelect. Libraries were 90 bp PE sequenced on an Illumina HiSeq2000 (BGI, China). Data was produced for bulk (1000 cells) MM and T cells, 20 MM SCs and 5 T cell SCs. Fastq were aligned to hg19 ref sequence using NovoAlignMPI (v3.02.03). Variant calling was performed using VarScan (v2.3.6) and variants were annotated using ANNOVAR. High confidence variants were called in the bulk tumour WES by pairwise comparison with bulk germline WES and by annotation against variant databases to exclude germline variants. Multiple quality control measures were employed to minimise false positives. Results and Discussion SC WES generated raw data that were similar to bulk WES, with comparable mapping to target (69-76% SC vs. 70% bulk) and mean fold coverage (56.8-59.1x vs. 59.7x bulk). On average, 82% of the exome was covered sufficiently for somatic variant (SV) calling ($\geq$ 5x), matching seminal published SC WES studies (70-80%) (Hou et al., Cell, 2012; Xu et al., Cell, 2012). We called 33 high confidence potentially deleterious SVs in the bulk tumour, 21 of which were also called in $\geq$ 1 SC exomes. SVs include mutations in genes involved in plasma cell differentiation, the MAPK pathway and known pathways in origins of B cell malignancy. Random SVs were validated by Sanger sequencing with 100% concordance in the bulk (15/15) and SCs (55/55). ICV was apparent from the SC exome variant data. Total variant counts varied considerably among SCs and most variant positions had at least several cells where no evidence of the variant existed. Bulk WES lacks crucial information: We called 23 variants in $\geq$ 2 SCs that were absent in the bulk. Of these, 7/7 amplifiable variants were re-sequenced to obtain 100% concordance. These variants are of high interest as they reveal a marked occurrence of subclonal mutations in the MM tumour that are not identified by bulk WES. They indicate that the mutational status of the MM genome may be substantially underestimated by bulk WES. Conclusion We establish the feasibility of SC WES as a method for defining true intraclonal genetic variation as a driver of cancer plasticity in MM.

PS-195
COMPARATIVE STUDY OF 18F-FDG-PET-CT AND MAGNETIC RESONANCE IN THE DIAGNOSIS OF SMOLDERING MYELOMA AND BONE PLASMOCYTOMA

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INTRODUCTION: Imaging techniques are essential in the diagnosis of multiple myeloma (MM), smoldering myeloma (SMM) and solitary bone plasmocytoma (SBP). The detection of lesions can imply changes in diagnosis and therapeutic attitude. IMWG has defined new biomarkers in the MMS workup, including the presence of at least one focal lesion >5 mm on column or whole-body magnetic resonance (MRI). This myeloma defining-event indicates treatment requirement. Regarding the SBP, 18F-FDG-PET-CT (PET-

CT) showed to be useful for assessing bone, extraosseous involvement and to filiate a possible multiple bone plasmacytoma (MBP) requiring systemic treatment. OBJECTIVES:To evaluate the concordance of the results obtained by MRI and PET-CT with regard to location and number of lesions in patients with suspected MMS and SBP. To determine the sensitivity of PET-CT compared with MRI. To assess a relationship between the metabolic activity of PET-CT (SUV max) and ISS-R. MATERIAL AND METHODS: •PET-CT and MRI were performed on 30 patients with MMS or SBP at the time of diagnosis. The maximum time interval between both techniques was 45 days. Results were jointly evaluated by radiologists and experts in Nuclear Medicine (NM). •Positive PET-CT was defined as an abnormal increase in FDG uptake and evidence of lytic bone destruction on CT. An increased uptake value (SUV max) >4 of each lesion was considered as pathological. •A positive MRI lesion was defined as a focal >5mm image and reported by the radiologist as suggestive of MM. •The concordance between the two techniques was calculated using the kappa index. RESULTS: In twenty cases out of 30 (67%), 22 with SMM and 8 with SBP, bone alterations were detected by PET-CT and / or MRI. Eleven cases out of 22 MMS (50%), were reclassified to MM following the results of PET-CT and/or MRI. Two out of 8 SBP (25%), were reclassified to MBP and one (12.5%) met MM criteria. Discordance in positivity was observed in 5 cases: in 2 patients extraosseous involvement was only detected by PET-CT while in 3 patients focal MRI lesions were not detectable by PET-CT. Regarding the positivity/negativity of the techniques, a good correlation was found between PET-CT and MRI (k = 0.658, p <0.05). The estimated sensitivity of PET-CT versus MRI was 83%. However, in 11 out of the 15 cases with positivity in the 2 techniques, a disagreement was observed regarding location and/or number of lesions. No correlation was found between SUV max and high ISS-R (3) or type of diagnosis. CONCLUSIONS: For the diagnosis of SMM and SBP, the assessment of Radiology and NM has demonstrated a good concordance between results in MRI and PET-CT. MRI would better detect focal bone lesions and PET-CT would provide additional extraosseous information. Both studies offer complementary information on the diagnosis of MMS and SBP, allowing the reclassification of a high percentage of patients to MM or MBP.

PS-196

Length of Hospital Stay is an independent Predictor of Overall Survival in Patients with systemic AL amyloidosis

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Introduction Systemic AL amyloidosis, a rare monoclonal immunoglobulin deposition disease, has outcomes dominated by degree of end organ damage. Patients have high healthcare resource utilisation due to advanced multisystem disease at presentation. We report here that a longer length of stay in hospital predicts for markedly poorer outcomes independent of organ involvement in AL amyloidosis. Patients and Methods All patients with a diagnosis of systemic AL amyloid admitted to the Royal Free Hospital from the July 2015 to August 2016 were included in this study. All patients had detailed baseline assessments as per standard protocol at diagnosis. Organ involvement was defined according to the international amyloidosis consensus criteria and staging was done according to the 2004 Mayo classification. Data on number of admissions and length of

stay were collected. Results A total of 69 patients were included in the study (Male 39 (56.5%):Female 30 (43.5%)). The median age was 66 yrs. The number of patients dominantly Kappa light chain and Lambda light chain was 17 (24.64%) and 52 (75.36%) respectively. The number of patients that had Mayo disease stage 1, 2, 3a and 3b was 7 (10.14%), 16 (23.19%), 33 (47.83%) and 13 (18.84%) patients respectively. The median NT-proBNP was 3577.5 ng/L, creatinine 99 umol/L, and dFLC 199 mg/L. The average length of stay was 12.4 days, with a total of 23 (33.3%) death. Median number of hospital admission was 1.4 and 21 patients had more than one admission. Median overall survival was not reached for the cohort (66% at 12 months) or for Mayo stage 1 and 2 patients. Median OS for mayo disease stage 3a and 3b was 3.192 and 0.499 years respectively. The 12 month survival for patients with <8 days inpatient stay was 94% vs. 62% for those > 8 days in hospital (median OS not reached vs. 1.6 yrs respectively). Hospital admission of > 8 days was an independent variable of overall survival (HR 2.4; 95% CI 1.3-4.3; p=0.003) in a model including cardiac staging. Conclusions Although cardiac involvement is an important marker of prognosis, we report that the length of hospital admission was a significant independent variable that could predict survival outcomes, irrespective of Mayo disease stage in patients with systemic AL amyloidosis. Further studies are planned to confirm these observations.

PS-197
Novel approach to study relationship between copy number variation and gene expression in multiple myeloma

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Background: Multiple myeloma (MM) is a lymphoproliferative disease characterized by the clonal expansion of neoplastic plasma cells. The molecular pathogenesis of MM represents a complex combination of genomic alterations and massive transcriptomic shifts. Our study represents integrated omics analysis of paired datasets obtained with genomic and transcriptomic high-throughput array techniques in order to disentangle functional relationships in MM. We hypothesize that the impact of DNA copy number variants (CNV) on the gene expression (GE) is not linear and can be modulated by molecular machinery. Methods: 66 newly diagnosed (ND) and 39 relapse patients were included in the analysis after signing informed consent form. Only autosomes and segments of DNA (100 Kbp long) with frequency of gain or loss at least 10% were further investigated. CNV and GE data from microarray platforms were integrated and analysed using co-inertia analysis (CIA). CIA is a multivariate method used to examine relationship between two datasets which contain the same set of samples. Based on weights on CIA axes, only the most important features (GE and CNV) entered the correlation and regression analyses. Final regression model included CNV

as predictor and variability of GE which cannot be explained by CNV (related to GE) and ploidy status as response variable. Results and Conclusions: CIA showed stronger correspondence between CNV and GE data in relapsed (RV=0.64) compared to ND patients (RV=0.44). In summary, the most important CNVs for relapse belong to 1p, 1q, 8p, 12p, 13, 14, 16q. Deletions and gains in these chromosomes as well as their clinical impact were previously described for MM and MGUS. Regression analysis revealed transcriptome changes in CNV-unrelated genes, especially in relapse cohort. Known role in MM pathogenesis have e. g. CCND1 (11q) and CCND2 (12p) that can be affected by CNV in 1q, 13 and 1q, 4p, 13, 14, respectively. Further significant associations between the GE (on chromosome) with CNV segments are: PLK2 (5q) with 1p or 19p, VPREB3 (22) with 13 or 19p, ADAM28 (8p) with 13 or 16q and CD79A (19q) with 1q, 13, 14 or 16q. Various CNVs in 1, 4p,8p, 13, 14, 16q or 19p can also affect members of SNORD families. SNORD genes were described in MM, but their role in disease development is still unknown. In conclusion, CIA followed by regression methods confirmed that GE is not direct consequence of CNV. Association of CNV and GE on different chromosomes was revealed. This approach represents a powerful tool in understanding the interaction of genome and transcriptome and the results help to pinpoint molecular targets for further investigation of the development of pathological processes in multiple myeloma.

PS-198
RalA and RalB are potential therapeutic targets in multiple myeloma which mediate cell survival independently of oncogenic RAS

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INTRODUCTION: RAS-dependent signaling via classical pathways such as MEK/ERK and PI3K/Akt mediates cell survival in multiple myeloma (MM). Ral is considered to be a putative effector pathway downstream of oncogenic RAS, and may promote proliferation, survival and drug resistance of MM cells. We used shRNA-mediated knockdown of RalA and RalB isoforms to appraise their role as potential therapeutic targets and analyzed their interconnection with oncogenic RAS. METHODS: First, we performed immunohistochemical staining of primary bone marrow trephines of MM patients and Western blotting in MM cell lines to evaluate Ral protein expression. Next, knockdown of RalA or RalB was achieved with transient or stable transfection of MM cell lines by electroporation and the effect on cell survival and apoptosis was measured with flow cytometry using annexin V-APC/propidium iodide staining. To test potential dependence of Ral on oncogenic KRAS or NRAS, Ral pulldown assays were applied. RNA sequencing was performed to compare RAS and Ral gene expression signatures. RESULTS: Both RalA and RalB isoforms were expressed in primary MM cells and MM cells lines, with RalA showing the most prominent and consistent protein expression levels. Depletion of RalA by shRNA-mediated knockdown strongly impaired

MM cell survival in two thirds of the tested cell lines, whereas depletion of RalB induced relevant levels of apoptosis in less than half of the cells. Surprisingly, Ral activity was independent of oncogenic KRAS or NRAS as shown by pulldown assays. Concomitantly, RNA sequencing revealed differing RAS and Ral gene expression signatures.

CONCLUSION: Ral constitutes a potential therapeutic target in MM whose constitutive activation is independent of the presence of oncogenic RAS mutations.

PS-199
Clinical impact and possible immunosuppressive function of soluble B7-H1 (PD-L1) in multiple myeloma

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Introduction: B7-H1 (PD-L1, CD274), a ligand for programmed death-1 (PD-1), is expressed on many different tumor cells including multiple myeloma (MM). We demonstrated that B7-H1 expressed on MM cells inhibits tumor-specific cytotoxic T lymphocytes (CTLs) through PD-1 and becomes resistant to apoptosis induced by antimyeloma agents through B7-H1-delivered signals in tumor cells [Ishibashi M, Cancer Immunol Res. 2016]. Recently, it has been reported that high levels of soluble B7-H1 (sB7-H1) are associated with poor prognosis in aggressive diffuse large B-cell lymphoma and MM. However, the clinical impact and function of sB7-H1 in MM patients remain unclear. To clarify this, we investigated serum sB7-H1 levels and clinical characteristics in MM. Materials and Methods: 1) Concentrations of serum sB7-H1 were measured using ELISA in 97 MM patients (18 asymptomatic and 79 symptomatic) and 17 healthy volunteers. 2) The binding of the recombinant B7-H1 extracellular domain with the PD-1-expressing Jurkat T cell line was examined using flow cytometry. PD-1 expression on Jurkat cells was induced by treatment with phorbol 12-myristate 13-acetate and ionomycin. Results: Serum sB7-H1 levels in MM patients (mean±SD; 45.0±31.9 pg/ml) were significantly increased in comparison with those in healthy controls (17.4±25.3 pg/ml) (P<0.001). Moreover, the levels of serum sB7-H1 in symptomatic MM (48.5±33.4 pg/ml) were higher than in asymptomatic MM (29.8±18.1 pg/ml) (P=0.0198). However, in contrast to a previous report, there was no significant difference in sB7-H1 levels according to the Revised International Staging System score. Next, we examined the differential clinical characteristics between the high (defined as >50 pg/ml, n=41) and low (≤50 pg/ml, n=56) serum sB7-H1 groups. MM patients in the high group had a significantly greater rate of symptomatic MM and Durie-Salmon type B disease in comparison with those in the low group (P=0.0032 and 0.0058, respectively). The percentages of clonal plasma cells tended to be greater in the high than in the low group (P=0.060). Furthermore, the levels of serum sB7-H1 were not significantly correlated with levels of cell-surface B7-H1 expression on myeloma cells or B7-H1 mRNA in CD138+ cells in bone marrow (BM). However, some patients with high levels of serum sB7-H1 had high expression of cell-surface B7-H1 on BM

plasma cells. 2) Recombinant B7-H1 was bound to PD-1-expressing Jurkat cells, and its binding was inhibited by monoclonal anti-PD-1 antibody. Conclusions: High levels of serum sB7-H1 were associated with symptomatic MM but not with advanced stage indicating poor prognosis. Moreover, serum sB7-H1 may suppress the antitumor immune response via CTLs. Further studies are in progress to clarify the functions of sB7-H1 in MM.

PS-200
Immune paresis in treated Multiple Myeloma involving adaptive as well as innate immunity: monocentric experience of 120 patients with serious infectious complications retrospectively analyzed.

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Survival of multiple-myeloma(MM)patients has improved in the last decade,with persistence of immunological-impairment that deteriorates their life-expectancy.Herein we described the occurrence of severe-infectious-events of grade 3-4 in a cohort of 120 MM-patients diagnosed from 1999-to-2015 in order to assess type and outcome of infections.Five of these were life-threatening(3viral interstitial-pneumonia and 2gram-negative-sepsis),three have required intervention of intensive-care(1 viral and 1fungal-pneumonia and 1 gram-positive-sepsis) and 68 have resulted in discontinuation of therapy(respectively 34 bacterial, 29fungal,3viral and 2parasitic-infectious-complications).We focused on time of development and number of prior therapeutic-lines and on disease-biological-aggressiveness.Our aim was to define risk-

factors and correct-antimicrobial-prophylaxis.Anti-infective prophylaxis used was acyclovir with bortezomib.In our study 10-patients presented a FUO without isolation of pathogens.They were 7-elderly-patients and 3 young in neutropenic-phases.They presented defervescence following antibiotic-therapy with piperacillin-tazobactam.110 patients showed complications with an etiology(70 bacterial, 20 viral,15 fungal and 5parasitic-infections).Pathogens encountered often were:Candida-albicans followed by Candida-parapsylosis and Aspergillus-flavus inside of fungal-infections,E.coli,Klebsiella-Pneumoniae, Streptococcus-mitis between bacterial-complications,CMV,Herpes-Zoster in viral-manifestations and Leishmania among parasitic-events.Advanced-age is a powerful risk-factor togheter with biologically-aggressiveness and relapse-condition.The majority of patients were older than 65-years(68%)in a relapse-setting (70%).Only 19% were fit according to frailty-score,39% frail and the predominant part(42%) unfit.Specifically, the majority of patients developing fungal-infections(86%)presented neutropenia due to chemotherapy and to previous-therapy with ImiDs.Most of patients with viral-infections(65%)showed lymphopenia and previous therapies-bortezomib-based.Bacterial-infections have shown mostly prevalent in neutropenic-phases usually in relapse-phases (62%)or in hypogammaglobulinemic patients(72%).Finally,most of parasitic-infections have been shown after high-doses-steroid-treatment and with more than 2 therapeutic-lines(100%).Variety of factors underlies susceptibility to infections including defect of innate and adaptive-immunity(neutropenia,hypogammaglobulinemia).Need for antimicrobial-prophylaxis depends on risk for and seriousness of infections. Based on our experience,in the first three-months of therapy with IMIDs we now begin prophylactic-antibacterial and antifungal-therapy (quinolone and fluconazole).All patients treated to date(20 in total)did not require therapy-

discontinuation.High-risk-patients should receive antimicrobial prophylaxis and trials on prophylactic-measures are needed.

PS-201
Secondary malignancies in patients undergoing autologous hematopoietic cell transplant for multiple myeloma

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Introduction Advances in treatment of multiple myeloma (MM) has improved overall survival in these patients (pts).A steady increase in the risk of secondary malignancies has been reported over the last decades in MM survivors. Estimated incidence of secondary acute myelogenous leukemia or myelodysplastic syndrome (t-MDS/AML) after treatment with alkylating agents is 1% -1.5% per year 2-10 years after primary chemotherapy. Recently, novel anti-myeloma treatments have been linked with an increase in secondary malignancies, but no solid relationship has been established yet. Materials and methods In a retrospective study, we analyzed the incidence of secondary malignancies (t-AML/MDS and solid tumors) in pts suffering from multiple myeloma who had undergone autologous hematopoietic cell transplantation (HCT) using high-dose Melphalan conditioning regimen in our BMT unit. Results Study population consisted of 192 consecutive pts with median age of 55 years (29-70), 56.5% of them being male, who were transplanted during a period of 28 years (1988-2016). Type of myeloma was IgG/A/D in 56%, 18.8% and 0.5% respectively, while 17.2% was light chain and 7% non-secretory. The majority of pts presented with k light chain myeloma (62.8%). There was almost equal distribution between ISS stages I and II (45% / 38.5%) and only 16.6% were diagnosed with advanced stage myeloma. Most pts received two lines of chemotherapy (60%) and all of them more than one. Treatment regimens before autologous HCT included VAD (63pts), Bortezomib-based (133pts), DCEP (8pts) and RD (29pts) and 34 pts received radiotherapy. Chemotherapy administration for mobilization was used in 18 pts (9.3%). Conditioning regimen before autologous HCT consisted of high-dose Melphalan (200mg/m2) and in case of renal insufficiency 140mg/m2. Incidence of a secondary malignancy was 5.7% after a median follow up period of 46 months. t-AML /MDS was diagnosed in 9 (4.68%) pts and 2 (1.02%) were diagnosed with breast and lung cancer respectively. Pts diagnosed with secondary malignancy were previously exposed in induction therapy to Melphalan (6), VAD (3), Bortezomib (3), high-dose cyclophosphamide as mobilization treatment (4) and radiotherapy (4). Cytogenetic analysis was available in 6 patients diagnosed with t-MDS/AML and the majority (4/6) presented complex karyotype. Abnormalities mainly observed were deletions and insertions in chromosomes 5, 7, 17. Patients with secondary malignancies had an overall survival of 68 months (26-178), however, after malignancy was diagnosed survival was very poor, four months only (1-130). In conclusion, secondary malignancies in patients with multiple myeloma after autologous HCT occur with a substantial frequency and have dismal prognosis. The role of novel treatment agents has to be elucidated. Further studies are needed to identify new risk factors and develop better surveillance strategies.

PS-202
Top-Down Immunoglobulin Light chain Sequence Determination in Patients with POEMS Syndrome

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Background: POEMS syndrome is a rare paraneoplastic syndrome associated with plasma cell dyscrasia. Diagnosing POEMS can be difficult as it manifests with varied clinical features (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes) that are common to multiple other conditions. Currently, diagnosis of POEMS syndrome requires clinical features of polyneuropathy and the identification of a monoclonal plasma cell proliferative disorder. Additionally, one of three major criteria (Castleman disease, sclerotic bone lesions, or increased levels of vascular endothelial growth factor VEGF) and one of six minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema and either thombocytosis or polycythemia) must be present. However, prior studies found that the monoclonal protein (M-protein) expressed in POEMS patients is restricted to immunoglobulin lambda light chain variable region IGLV1-40 and IGLV1-44. This phenomenon can be leveraged to rule out POEMS from consideration in favor of more common plasma cell proliferative disorders that are not light chain restricted. Objective: The goal of this study is to develop a top-down mass spectrometry assay for determining the IGLV gene of the M-protein from patient serum. Methods: Serum proteins were denatured with trifluroethanol, reduced with dithiothreitol, and alkylated with idocoacetamide. Processed proteins were loaded and separated on a ProSwift RP-4H (500μm, x 10cm) at a flow rate of 35μl/min, using a Dionex Ultimate 3000® RSLCnano system . Eluting proteins were analyzed using a Thermo Orbitrap Elite mass spectrometer configured to look at the mass range of LCs and selecting the most abundant LC clones for fragmentation in HCD, CID, and ETD modes. Resulting protein MS/MS spectra were processed using ProSight software configured to match the fragments against a LC variable region sequence template database. For each MS/MS, ProSight reported the top scoring IGLV based on number of fragment matches. Results: We tested this method with serum samples obtained from six patients with AL amyloidosis whose pathogenic M-protein clone was sequenced using bone marrow plasma cell sequencing. The tested IGLVs are (N=3 LV1-57, N=2 LV1-44, and N=1 LV1-40). The top-down MS method successfully identified the IGLV of the pathogenic clone in four of six patients (N=2 LV1-44 and N=2 LV1-57). One sample that failed the clonotyping had very little signal upon fragmentation, suggesting that the abundance of the pathogenic clone was below our limit of detection. The IGLV clone of the second failed sample was assigned to LV1-47 (LV1-40 is the truth), a close homologue of the true clone. Conclusions: We have developed a top-down LC-MS/MS method that is capable of determining the LC gene selection of M-proteins, which should aid in the diagnosis of patients with POEMS syndrome.

PS-203
COMMON REASONS FOR CHANGE OF CHEMOREGIMENS IN MULTIPLE MYELOMA: REAL WORLD, SINGLE CENTER EXPERIENCE

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Introduction: Multiple myeloma (MM) is considered as a relapsing and remitting disease with no cure as of date. Chemotherapy is the backbone in the treatment of MM in real world scenario due to non-affordability to ASCT. We

tried to study the major reasons for the change in chemo regimens in the real world outside clinical trial setting. Aim: To analyze the factors affecting the change of therapy regimens in MM patients in real world setting. Patients and methods: It is a retrospective single center study conducted at a tertiary care center from North India. Records of all consecutive patients with MM of either gender that were managed from 01 Jan 2010 to 31 Dec 2015 were reviewed for the change of therapy and the reasons involved. JMP ver 13.0.0 (SW) was used to analyze the data. Results: The median age of the study cohort was 60y (18-88) with male predominance (61%) and a mean monthly income of INR 14608. The commonly used first-line regimens were TD (27.68%), VCD (21.8%), VTD (17.5%), MPT (6.5%), VRD (1.52%), and other combinations (25%). The chemo regimen was changed more than once in 26.5%, 9 times (n-4), 8 times (n-4), 7 times (n-4), 6 times (n-7), 5 times in (n-11), 4 times (n-13), 3 times (n-22) and 2 times (n-45). In those receiving second-line therapy, the first line therapy was changed due to clinical relapse in 25.4%, therapy related toxicity in 21.5%, biochemical relapses in 21.5%, financial non-affordability in 4.9%, development of other comorbidities in 2.9%, and loss to follow-up in 1.9%. Contrary to the belief, the commonest reason for the change of any line of therapy was the persistence of disease in 48.4%, drug-related toxicity at 45.3% and financial constraints in 6.2%. Financial constraints played an indirect role in changing chemo-regimens by influencing the choice of a suboptimal regimen. This was evidenced by the fact that finances were a major reason (79%) for choosing the type of regimen other than those dictated by the academic guidelines. Among the regimens which required a change, TD and VCD were the commonly changed first line regimens; whereas TD was the most changed 2nd line regime. Despite the toxicity (mainly neuropathy), thalidomide-based regimens were the commonly prescribed 1st and 2nd line therapy being the cheapest of all available options. Financial constraints as the cause of the change of therapy were commonest with VCD combination. The commonest cause of change more than 5th line therapy was non-responsive disease, with the same set of patients requiring up to 9th line therapy with multiple drugs. Conclusion: Change of therapy was mainly due to progression/ persistence of disease or drug-related toxicity. Financial constraint played a major role in therapeutic decision making more than the prevailing guidelines. Similar studies in larger scale in a multi-centric fashion from the real world are crucial to guide the health policy makers.

PS-204
Is 18F-FDG-PET/CT a good MRD marker in patients with multiple myeloma? Comparison and correlation with biochemical markers/ flow cytometry.

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Background: Multiple myeloma is a heterogeneous disorder with varied responses to chemotherapy. The response criteria are defined based on biochemical assays, bone marrow (BM) examination, flow cytometry and molecular assays. Lately, PET/CT is employed in MRD analysis. We aimed at studying the correlation of 18F-FDG-PET/CT with various biochemical markers, bone marrow plasma cells, and flow cytometry MRD analysis as a cross-sectional comparison at a given time point in patients post myeloma therapy. Methods: This is a single-center non-interventional study as part of PIPET-M trial. Patients with multiple myeloma underwent 18F-FDG-PET/CT, the biochemical evaluation including (SPEP, UPEP, SIFE, SFLC, β2M, LDH) and BM examination (for plasma cells percentage and flow cytometry

for MRD) as part of the end of treatment analysis. Patients were included after induction chemotherapy, pre-autologous transplant (within 30 days) or post-transplant (Day 100) for analyzing the efficacy of therapy. PET-positivity was based on the PIPET-M staging (A validated staging system developed by the authors). Results: A total of 72 patients were screened of which 52 patients underwent PET/CT, the biochemical evaluation including (SPEP, UPEP, SIFE, SFLC, β2M, and LDH) and bone marrow examination. Concurrent flow cytometry for MRD was done only in 11 patients. PET positivity had no relation with the pre-transplant biochemical markers (SPEP, UPEP, SIFE) [{chi}2 - (1, 53)-0.34, p-0.56; (1, 52) - 2.18, p-0.14; (1, 52) – 0.32, p-0.57 respectively] or BM plasma cell percentage (p-0.64). In PET positive patients, β2M and LDH were higher (p - 0.032), whereas SFLC ratio though higher was not statistically significant (p-0.61). There was a good agreement between PET positivity and MRD by flow cytometry (Cohen's {kappa} - 0.662, p < 0.001). Conclusions: 18F-FDG-PET/CT is a good marker for MRD analysis with good agreement with flow cytometry and disease activity markers such as β2M/ LDH. It's poor correlation with SPEP, UPEP, SIFE and BM plasma cell percentage can be secondary to undetectable levels of these markers in many patients (~ 84%) after therapy. A comparison of these markers for prognosticating PFS/OS is further warranted. Clinical trial information: U1111-1177-8850, REF/2015/12/010356.

PS-208
Prevalence and Predictors of Treatment Among Newly Diagnosed Symptomatic Multiple Myeloma (NDMM) Medicare Beneficiaries in the U.S.

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Objective:We assessed the prevalence of, and determinants associated with receipt of cancer-directed therapy among NDMM Medicare beneficiaries. A previous study in the Surveillance, Epidemiology, and End Results (SEER) cancer registry found that among all adults with MM diagnosed in 1999, 2003 and 2007, 29%, 34% and 19% did not receive MM-directed treatment (Warren, et al. JNCI, 2015). Methods:This retrospective cohort study used SEER-Medicare data to identify patients (pts) >65 years with NDMM between 2007-2011 and continuous enrollment in Medicare Parts A and B (12 months [mos] pre-) and in Part D (2 mos pre-) through 6 mos post-diagnosis (dx). Pts with CRAB symptoms at dx (hypercalcemia, renal insufficiency, anemia and bone disease) found based on ICD-9 dx codes in claims from 6 mos pre- to 1 mo post-MM dx were selected and followed until death or censoring due to non-continuous Medicare enrollment. We excluded pts who died within 6 mos. MM drug therapy was identified from claims during the follow-up period using billing codes: bendamustine, bortezomib, cisplatin, cyclophosphamide, (liposomal) doxorubicin, interferon, etoposide, lenalidomide, melphalan, thalidomide, vincristine, vorinostat and dexamethasone monotherapy (>90 days), or stem cell transplant. Charlson Comorbidity Index (CCI) was derived based on claims within 1 year pre-dx. Baseline characteristics were compared using t-tests and Chi-square tests. Multivariable logistic regression was used to evaluate predictors of treatment. Results:Of 3,641 NDMM pts, 943 (25.9%) died within 6 mos of dx. Among 2,698 pts surviving at least six mos, 2,156 (79.9%) received MM-directed therapy during follow up.

Those who initiated therapy were younger compared to untreated pts (mean age: 75.8 vs 79.3 years), had a lower comorbidity burden (CCI 2+: 34.9% vs 52.5%), and were more likely to be married (p<.001 for all). Among those who did vs did not receive treatment, 14% vs. 21% were African American (p=0.001). Cardiovascular disease at baseline was more prevalent among untreated (50%) versus treated (38%) patients (p<0.001). In multivariate analysis adjusted for year of dx and CRAB symptoms, the odds of treatment decreased with older age, African American race, Medicaid dual eligibility, higher CCI score and cardiovascular disease prior to dx. Married pts were more likely to receive treatment. Of those who did not receive treatment 15% used hospice in the 12 mos following dx versus 8% of those who did receive treatment (p<.001). Conclusion:Among NDMM pts >65 years, ~20% did not receive MM-directed therapy. Treatment was associated with younger age and a lower comorbidity burden. Racial disparities, with a lower proportion of African American pts treated were also observed. Future research is needed to assess the extent to which these determinants reflect patient preferences versus other factors, such as barriers to treatment access.

PS-210

Absolute Lymphocyte Count and Immunoparesis: Impact on clinical outcomes for non-transplant eligible MM patients

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Introduction Recent studies have demonstrated that absolute lymphocyte count (ALC) and Immunoparesis (decrease of uninvolved Immunoglobulins) are prognostic indicators of survival in some hematological malignancies. Based on the above mentioned we aim to assess the role of ALC and Immunoparesis on survival outcomes (Overall and Progression-Free Survival) for MM patients that are not eligible for ASCT (NTE) treated at our Institution. Methods All consecutive NTE patients treated at our center from 01/2008 to 10/2016 were evaluated. Definitions of response and progression were used according to the EBMT modified criteria. ALC was assessed as a continuous variable and dichotomized, based on finding the optimal cut-off point based on the log-rank statistics. Two-sided Fisher exact test was used to test for differences between categorical variables. Survival curves were constructed according to the Kaplan-Meier method and compared using the log rank test. A p value of <0.05 was considered significant. All statistical analyses will be performed by using the SPSS 22.0 software. Results Clinical characteristics are shown in Table 1. 161 consecutive NTE MM cases were evaluated. At the time of analysis, 49.7% (80 patients) are still alive and 98 (60.9%) have already progressed. Immunoparesis at diagnosis was observed in 88.7% of cases. Involvement of 2-3 Ig's was seen in 58.2% of patients. Furthermore, median ALC at diagnosis was 1.3× 109/l; and 8.1% of cases exhibited severe lymphopenia (<0.5× 109/l). Median OS was similar irrespective of the degree of immunoparesis (p=0.9) and ALC (p=0.2). In addition, median PFS did not differ among patients with immunoparesis and ALC <0.5× 109/l compared to those without immunoparesis and ALC> or equal to 0.5× 109/l (p=0.6 and 0.1, respectively). Different cut-off values were assessed for ALC with similar results (> or < 0.8, 1.0, 1.4, 1.5 and 2.0) In conclusion, Immunoparesis and ALC, although described as important predictors of clinical outcomes in patients with MM, did not appear to be good prognosticators in the setting of NTE MM. Prospective studies assessing subset of cells and/or immunoglobulin reconstitution after therapy are warranted. Table 1. Clinical

Characteristics of NTE MM patients treated at TBCC Characteristic N=161 Age (median) 74.4 Gender Male Female 96 (59.6%) 65 (40.4%) Hb (g/L) 106 Calcium (μmol/L) 2.34 Creatinine (μmol/L) 104 B2microglobulin (μmol/L) 4.38 Albumin (g/L) 31 Absolute Lymphocyte Count (median) 1.3 Stage I Stage II Stage III 16.4% 45.9% 37.7% LDH (IU/L) 176.5 BMPC (%) 30% Treatment regimen: CyBorD VMP Lenalidomide and Dexamethasone Bortezomib and Dexamethasone 31.1% 26.1% 19.3% 23.6% Immunoparesis 0 1 2 3 ALC >0.5

PS-205
Oligosecretory and non-secretory multiple myeloma: Incidence, Clinical characteristics and Outcomes

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Patients with multiple myeloma (MM) that present at diagnosis with serum monoclonal protein (MIg) of <1 g/dl and a urine MIg level <200 mg/day (defined as oligosecretory MM) or, less commonly, with negative tests in serum and urine for the presence of a monoclonal protein (non-secretory) are commonly excluded from participation in clinical trials due to "undesirable disease". The serum FLC assay can be used to monitor many of these patients, if FLC ratio is abnormal and the involved FLC level is ≥100 mg/L. There is, however, a concern whether patients with oligosecretory or non-secretory disease may have different biology and outcomes than patients with "secretory" MM. Among 652 consecutive patients with complete baseline data on serum and urine PEP and immunofixation electrophoresis, who were diagnosed and treated in the Department of Clinical Therapeutics (Athens, Greece) from 2006 to 2015, we identified 52 (8%) patients with serum MIg<1 gr/dl and urine MIg<0.2 gr/day (oligosecretory), including 14 (2%) with negative serum and urine immunofixation (non-secretory). Compared to patients with secretory MM, patients with oligosecretory MM were younger (p=0.09), had less often anemia (p<0.001) or severe renal dysfunction (p=0.05), less extensive bone marrow plasma cell infiltration (p=0.013), high risk cytogenetics [any of del17p, t(4;14) or t(14;16)] (in 10% vs 23%, p=0.1) and were more often ISS-1 (p<0.001); the respective revised-ISS disposition in stages -1,-2 and -3 was 30%, 55% & 15% vs 17%, 62% & 22% respectively (p=0.12). Incidence of lytic bone disease was similar (p=0.22), as well as the extent of bone disease (p=0.13), but hypercalcemia (calcium≥11.5 mg/dl) was less common (6% vs 12%, p=0.17). Median involved FLC (iFLC) for patients with oligosecretory disease was 378 mg/l (range 3-2350) and 66% had iFLC ≥100 mg/L. Treatment was similar to that of other MM patients. Median follow up is 50 months; the 5-year OS for patients with oligosecretory disease is 58% vs 48% for the rest of the patients (p=0.3). Patients with non-secretory disease (both serum and urine immunofixation negative) compared to other MM patients, were younger (p=0.02), less anemic (p=0.013), only one patient (7%) had eGFR<30 ml/min (vs 23%, p=0.17), were more often ISS-1 (50% vs 24%) than ISS-2 (21% vs 33%) or ISS-3 (29% vs 43%) (p=0.08), had similar bone marrow plasma cell infiltration, but, lytic bone disease (92% vs

75%, p=0.15) and hypercalcemia were more common (21% vs 12%, p=0.25). No high risk cytogenetics were detected in patients (n=5) with available iFISH. Only 2/12 patients had normal FLC ratio and thus could be rated as "true" non secretory myeloma. The other patients had abnormal FLC ratio and 6/12 had iFLC≥100 mg/L. Patients with "non-secretory" myeloma had a trend for longer survival (5 year OS 68% vs 48% for the others, p=0.12).

2. Therapy and Outcomes

PS-206
Prior Lenalidomide Resistance and the Impact of IMiD-free interval in patients treated with Pomalidomide and Dexamethasone

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Pomalidomide with low dose dexamethasone (Pd) is a standard treatment for patients who have failed both Lenalidomide (LEN) & Bortezomib (BOR). However, it remains unclear what is the activity of Pd when administered immediately after refractoriness to LEN and what is the impact of the time from the administration of LEN to initiation of Pd (IMiD-free interval). We analyzed the outcomes of 116 consecutive MM patients after failure of both LEN & BOR who received pomalidomide 4 mg with weekly dexamethasone. Median age was 62 years (range 38-86), median number of prior treatments was 4 (range 1-9), 58% had prior ASCT, 73% were refractory to last BOR regimen and 90% refractory to last LEN regimen. All patients had MM refractory to the last regimen, but 40% had achieved a ≥PR before development of refractoriness. Just prior to Pd BOR was given in 62 (53%), LEN in 35 (30%) and conventional chemo in 19 (17%) patients. On intent to treat, 34 (29%) achieved ≥PR (CR:3%, VGPR:7%, PR:19%). Patients who received LEN just prior to Pd had ≥PR rate of 26% vs 33% if had BOR and 21% for other regimens(p=0.55). Among patients with<="" div="">

PS-207 (d)
Daratumumab, Lenalidomide and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in RRMM Based on Prior Lines and Treatment Exposure: POLLUX

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Introduction: Daratumumab, a human CD38 IgGκ monoclonal antibody, demonstrates efficacy and tolerability as a single agent or with established standard of care regimens for RRMM. To assess whether patients who have relapsed or become refractory to established standard of care regimens benefit from subsequent DRd treatment based on prior lines of therapy (LOT), subgroups were analyzed within the POLLUX study. Methods: Patients with ≥1 prior LOT were randomized (1:1) to receive Rd (lenalidomide 25 mg PO on Days 1-21; dexamethasone 40 mg PO weekly) ± daratumumab (16 mg/kg IV once weekly for 8 weeks, every 2 weeks for 16 weeks, then every 4 weeks until progression). Lenalidomide-refractory patients were not eligible. Using next generation sequencing, cytogenetic risk status was defined as having any of t(4;14), t(14;16), or del17p abnormalities. Results: Patients received a median (range) of 1 (1-11) prior LOT; 52% received 1 prior LOT and 6% received >3 prior LOT. 18% were lenalidomide-pretreated and 21% were refractory to bortezomib. After median follow-up of 17.3 months, DRd significantly prolonged progression-free survival (PFS) compared with

Rd (median not reached [NR] vs 17.5 mo; HR, 0.37; 95% CI, 0.28-0.50; P<0.0001). PFS was significantly prolonged among patients who received DRd >12 months after last prior treatment vs Rd (median NR in both groups; HR, 0.37; 95% CI, 0.23-0.61; P<0.0001) and among patients who received DRd ≤12 months after last prior treatment vs Rd (median NR vs 10.3 mo; HR, 0.38; 95% CI, 0.26-0.55; P<0.0001). Overall response rate (ORR) was significantly higher for DRd vs Rd in the >12 month subgroup (96% vs 86%; P=0.0038) and ≤12 month subgroup (90% vs 66%; P<0.0001). Among lenalidomide-pretreated patients receiving 1 to 3 prior LOT (DRd, n=46; Rd, n=45), PFS was also significantly prolonged with DRd vs Rd (median NR in both groups; HR, 0.45; 95% CI, 0.20-0.99; P=0.042); 18-month PFS rates were 79% vs 59%, respectively. Higher ORR (87% vs 67%; P=0.022) and minimal residual disease (MRD)-negative rates (28% vs 4% at 10–5 sensitivity; P=0.0013) were observed with DRd vs Rd. In patients who were refractory to bortezomib receiving 1 to 3 prior LOT (DRd, n=54; Rd, n=49), significantly longer PFS was observed in DRd vs Rd (median: NR vs 10.3 mo; HR, 0.51; 95% CI, 0.28-0.91; P=0.021); 18-month PFS rates were 65% vs 40%. ORR was 92% in DRd and 68% in Rd (P=0.0024), with higher MRD-negative rates in DRd vs Rd (22% vs 6% at 10–5 sensitivity; P=0.017). Additional efficacy data, including analyses by MRD and risk status across various subgroups, will be presented at the meeting. Conclusions: DRd significantly improves outcomes for RRMM patients regardless of time since last therapy, prior exposure to lenalidomide, or refractoriness to bortezomib. These results suggest DRd can be sequenced after patients relapse while on lenalidomide or become refractory to bortezomib.

PS-209
Predictors of Treatment (tx) with Triplet First-Line Therapy (1LT) among Transplant-Ineligible Patients (pts) with

Newly Diagnosed Multiple Myeloma (NDMM) in Routine Clinical Care

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BACKGROUND: Triplet tx with immunomodulators (IMIDs) & proteasome inhibitors (PIs) is an increasingly accepted strategy to optimize outcomes in NDMM. But use of triplet 1LT (T1LT) in routine care has not been systematically examined. We assessed adoption of & factors influencing tx choice with T1LT in a US cohort of NDMM pts. METHODS: In this retrospective electronic medical record database study, adult NDMM pts starting 1LT between 1/1/2008 & 12/31/2015 were identified using ICD-9/10 diagnosis (dx) codes and followed 1 year (yr) prior to dx to death/loss-to-follow-up/or end-of-study. Pts having 1LT transplant were excluded. Induction 1LT was defined as: PI-based: bortezomib or carfilzomib; IMID-based: lenalidomide, thalidomide, or pomalidomide; or Other: dexamethasone (dex) mono-tx >90 days, bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine. T1LT included any 3+ drug regimen; nonT1LT included any 1-2 drug regimen. CRAB symptoms (renal insufficiency [RI], anemia, bone disease [dz], & hypercalcemia [HC]) were identified with ICD codes or labs within 6 months (mo) prior to 1 mo post-dx. Charlson comorbidity index (CCI) was derived from ICD dx codes within 1 year pre-dx. High-risk (HR) cytogenetics were defined as del(17p), t(4;14), t(14;16), &/or 1q21 gain. Logistic regression was used to estimate odds ratios (ORs) & 95% confidence intervals (CIs) for predictors of T1LT use. RESULTS: Among 2070 NDMM pts, 631 pts (30.4%) initiated T1LT with PI+IMID+other (35.8%), PI or IMID+others (62.0%), or Other (2.2%). In 1439 pts (69.5%) with nonT1LT, the majority of regimens were: PI+/-other (43.9%; largely bortezomib+/-dex), IMID+/-other (38.4%, largely lenalidomide+/-dex), & other (12.7%). The T1LT group was younger (mean age: 67.3 vs 71.3yrs), more likely to have known HR cytogenetics (15.9% vs 8.2%), HC (27.6% vs 22.2%), & bone dz (38.0% vs 30.7%) than the nonT1LT group (P<0.01, for all), but a similar CCI score (mean: 1.2 for each). The use of T1LT increased significantly over the study period (P<0.01) with 25% in 2008 & 39% in 2015. In multivariate analysis (adjusted for gender, race, yr of dx, anemia, bone dz, RI, HC), younger age (<75 yrs) & HR cytogenetics were associated with higher odds of T1LT (OR: 2.22 [95%CI: 1.78, 2.78]; OR: 2.15 [95%CI: 1.58, 2.93], respectively; P<0.0001). A significant geographic variation was noted with lower likelihood of T1LT use in the Southern (OR: 0.44 [95%CI: 0.35, 0.57]) & Western (OR: 0.61 [95%CI: 0.41, 0.57]) but not Northeastern (OR: 1.15 [95%CI: 0.84, 1.56]) compared to Midwest region. CCI, ISS stage, & cardiovascular dz were not independently associated with receipt of T1LT. CONCLUSIONS: In this NDMM cohort, use of T1LT increased in latter yrs, but most pts still did not receive T1LT in routine care. Younger age, HR cytogenetics, & geographic region but not comorbidity status influenced tx choice with T1LT.

PS-211
Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) induction followed by ASCT with Bor-HDM conditioning regimen: A single center experience

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Introduction Preclinical and clinical data suggest that bortezomib in combination with high-dose melphalan (Bor-HDM) provides with a synergistic effect able to improve response for MM patients undergoing auto-SCT. In the present study, patients receiving Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) induction followed by ASCT with Bor-HDM were evaluated. Methods All consecutive patients treated with CyBorD induction at our center from 01/2010 to 10/2016 were evaluated. All patients received induction chemotherapy before undergoing auto-SCT. Patients received conditioning with HDM at 200 mg/m2 (or adjusted as per renal failure) and Bortezomib at 1 mg/m2 to 1.3 mg/m2 (as per physician discretion) on days −5, −2, 1, and 4 (Bor-HDM). Definitions of response and progression were used according to the EBMT modified criteria. MRD negativity was assessed by flow cytometry at day-100 post-ASCT. Results Clinical characteristics are shown in Table 1. 109 consecutive MM cases receiving CyBorD induction were conditioned with Bor-HDM. At the time of analysis, 92.1% (101 patients) are still alive and 17 (15.6%) have already progressed. At day-100 post ASCT, 96 patients were evaluable for response. Briefly, ORR of 98%, with CR/VGPR rate of 82.2% was seen in the Bor-HDM group. MRD negative CR was observed in 32.6% of cases at day-100 post-ASCT. Median OS and PFS have not been reached with a median follow-up of 18.1 months. In conclusion, CyBorD followed by Bor-HDM is an efficacious approach for patients with MM and overall seemed to be well tolerated. Our data is one of the first to show the impact of this regimen on MRD negativity rates after receiving Bor-HDM conditioning, suggesting that higher rates of MRD negativity

are seen with Bor-HDM compared to our historic control group (data not presented). Further evaluation on a prospective manner and longer follow-up is required to assess the impact of Bor-HDM on OS and PFS. Table 1. Clinical Characteristics of patients with MM undergoing single auto-ASCT treated with CyBorD induction at our Institution Characteristic Bor-HDM (109) Age (median) 58 Gender Male Female 70 (64.2%) 39 (35.8%) Hb (g/L) 104 Calcium (μmol/L) 2.33 Creatinine (μmol/L) 86 B2microglobulin (μmol/L) 3.2 Albumin (g/L) 32 Stage I Stage II Stage III 25 (22.9%) 51 (46.8%) 33 (30.3%) LDH (IU/L) 174 BMPC (%) 40% Heavy chain: IgG IgA IgD Biclonal IgM FLC oncly 52 (47.7%) 29 (26.6%) 0 1 (0.9%) 1 (0.9%) 26 (23.9%) Light chain: Kappa Lambda Biclonal 63 (57.8%) 45 (41.3%) 1 (0.9%) High risk (t(4;14), t(14;16), p53 del, del 13q by CC Standard risk 28.7% 71.3%

PS-212
Diffusion Weighted Whole Body MRI for evaluation of early response in Multiple Myeloma

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Background. Magnetic resonance imaging (MRI) has been included into the procedures needed to define active myeloma, according to the presence of more than one focal lesion. Myelomatous lesions in MRI can show two main patterns of bone marrow involvement i.e. focal or diffuse, that might also coexist in the same patient. Whole body Diffusion Weighted Imaging (DWI)-MRI represents a non ionizing radiation imaging modality for quantitative evaluation of disease burden. The aim of this study is to evaluate the modifications of the Apparent Diffusion Coefficient (ADC) in myelomatous lesions of active MM patients before and after induction therapy and the correlation with patient response to induction treatment according to IMWG criteria. Material and Methods. We prospectively evaluated a homogeneous cohort of 18 patients with diagnosis of active MM eligible for ASCT. All patients underwent WB DWI-MRI before and after induction chemotherapy (mean 21 weeks, range 14-24). Quantitative analysis of ADC maps of myelomatous lesions was performed according to focal and diffuse patterns. Lesions were evaluated by quantitative image analysis including measurement of the mean ADC. Imaging results were compared to laboratory as determined by the clinical gold standard. Results. At the baseline DWI-MRI evaluation, ten out of 18 patients presented only a diffuse pattern while in the remaining 8 cases the coexistence of focal lesions with diffuse pattern (7 cases) or presence of focal lesions only (one case) was documented. Analysis involved 79 lesions, with a number of measurements per patient ranging from 1 to 8 (mean 4.39 ± 2.03). All patients were treated with bortezomib-based

three drugs induction therapy obtaining an ORR of 78% including 2 VGPR (14%) and 5 CR (35%). At the end of induction, a statistically significant increase of ADC values was demonstrated in DWI-MRI in therapy responding patients (average of Δ(ADC): 0.32 ± 0.73 in responders and -0.06 ± 0.36 in non-responders). More specifically, focal lesions showed a strongly significant increase of ADC in responders (OR=16.2, 95% CI 3.87-67.4, p-value=0.0001), whereas any significant variation in non-focal lesions ADC between responders and non-responders group was demonstrated (OR=0.93, 95% CI 0.17-5.18, p-value=0.94). Discussion. In this study, in a homogeneous series of newly diagnosed active MM patients eligible to ASCT, we provided evidence that changes of ADC value following induction therapy could be a predictor of the early therapy response, provided that focal lesions are considered. Although our results are preliminary, initial clues are promising for investigating the use of this technique as an additional quantitative tool for a better definition of early response to therapy, opening new scenarios in the selection of patients who might potentially benefit from different therapies.

PS-213
Second Stem Cell Transplant in Multiple Myeloma: 15 year data from transplant centre from India

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Introduction: Majority of myeloma patients treated with an initial Autologous stem cell transplant (auto-SCT) eventually relapse. Second SCT has been utilized as part of care of relapse and high risk Myeloma patient. Patients who relapse early after 1st HCT are difficult to

salvage with repeat auto-HCT. Alloeneic SCT (Allo-SCT) is experimental and can be offered to selected patients with early relapse post 1st auto-HCT. We, hereby present our data of second transplant in myeloma. Material and methods: This is a retrospective study, whereby records of all patients who underwent ASCT at our centre from the year 2003 to 2016 were analysed. Those who underwent second transplant were included. Results: A total of 141 patients received 1st ASCT during study period. Out of 141 patients, 9 patients (6 males, 3 females) underwent a second stem cell transplant (allogeneic 3 and autologus 6) either to salvage (3 allo and 3 auto) or as a part of planned tandem transplant strategy (n=3). The median age was 55yr (34-67 yr) and 4 were ISS 3. Median interval between transplants was 522 days (119-1931), with 4 patients in PR and 5 in VGPR/CR prior to transplant. Mean time to progression after first ASCT was 27 months (8-46). Conditioning regimen was Fludarabine-Cyclophosphamide (n=2) or Fludarabine-Melphalan (n=1) for allogenic and high dose Melphalan (140-180) in ASCT. Plerixafor was used for stem cell mobilization in 4/6 ASCT. Mean CD 34 dose was 4.6 x 10*6cells/kg (2.34 – 6.8 x 10*6cells/kg). Median of 12 and 13 days were required to achieve neutrophil and platelet engraftment respectively. All patients had febrile neutropenic episodes, with gram negative sepsis in two of them. Best response post-transplant was more than VGPR in all patients. Time to relapse was 454 days and 694 days in two ASCT patient, while other 4 are yet to relapse and average 114 days in Allo transplants patients (managed with DLI + chemotherapy with variable response). Post allogenic transplants, all patients had severe graft vs host disease, and two of them have succumbed to GvHD related complications. Median Progression Free Survival post second HCT was 10 months (2-23). Conclusion: Second ASCT is a feasible but rarely utilized option in Indian settings with acceptable mortality and response rates. Allogenic SCT have transient responses, complicated by severe graft vs host disease and

early relapses; requires more experience. Option of collecting enough stem cells and freezing them for later use should be kept open in patients undergoing 1st auto-HCT.

PS-214
Survival Outcomes of Younger (≤ 50 years) Myeloma Patients

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Introduction: Multiple myeloma is a disease affecting the elderly, with a median age of diagnosis of 71 years. With the advent of novel therapies and increasing use of high dose therapy (HDT)/ autologous stem cell transplant (SCT), outcomes among the elderly myeloma patients have been improved significantly, and majority may be live to their full life-expectancy. Similar survival expectations among younger patients to achieve their life expectancy seems implausible goal. We have evaluated the survival outcomes of younger myeloma patients (≤ 50 years) in the current millennium to evaluate the benefit this specific group has achieved with the modern myeloma regimens. Methodology: Of the 2931 patients diagnosed with plasma cell dyscrasias from 01/2000 until 12/2014, we identified 414 younger patients (≤ 50 years) of myeloma who were seen and treated at Winship Cancer Institute, Atlanta. Labs at initial diagnosis, risk status, induction regimens, transplant and maintenance status, progression and overall survival results were obtained from the myeloma database. Statistical analysis including survival statistics were generated using SAS Version 9.4. Results: Of the 414 patients (212M,

202F) included in the analysis, 193 (47%) are African American and 167 (40%) are Caucasian. The diagnostic presentation includes ISS stage 3 disease: 116 patients (28%), high-risk disease: 65 patients (15.7%), anemia: 114 patients (27.5%), hypercalcemia: 64 patients (15.5%) and renal failure: 61 patients (14.5%). 192 patients (47%) received a three-drug induction regimen, 355 patients (86%) underwent an autologous SCT and 219 patients (53%) received a maintenance regimen. 76 patients (18%) and 8 patients (2%) received second and third autologous SCTs respectively. 87% patients achieved ≥VGPR as the best response. The median PFS1 (First progression free survival) is 48.9 months (median follow up: 60 months) and median OS (Overall survival) is 166 months (median follow up: 65 months). 5-year relative OS is 81.6% and 10-year relative OS is 57.6 %. The OS is differed by risk group (high risk vs standard risk - 106 vs 130 months, p=0.007) and by maintenance (yes vs no - 175 vs 109 months, p=0.001). Median OS for patients with del 17p is 75 months and for patients with t (4;14) is 106 months. 7 patients developed SPM- Secondary primary malignancies (4 patients received IMiD maintenance). Conclusion: 5-year and 10-year relative survival rates are 82% and 58%, respectively for the younger myeloma patients. These rates have been significantly improved from the IMWG report of 10-year relative survival rates of 43% among patients receiving autologous SCT (Ludwig, 2008). Patients who were standard risk and those that received maintenance have significantly higher OS. Median OS of 166 months and PFS1 of 49 months certainly reflect the impact of the modern therapeutic myeloma agents on the survival of younger patient population.

PS-215
Efficacy and Tolerability of the Histone-Deacetylase Inhibitor Panobinostat in Clinical Practice

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The histone-deacetylase inhibitor panobinostat (PAN) has shown efficacy in phase II and III trials for multiple myeloma (MM) and has gained market approval in combination with bortezomib (BTZ) and dexamethasone (DEX). We retrospectively report our single center experience with PAN/BTZ/DEX (FVD) in a heavily pretreated patient population (n=24) with a high degree of proteasome inhibitor (PI) and IMiD refractoriness. The median age at treatment initiation was 67 years (range 49-87) and the number of prior lines of treatment was 5 (range 2-17). Fourteen patients (58%) had high risk cytogenetic aberrations according to fluorescence in situ hybridization diagnosed at any time before FVD initiation and 11 of 20 patients (55%) evaluable for ISS at diagnosis had stage II/III disease. PI and IMiD refractoriness was present in 13 (54%) and 21 (88%) patients, respectively. Twelve patients (50%) were refractory to BTZ and 7 (29%) to carfilzomib (CFZ); 6 patients (25%) were double refractory to BTZ and CFZ. In 22 evaluable patients, overall response rate (≥ PR; ORR) was 32% (7/22) and clinical benefit rate (≥ MR; CBR) was 50% (11/22). Median progression free survival (PFS) and overall survival (OS) were 3.3 and 9.8 months. Marked differences between BTZ sensitive and BTZ refractory patients were observed. ORR was 64% (7/11) vs. 0% (0/11) and CBR was 73% (8/11) vs. 36% (4/11), respectively; 73% (8/11) of the BTZ refractory patients achieved at least SD. Median PFS was 6.3 vs. 1.7 months and median OS immature vs. 5.1 months in BTZ sensitive and BTZ refractory patients,

respectively. The only patient refractory to CFZ but sensitive to BTZ achieved VGPR and PFS of 6.3 months, suggesting discrete mechanisms of resistance to different PIs. Fatigue/asthenia was reported by 82% of patients and was mainly CTCAE grade 2 (52%). Thrombopenia occurred in 95% and was mainly grade 3/4 (85%). Diarrhea was reported by 19% and was grade 1/2 in all cases. Peripheral neuropathy newly occurred or worsened in 29% with 24% grade 1/2. Other adverse events with grade ≥ 3 included atrial fibrillation (2x), liver failure and hypocalcemia,. Nineteen patients (79%) initiated treatment with full dose PAN; doses were reduced and/or discontinued either upfront or during treatment in 16 patients (67%). In conclusion, FVD showed efficacy in a heavily pretreated MM patient population with a high degree of high risk patients and patients refractory to novel agents including PI. With dose reductions in a significant proportion, treatment was tolerated by most patients. However, caution should be exercised especially in elderly patients with restricted general condition where upfront dose reduction seems an appropriate measure to reduce the risk of severe adverse events. Efficacy also in patients refractory to the second generation PI CFZ warrants further investigation of FVD in this difficult to treat patient population.

PS-216
High cut-off hemodialysis combined with bortezomib-based therapy in multiple myeloma patients with severe renal impairment

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Severe renal impairment is a defining feature of symptomatic multiple myeloma (MM) and an adverse prognostic factor. Rapid initiation of anti-MM treatment, especially with bortezomib (BTZ)-containing regimens improves renal function and prognosis. High cut-off hemodialysis (HCO-HD) reduces serum free light chain (SFLC) levels and thereby may alleviate renal toxicity. Several uncontrolled and/or retrospective analyses have suggested a benefit for the addition of HCO hemodialysis in the treatment of MM patients with severe renal impairment; however the first randomized controlled trial (EuLITE) recently demonstrated no benefit of HCO vs. conventional hemodialysis when combined with BTZ-based therapy. In this single-center retrospective analysis we report the Heidelberg experience with HCO-HD and BTZ-based therapy. Twenty-nine MM patients with severe renal impairment received HCO-HD in combination with systemic therapy between 2010 and 2016. Twenty-four patients (83%) had newly diagnosed MM (NDMM) and 5 (17%) relapsed and/or refractory MM (RRMM). Median serum creatinine was 6.1 mg/dl and median glomerular filtration rate (GFR) according CKD-EPI was 8.1 ml/min. Median involved sFLC level was 9195 mg/l and cast nephropathy was confirmed in all patients who underwent kidney biopsy (n=27; 93%). HCO-HD was initiated within a median of 5 days (range 1-14) after hospital admission and performed for a median of 10 sessions (range 4-22). Systemic therapy was initiated a median of 6 days (range 0-21) after hospital admission and contained BTZ in 28 patients (97%), most frequently in combination with cyclophosphamide and dexamethasone (VCD; 66%) or doxorubicine and dexamethasone (PAD; 21%). Twenty-six patients (90%) achieved ≥ PR in a median of 10 days and 21 patients (72%) achieved ≥ VGPR. Median reduction in sFLC level at day 12 and at the time of maximum reduction were 89% and 99%, respectively, resulting in a median sFLC level of 742 mg/l and 84 mg/l, respectively. Nineteen patients (66%) became hemodialysis-

independent after a median duration of 13 days (range 7-128), whereas 10 patients (34%) required permanent hemodialysis. In patients achieving hemodialysis independence renal function improved from a median GFR (CKD-EPI) of 9.7 ml/min to 69.6 ml/min. Eighteen of 19 patients (95%) who became dialysis independent achieved a reduction of sFLC to 500 mg/l or less as compared to only 4 of 10 patients (40%) who required permanent dialysis. The median lowest sFLC level during treatment was 27 mg/l and 465 mg/l in hemodialysis independent and dependent patients, respectively; time to PR was 10 and 17 days, respectively. In conclusion, HCO-HD in combination with BTZ-based therapy resulted in hemodialysis independence in 66% of patients. Patients becoming hemodialysis independent had a shorter time to PR and a deeper reduction of sFLC levels than patients who remained on permanent hemodialysis.

PS-217
Early Bortezomib Failure Predicts Shorter PFS: A retrospective analysis from 4 tertiary centres in Victoria, Australia

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Aim: To compare patients with newly diagnosed multiple myeloma (NDMM) with bortezomib responsive and resistant disease (defined as <PR after 2 cycles) and assess the impact on clinical outcome particularly progression-free survival (PFS) and overall survival (OS).

Method: Retrospective review of all patients identified with NDMM treated with upfront bortezomib in four tertiary centres in Victoria, Australia between 1st of January 2009 and 1st of March, 2016. Bortezomib responsiveness was defined as achievement of PR or better after completing 2 cycles of any bortezomib containing therapy (total eight doses of bortezomib). Prior radiotherapy was allowed. Data were analysed via log rank tests for PFS and OS using SAS (V9.4) software. Predictors of bortezomib resistance were assessed by chi-square analysis.

Result: A total of 187 eligible patients were included (147 bortezomib responsive and 40 bortezomib resistant patients). Bortezomib resistance was associated with shorter median PFS, 27.4 (95%CI: 16.3, 30.8) vs 30.4 (95%CI: 23.4, 37.1) months (log-rank p= 0.047) with a median potential follow up of 27.4 vs 29.7 months in the resistant and responsive groups respectively. Estimated PFS at 12 months was 68.0% (95%CI: 50.3%, 80.5%) vs 88.3% (95%CI: 81.2%, 92.8%) and, at 24 months, 60.4% (95%CI: 41.7%, 74.7%) vs 60.0% (95%CI: 49.9%, 68.6%) in the resistant and responsive groups respectively, indicating non-constant hazard in the resistant group. Bortezomib resistance was not associated with higher ISS (ISS3 24% vs 15%, p=0.17), high risk cytogenetics (17p del or t(4;14)) (23% vs 23%, p= 0.99), MM sub-type (p= 0.63) or length of bortezomib cycle (21 vs 35 day p= 0.56)). In responders (n=147), maintenance therapy was associated with improved PFS (p=0.021), and PFS at 24 months was, 70.7% (95%CI: 57.3%, 80.5%) vs 46.9% (32.0%, 60.5%) in those who received maintenance therapy and those who did not respectively. In non-responders (n=40) PFS at 24 months was 68.8% (95%CI: 35.7%, 87.3%) vs 54.9% (31.6%, 73.2%) in those patients who received maintenance therapy and those patients who did not respectively (p=0.84). Median OS has not been reached in either the bortezomib resistant or responsive groups however estimated OS at 24 months is

82.8% (95%CI: 62.8%, 92.7%) vs 89.5% (95%CI: 81.5%, 94.1%) in the resistant and responsive groups respectively.

Conclusion: Bortezomib resistance is a poor prognostic factor and is associated with a shorter PFS. Consideration of early therapy change, maintenance therapy and/or referral for assessment for allograft in eligible patients appears to be warranted.

PS-218
The impact of thalidomide, zoledronate and high-dose therapy with autologous stem cell support on patient reported outcomes in multiple myeloma: Results of the quality of life substudy of the MRC Myeloma IX randomised controlled trial

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Background: There is little published data on health-related quality of life (QoL) in large series of systematically treated patients with multiple myeloma (MM). Methods: MRC IX enrolled 1970 patients with MM of all ages between 2003 and 2007 from 120 centres in the United Kingdom. In the intensive pathway (I), patients were randomized to CVAD (cyclophosphamide, adriamycin and dexamethasone) or CTD (cyclophosphamide, thalidomide and dexamethasone) followed by high-dose melphalan with supporting autologous stem cell transplantation (HDM+ASCT). Non-intensive (NI) pathway patients were randomized to MP (melphalan and prednisolone) or an attenuated CTD (CTDa) regimen. Patients in both pathways were randomized at study entry to either sodium clodronate or zoledronate. Patients who completed induction therapy were randomized to maintenance with thalidomide or observation. The study has reported primary and secondary endpoints. However, the impact of the investigated treatments on the secondary endpoint of patient-reported QoL has yet to be reported. The aims were to investigate the QoL during induction chemotherapy and bisphosphonate treatment and in the long-term (during maintenance). The QoL instruments were the European Organisation for Research and Treatment of Cancer QLQ-C30 and MY24. The study protocol defined four subscales of primary interest (global health, pain, fatigue and physical functioning) at 3, 6 and 12m post-induction and post-maintenance randomisation. Linear regression models estimated the effect of induction chemotherapy on each subscale at each time point, adjusting for baseline subscale, bisphosphonate, international staging system, age, sex and haemoglobin, calcium, creatinine and platelets. Missing questionnaire data and baseline variables were imputed using multiple imputation by chained equations. Imputation was conducted separately on data in the intensive and non-intensive pathways and the maintenance population, respectively. Rubin's rules were used to combine parameter estimates and perform significance tests. Results: 1819 patients (1061 I, 758 NI) consented to the QoL substudy and 78.2% returned questionnaires at trial entry. Questionnaire return rates were good amongst those continuing on study in induction (86.4% at 3m, 85.3% at 6m, 82.6% at 12m, 80.1% at 2y, 78.5% at 3y, 79.0% at 4y and 78.6% at 5yr) and maintenance (92.2% at 3m, 93.0% at 6m, 91.3% at 12m, 92.0% at 2y, 89.3% at 3y, 85.1% at 4y and 83.9% at 5y). Statistical analysis is being finalised and results

and interpretation will be presented at the meeting. Conclusion: Our results will provide evidence with respect to the impact on health-related QoL of an immunomodulatory agent, bisphosphonates, HDM+ASCT and maintenance in a large phase III study and will inform the approach to developing assessment strategies in future trials.

PS-219
Lenalidomide at the dose of twenty-five mg every other day in patients affected by multiple myeloma and renal failure : a real-life experience

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Lenalidomide, available as oral compound, is an IMiD with both antiproliferative and immunomodulatory activity which is largely used in the management of newly diagnosed, relapsed or refractory MM and as maintenance therapy after autologous stem-cell transplantation. Due to its renal route of excretion, it is mandatory to adjust lenalidomide dose in patients with RI, guided by Creatinine Clearance (ClCr), in order to impede a systemic prolonged exposure that could boost myelosuppression. With normal renal function, lenalidomide reaches its maximal plasma concentration after a median time of 0.6-1.5 h, and it is cleared by glomerular filtration and active tubular secretion in 3 to 4 hours. Serum half-life increases up to 9 hours if moderate/severe renal impairment is present (creatinine clearance <50 or <30 mL/min, respectively). In the latter cases a reduction of the daily dose is recommended. Dose adjustment based on RI severity decreases the daily amount of lenalidomide from 15 up to 5 mg (in patients undergoing dialysis); other studies include a schedule with 10 or 15 mg every other days. However, there is no theoretical assumption against the possibility that protracting the time of full standard doses can be equally effective and tolerated by patients requiring reduced doses. In this report, we describe our retrospective experience on the administration of lenalidomide 25 mg every other day for patients with MM and RI. From March 2014 to February 2016, 19 consecutive patients, 11 female and 8 male, with a median age of 63.3 years (range: 49-81) affected by advanced, resistant and progressive MM (median number of previous treatment lines: 3, range : 1-5, all including bortezomib) with concomitant renal failure not in dyalitic support (median calculated ClCr 36.4 ml/min, range : 18-66) were treated, after informed consent, with monthly 21-day courses of 25 mg lenalidomide every other day and dexamethasone (20-40 mg on days 1-8-15-22, every 28 days). Disappearance of urinary light chain and reduction of serum creatinine (complete response) were detected in 7 patients (36.8%); 3 patients (15.7%) had a very good partial response, 3 (15,7%) had a partial response, 4 of them (21.0%) were in stable disease, whereas 2 patients (10.5%) had signs of progressive disease. Overall response ratio was 68.2%. More than half of the patients (11/19, 57.8%) had a renal response (median calculated ClCr 51.5ml/min, range 20-148). Median progression free survival was 8 months (range 3-18 months). No patient experienced grade 4 myelotoxicity; four patients required red cell transfusions for grade 3 an

PS-220
SUMOylation and c-Myc Form Feed-Forward Loop Via miR-34b/c Targeted Gene Expression Program

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C-Myc is a key driver in more than 60% of multiple myeloma. Recent studies have suggested that Small ubiquitin-like modification (SUMOylation) is critical to c-Myc-dependent oncogenesis; however the mechanism of how SUMOylation is involved in c-Myc-dependent oncogenesis is not well understood. Through genome-wide miRNA profiling, we identified miR-34b/c as one of the most elevated microRNAs induced by knockdown of the SUMO E1 enzyme. MicroRNAs are non-coding RNAs that target mRNAs to inhibit their translation and induce their degradation. The use of anti-miR and Dicer knockdown demonstrated that increased miR-34b/c are responsible for reduced levels of miR-34b/c targets, including c-Myc. In addition to inhibiting c-Myc expression, miR-34b/c inhibit an array of proteins involved in oncogenesis and inhibit cancer cell viability, stemness and metastasis. We identified SUMOylation of AKT as playing an important role in miR-34b/c transcription by FOXO3a. Because c-Myc activates the expression of SUMO E1 and E2 enzymes in multiple myeloma and other cells, reduction of c-Myc through SUMOylation inhibition suppresses the expression of SUMO E1 and E2 enzymes that leads to further inhibition of SUMOylation. Therefore, this study reveals a feed forward mechanism to suppress c-Myc levels through inhibiting SUMOylation. Consistent with the mechanistic findings, small molecule inhibitors of SUMOylation potently suppress c-Myc expression and have strong anti-cancer effects on multiple myeloma cell lines and primary patient samples. These data suggest that SUMOylation is a novel target for treatment of multiple myeloma.

PS-221
Proteasome inhibitor based induction

improves outcomes only in transplant eligible NDMM patients

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Background: Immunomodulatory drugs (IMiDs: e.g. thalidomide and lenalidomide) and proteasome inhibitors (PI: e.g. bortezomib) have become the mainstay of NDMM therapy. Both IMiD and PI based therapies can achieve optimal response and improve survival, in both transplant eligible and ineligible patients. Methods: Data on 96 newly diagnosed patients from myeloma clinical audit within Thames Valley Cancer Network was used in this study. Analysis included 45 patients treated with a PI-based therapy (VTD or Vel), and 51 patients treated with an IMiD-based therapy. Three outcome indicators were measured for all patients until censor date. Time to next treatment 1 (TTNT1) is the time from end of 1st line therapy to beginning of 2nd line therapy. TTNT2 is time from end of 1st line therapy to beginning of 3rd line therapy. Overall survival (OS) was measured from start of therapy to censor date or death. Kaplan–Meier survival plots were generated to compare outcomes between the two cohorts based on transplant eligibility. In transplant ineligible patients, median follow-ups in months were 63.5 (Thal) and 17 (VTD+Vel). In transplant eligible patients, median follow-ups in months were 51 and 10 in IMiD and PI cohorts respectively. Results:Median age was 67 (Thal), 58.5 (VTD), 61 (VTD or Vel), and 67 (IMiD). Cytogenetics for the total 96 patients were: standard risk (29), high risk (7), and unknown (60). In transplant ineligible patients, median TTNT1 were 13 months and 15 months in (VTD+Vel) and

(Thal) cohorts, respectively. The difference was not statistically significant (p=0.9822). In transplant eligible patients, median TTNT1 in the IMiD group was 10 months. This was not reached in the VTD cohort. The difference was statistically significant (p=0.0017). In transplant ineligible patients, median TTNT2 were 25 months and 40 months in (Thal) and (VTD+VEL) cohorts, respectively. The difference was not statistically significant (p=0.2829). In transplant eligible patients, median TTNT2 in the IMiD cohort was 36 months. This was not reached in the VTD cohort. The difference was not statistically significant (p=0.8878). In transplant ineligible patients, median OS in Thal group was 48 months. This was not reached in (VTD+Vel) group at censor date. The difference was not statistically significant (p=0.9725). In transplant eligible patients, median OS was not reached in either cohorts. The difference was not statistically significant (p=0.3019). Conclusion:No significant differences in TTNT1 or 2 or OS were noted in transplant ineligible cohorts between PI or IMiD-based induction therapy. In transplant eligible patients however, PI-based cohort demonstrated a significantly better median TTNT1 compared to the IMiD cohort, whereas differences in TTNT2 and OS were not significant. Larger patient numbers as well as longer follow-up (in the PI-based cohort) are required to enable a better interpretation of outcomes.

PS-222
Long-term reversibility analysis of peripheral neuropathy in multiple myeloma patients treated with Bortezomib.

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Introduction: Peripheral neuropathy (PN) is a significant dose-limiting toxicity of bortezomib. The introduction of subcutaneous (SC) administration has reduced the incidence and severity. In most studies PN is described as reversible upon completion of treatment. We analysed the incidence of PN and the reversibility at long-term follow up. Patients and methods: We analysed MM patients (pts) treated in first line with SC bortezomib from May 2013 to May 2016 with different regimens in three haematological units. Reversibility analysis was performed at the end of treatment and for a long period of time (at least 6 months after the end of bortezomib treatment). Results: Sixty-two patients with MM were included. Median age was 68 years (34-84), 33(53%) were male. Myeloma subtypes were: 53% IgG, 29% IgA, 15% BJ and 3% non-secretor. Regimens of treatment were: 34% VMP, 32% VTD, 11% VRD, 7% VCD and 16% VD. Three pts (5%) had PN prior to initiation treatment (grade (G) 1: 2 pts; G2: 1 pt). Fifty-nine pts (95%) received SC bortezomib at 1,3 mg/m2 dose, 3 pts received reduced dose due to previous PN (2 pts at 1,0 mg/m2 and one patient at 0,7 mg/m2). Eighteen pts (29%) no completed pre-defined treatment due to toxicity (16%), progression (3%), comorbidities (3%) and other causes (7%). Thirty-six pts (58%) developed PN during treatment: 26% G1, 27% G2, 3% G3 and 2% G4. PN based on treatment: VMP: 57%(G1: 14%, G2: 38%, G3: 5%), VTD: 65%(G1: 35%, G2: 25%, G3: 5%), VRD: 57%(G1: 14%, G2: 43%), VCD: 75%(G1: 50%, G4: 25%), VD: 40%(G1: 30%, G2: 10%). Patient who developed PN grade 4 and one patient with PN grade 3 had PN at diagnosis, grade 2 and 1, respectively. Only 3 patients (5%) discontinued treatment for PN. Twenty-five pts (81% of total PN) developed PN during first 4 cycles of

treatment. There was no difference in the incidence of PN due to age, gender or previous diabetes. At the end of treatment 20 pts (55%) had reduced grade of PN, totally resolved in 8 pts and partially in 12 pts. Reversibility for a long time was performed in all patients with PN at end of treatment, except for 3 patients who died before 6 months of follow-up (n=25). Only 2 patients with grade 1 PN at the end of treatment was complete resolve for a long time. Eight pts with grade 2 PN decreased at grade 1; others patients (60%) no changes (G1: 7 pts, G2: 6 pts, G3: 1 pt; G4: 1 pt). Conclusions: This analysis, based on usual clinical practice, confirms that PN is a common toxicity of bortezomib's treatment despite its subcutaneous administration. However, the majority of patients had grade 1 or 2 PN developing in the first cycles of treatment. Bortezomib combination in triple regimens shows an incidence higher than the double regimen. Reversibility analysis shows that majority of patients (60%) no changes in the PN severity despite the long-term follow-up, especially in patients with high grade of PN developed during treatment.

PS-223
Outcome of Third Salvage Autologous Stem Cell Transplantation in Multiple Myeloma

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Background. Autologous stem cell transplantation (ASCT) remains a gold standard treatment for younger patients with multiple myeloma (MM. The outcome of third salvage ASCT has not yet been analyzed. Methods. Between 1997 and 2010, 1288 MM patients who had received at least 3 ASCT were registered in the EBMT database. The conditioning regimen for the third transplant was high dose melphalan alone or in combination with busulfan or bortezomib. We could distinguish two main groups: 417 patients who received tandem ASCT and then a third ASCT after single relapse (AARA group) and 72 patients who received one ASCT, a second ASCT after first relapse, and a third ASCT after second relapse (ARARA group). Results. We compared the two groups AARA vs ARARA. A third ASCT was performed in the AARA group in more recent years (p=0.047). The status at third ASCT was different: CR, 5% vs 4%: VGPR or PR, 45% vs 19%: MR or stable disease, 12% vs 15%: primary refractory/progressive disease, 38% vs 62% (p<0.001). A Karnofsky score of >70% at third ASCT was reported in 91% vs 90% of cases. The conditioning regimen at third ASCT was different between the two groups: melphalan

200 mg/m2, 42% vs 18%: melphalan 140 mg/m2, 6% vs 12%: other 52% vs 70% (p=0.018). The median age at third ASCT was 59 vs 61 years. There was a trend to a longer time between first ASCT and first relapse (27 vs 22 months (p=0.056)) in the AARA group while the interval between first ASCT and third ASCT was much shorter (44 vs 64 months (p<0.001)). The time between the last relapse and third ASCT was similar (9 vs 11 months (p=0.4)). The median follow-up was similar (70 vs 73 months (p=0.9)). Engraftment was similar (96% vs 93% (p=0.35)).The best response achieved after the third ASCT was superior in the AARA group: CR, 32% vs 12%: VGPR or PR, 60% vs 71% :MR or SD, 4% vs 14%: progression, 4% vs 3% (p<0.001). The median OS after third ASCT was much higher in the AARA group: 30 vs 19 months (p=0.01). The causes of death were: relapse/progression, 84% vs 84%: second primary malignancies (SPM), 0.4% vs 3.6%: other, 16% vs 13%. There was a trend to more SPM including both hematologic and solid tumors in the ARARA group (p=0.068) with a shorter median time to SPM, 12 vs 42 months (p=0.004). Focusing on the AARA group, the longer the time from tandem ASCT to first relapse, the better the OS after the third transplant: if relapse occurred within 12 months of tandem ASCT, median OS of 13 months: within 18-24 months, OS of 29 months: within 36-60 months, OS of 59 months. Conclusions. A third ASCT is feasible in MM with more than 80% of patients achieving at least PR although with increased non relapse mortality. This treatment is mostly used in one of two scenarios: tandem ASCT followed by relapse and a third ASCT. In this AARA group, if relapse occurred more than 3 years after the initial tandem ASCT, the median OS after third ASCT was more than 4 years.

PS-224
Late vs Early Response and Depth of Response Are Associated with Improved

Outcomes: Post-hoc Analysis of Phase 3 TOURMALINE-MM1 Trial (NCT01564537) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Depth of response has been associated with improved PFS and OS. However, little is known about the association of response kinetics with outcomes. Some evidence suggests that early responders may have compromised long-term outcomes compared with slow responders, but these studies were based in the era prior to novel MM agents. We analyzed long-term outcomes by time to best response and depth of response in TOURMALINE-MM1, a randomized, double-blind, placebo-controlled phase 3 study of ixazomib plus lenalidomide-dexamethasone (IRd) versus placebo-Rd in pts with RRMM, results of which led to the approval of ixazomib, in combination with Rd, for pts with MM who have received at least 1 prior therapy. The study met its primary endpoint at the first pre-specified analysis; a subsequent analysis for

survival was performed after a median follow-up of ~23 mos. Data reported here are from the 23-mo analysis. PFS was analyzed post-hoc in subgroups defined by quality of response and subgroups defined by time needed to achieve the confirmed best response (early and late responders had time to best confirmed response 0–4 mos or >4 mos, respectively). To avoid statistical bias in evaluating PFS in early vs late responders, two sensitivity analyses were performed: duration of response was analyzed in early and late responders; landmark analyses of PFS were conducted independently for subgroups of pts achieving PR and ≥VGPR, using landmarks of 6 and 9 mos, respectively. At data cut-off, 676 pts pooled across the IRd and placebo-Rd arms had best confirmed responses of 2% stringent CR (sCR), 11% CR, 38% VGPR, 30% PR, 13% stable disease (SD), and 6% PD. When analyzed in pt subgroups defined by depth of response, PFS showed a strong association with depth of response, with pts achieving CR or sCR having the longest PFS. In pts who achieved ≥PR, 174 (61%) and 109 (39%) pts in the IRd arm, and 159 (60%) and 106 (40%) pts in the placebo-Rd arm were defined as early and late responders, respectively. Median PFS was prolonged among late vs early responders in the IRd and placebo-Rd arms: NE vs 18.5 mos, and NE vs 14.9 mos, respectively. A similar trend was seen across both treatment arms for duration of best confirmed response: median: 23.1 vs 16.5 mos and NE vs 12.6 mos in the IRd and placebo-Rd arms, respectively. Similar results were seen in sensitivity analyses of PFS for subgroups of pts achieving PR and ≥VGPR, using landmarks of 6 and 9 mos, respectively. Among all patients, rates of grade ≥3 AEs in early and late responders were 74% and 74% with IRd, and 68% and 70% with placebo-Rd. Longer time to best confirmed response over prolonged duration of therapy, as well as deeper responses, appears associated with improved outcomes with both IRd and placebo-Rd in pts with RRMM. Notably, the longer duration of therapy needed to achieve best response did not appear associated with additional toxicity burden.

PS-225
A Multicenter phase I/II EMN Study of Carfilzomib in Combination with Bendamustine and Dexamethasone (CBd) in Relapsed and/or Refractory Patients with Multiple Myeloma.

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Introduction: Carfilzomib and Bendamustine were approved for the treatment of relapsed/refractory MM (RRMM). Combinations including a proteasome inhibitor (PI) and alkylating agents, showed a good efficacy with an acceptable toxicity. In this phase I/II study we assessed the combination of Carfilzomib plus Bendumustine and low dose Dexamethasone (CBd) in RRMM patients. Methods: RRMM patients with ≥2 lines of prior therapy were eligible. The primary objective of the phase I part of the trial was to determine the

maximum tolerated dose (MTD) of CBd combination. Treatment consisted of 28-day cycles of Bendamustine 70 mg/m2 on day 1 and 8, Carfilzomib (escalating dose) on day 1,2,8,9,15,16 and dex 20 mg/m2 on day 1,2,8,9,15,16,22 and 23. After receiving 8 cycles, responding patients continued with maintenance with Carf/dex only on two consecutive days every 14 days until progression. Based on the safety/efficacy profile of the phase I portion of the trial, recommended phase II dose was 27 mg/m2 (Gramatzki M, et al. ASH 2016). The primary objective of the phase II portion of the study was to determine the rate of very good partial response (VGPR). Data cut off was November 21st, 2016. Results: A total of 45 patients were enrolled; 41 patients could be evaluated for response and efficacy. Median age was 67 years. Median time form diagnosis was 5.8 year, median number of prior lines was 4 (range 2-9); 85% of patients had received a previous transplant, 88% bortezomib treatment and 88% immunomodulatory agents. Median follow-up was 5.95 months. At data cut-off, 43% of patients achieved at least a partial response, including 28% VGPR; 49% of patients had a stable disease, with an overall benefit of 92%. Median progression-free survival was 11.4 months and 1-year overall survival was 75%. The most frequent grade 3-4 adverse events (AEs) were hematological (lymphopenia 51%; neutropenia 29%, thrombocytopenia 27%). Grade 3-4 non-hematological AEs (≥5% of patients) were infections (12%), dyspnea (7%), cardiac events (7%) and thromboembolism (7%). Main serious adverse events were infections, cardiac and thromboembolic (4 patients each). Conclusions: The combination of CBd provides is effective for patients with RRMM, many of whom may have persisting side effects deriving from prior therapies. In this heavily pretreated population, prophylaxis of infections should be mandatory, and cardiopulmonary and vascular signs need attention and careful monitoring.

PS-226
High dose chemotherapy with autologous stem cell transplantation for multiple myeloma: Outcomes at Tata Memorial Centre.

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Background: High dose chemotherapy followed by autologous stem cell transplantation(ASCT) is the current standard of care for multiple myeloma(MM) patients. We analysed the outcomes of 85 consecutive patients of MM who underwent ASCT at our centre between 2007 and 2016. Methods: All patients of MM who underwent ASCT in this period were included. Pre-transplant chemotherapy regimens were bortezomib based(47%), lenalidomide(len)/thalidomide(thal) based (21%), bortezomib and len/thal(28%), anthracycline based(2%), or with oral melphalan(1%). Responses to chemotherapy were assessed by serum protein electrophoresis(SPEP), free light chain assay(FLC) and urine Bence Jones protein(BJP). Complete response(CR) was defined as absence of M band or BJP, very good partial response(VGPR) was defined as > 90% decrease in M band or BJP, partial response(PR) was defined as > 50% decrease in M band or BJP and progressive disease(PD) as > 25 % increase in M band or BJP from baseline. Peripheral blood stem cell mobilisation was done using cyclophosphamide and filgrastim(GCSF) in most (93%) or GCSF alone (7%). Baseline cytogenetics were risk stratified according to mSMART guidelines. High dose chemotherapy used was melphalan 200 mg/m2. OS and PFS were calculated by Kaplan Meier

method. Prognostic factors evaluated for OS were ISS stage, baseline cytogenetics, extramedullary disease, pretransplant and post-transplant response by SPEP/FLC assay and pretransplant PET-CT status. Results: Median age at transplant was 49 years. Extramedullary disease was present in 19%. ISS stage I was seen in 31%, stage II in 24% and stage III in 43%. Baseline cytogenetics were done in 60(73%) of which 23(38%) patients had low risk, 22(37%) had intermediate risk and 15(25%) had high risk cytogenetics. Pre-transplant 93% had a chemosensitive disease i.e. they had either CR in 28(33%), VGPR in 33(39.0%) or PR in 18(21%) to chemotherapy. Stable disease(SD) and PD was present in 1.2% and 5.9%. Median time from diagnosis to transplant was 10.5 months. Post-transplant CR rate at day 100 was 38%, VGPR 35%, and PR or SD in 16.5%. Median Follow up period was 32 months. Median time to progression was 24 months. The 3 year PFS and OS were 58% and 91% respectively. The factors affecting 3 year OS were pre transplant response status(CR + VGPR- 95% vs PR+SD 86% vs PD 53%; p= 0.00), presence or absence of extramedullary disease(79% vs 94%; P=0.02) and PET-CT negativity or positivity(with or without CR and VGPR) pretransplant (PET-CT negativity + VGPR/CR- 100% , PET-CT negativity without VGPR/CR- 100%, PET-CT positivity with VGPR/CR-93%, PET positivity without VGPR/CR- 65%; P=0.004). Conclusions: Three year OS for MM patients who underwent ASCT at Tata Memorial centre was 91 %. Extramedullary disease at baseline and pre-transplant disease status with PET-CT and SPEP/BJP are important prognostic factors affecting OS.

PS-227
Lenalidomide and low-dose dexamethasone for treatment of relapsed/refractory multiple myeloma: real-world treatment patterns from the PREAMBLE study

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Introduction: Combination therapy with lenalidomide and dexamethasone is a mainstay of treatment for multiple myeloma (MM). Registrational trials for lenalidomide used high-dose dexamethasone (hi-dex; >160 mg/28-day cycle); however, more recent trials in newly-diagnosed MM (NDMM) and relapsed/refractory MM (RRMM) have used low-dose dexamethasone (lo-dex; ≤160 mg/28-day cycle). Lo-dex has shown improved tolerability vs hi-dex in NDMM [1], reflected in the label and in clinical practice, but the label is yet to be updated for RRMM. Owing to a lack of evidence, multiple international treatment guidelines for NDMM or RRMM do not specify dexamethasone dosing. PREAMBLE (NCT01838512) is an ongoing, observational, international cohort study exploring real-world outcomes in patients with MM. In this analysis, we examined treatment patterns of patients with RRMM receiving lenalidomide + dexamethasone in PREAMBLE. Methods: Eligible patients were aged ≥18 years, had a diagnosis of RRMM with ≥1 prior therapy and initiated treatment ('index therapy') with an immunomodulatory drug (IMiD), proteasome inhibitor (PI) or IMiD+PI within 90 days before, or 30 days after study enrollment. Results: At data cut-off (September 1, 2016), data were available for 924 patients, with a median follow-up of 19 months. Of these patients, 349 (38%)

received a lenalidomide-based index therapy; median age was 70 years and 199 (57%) were male. 186 (53%) patients had 1 prior line of therapy, 100 (29%) had 2, 35 (10%) had 3, 28 (8%) had >3. 121 (35%) patients had prior hematopoietic stem cell transplantation; 99% (147/149) of transplantations were autologous. 276 patients (79%) had relapsed MM and 73 (21%) had refractory MM; 78/198 (39%) patients had International Staging System stage III disease. Median (Q1–Q3) time from diagnosis to start of index therapy was 31 (18–55) months. Most patients (219, 63%) received index therapy with lenalidomide + dexamethasone, 51 (15%) received lenalidomide + dexamethasone + cyclophosphamide and 34 (10%) received lenalidomide alone. Median (Q1–Q3) total dose/cycle was 525 (315–700) mg for lenalidomide (n=216) and 160 (80–160) mg for dexamethasone (n=213). The majority of patients (198/213, 93%) received lo-dex: per cycle, 82 (38%) received 0–80 mg and 116 (54%) received 81–160 mg. 15 patients (7%) received hi-dex: per cycle, 5 (2%) received 161–240 mg, 4 (2%) received 241–320 mg, 2 (1%) received 401–560 mg and 4 (2%) received >560 mg. Conclusion: Real-world data from patients with RRMM suggest the majority of patients who receive a lenalidomide-based index therapy receive low-dose dexamethasone. Further analyses may inform revision of international treatment guidelines for RRMM. Study sponsored by Bristol-Myers Squibb. Ref: 1. Rajkumar et al. Lancet Oncol 2010;11:29–37

PS-228
Single-Arm, Phase 2 Study of Elotuzumab in Combination With Pomalidomide and Dexamethasone in Patients With Multiple Myeloma Who Are Relapsed/Refractory to Lenalidomide: Initial Safety Data

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Introduction: Elotuzumab is indicated with lenalidomide (Len) and dexamethasone (dex; ELd) for patients (pts) with multiple myeloma (MM) and 1–3 prior therapies. In a Phase 3 trial in relapsed/refractory MM (RRMM), ELd reduced the risk of progression/death by 30% vs Len/dex and demonstrated an acceptable safety profile [Lonial S et al, NEJM 2015;13:621–31]. However, novel therapies for MM pts refractory or intolerant to Len are needed. Pomalidomide (Pom), a novel immunomodulatory drug, showed activity in Len-refractory pts [San Miguel J et al. Lancet Hematol 2013;14:1055–66] and enhanced elotuzumab efficacy in a mouse model. Pom was therefore combined with elotuzumab and dex (EPd) in this Phase 2 multicenter single-arm study (NCT02612779). Here we report first interim safety data from this ongoing study. Methods: Pts with measurable MM, 1–2 prior therapies and disease progression during/after last therapy were treated with elotuzumab (10 mg/kg IV weekly for two 28-day cycles; 20 mg/kg IV once per cycle thereafter), Pom (4 mg orally, Days 1–21 of each cycle) and dex (pts ≤75 years: 40 mg weekly equivalent; pts >75 years: 20 mg weekly equivalent) until disease progression, unacceptable toxicity or withdrawal of consent. Patients must have had ≥2 cycles of Len (full dose) to which they were relapsed or refractory, but could not have received Pom. Primary endpoint was progression-free survival;

additional endpoints included overall survival, objective response rate and safety. Results: At time of analysis (November 2, 2016), 53 pts had received ≥1 dose of EPd. Among these 53 pts, median (range) age was 67 (39–88) years, 55% were male, 83% were white. International Staging System stage is available for 41 patients: 22 stage I, 12 stage II, 7 stage III. After a median of 2.3 months' treatment (Tx; median of 3 Tx cycles), 41/53 (77%) pts were still on Tx. The most common reasons for discontinuing Tx were disease progression (n=3, 6%), AEs (n=2, 4%), withdrawal of consent (n=2, 4%) and 'other' reasons (n=2, 4%). In total, 41/53 pts (77%) had ≥1 AE; AEs occurring in ≥15% of pts were fatigue (36%), cough (19%), anemia (19%), diarrhea (17%), constipation (15%), neutropenia (15%) and thrombocytopenia (15%). Two pts had Grade 5 AEs (1 had pneumonia and cardiac arrest, 1 had pneumococcal sepsis). Serious AEs occurred in 12 pts (23%), most commonly pneumonia (11%), urinary tract infection (6%) and hypercalcaemia (4%). Three pts had infusion reactions (chills and back pain, hypertension, cough and throat irritation); all Grade 1–2 during cycle 1 (2-mL/min infusion rate). Conclusion: In this on-going study, initial data suggest that EPd is well tolerated and has a safety profile consistent with ELd. Future analyses will characterize the efficacy of EPd among pts with RRMM who are relapsed or refractory to lenalidomide. Study support: BMS. Writing assistance: M Thomas, Caudex, funded by BMS.

PS-229
The Effect of Clinically Relevant Concentrations of Daratumumab on the Performance of Freelite® Immunoassays

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Background: Monoclonal antibody (mAb)-based therapies represent a major advance in the management of haematological malignancies. In multiple myeloma, these can be detected as a discrete band on both serum protein electrophoresis (SPE) and serum immunofixation electrophoresis (IFE), confounding the use of these tests for monitoring treatment response. Daratumumab (Darzalex®), a human CD38 IgG1-κ mAb, is both FDA and EMA approved as monotherapy for heavily treated MM. Serum free light chain (FLC) assessment by Freelite® has become a diagnostic standard as an alternative to 24 hr urine electrophoresis and is a widely available assay that may aid in disease monitoring of daratumumab-treated patients. The aim of this study was to establish if clinically relevant concentrations of daratumumab interferes with kappa and lambda Freelite immunoassays. Methods: The plasma concentration of daratumumab peaks at approximately 0.9 g/L after 8 weekly doses of 16 mg/kg monotherapy. Interference studies were performed by spiking daratumumab (at final concentrations of 0.125 – 1 g/L) or a saline control into patient sera, including clinical samples containing ~10, 50 or 100 mg/L kappa or lambda FLCs. Interference was defined as a change in the reported values outside of the normal analytical variation for Freelite assays (+/- 15%). The presence of kappa or lambda FLCs in daratumumab preparations was tested by preparing serial dilutions of the drug in saline solution. Serum FLCs were measured using the Freelite assay (Binding Site, Birmingham, UK) in accordance with the manufacturer's instructions. Results: No significant deviations in kappa or lambda FLC values were observed when daratumumab was diluted into patient samples containing 10, 50 or 100 mg/L FLCs. 0.8 mg/L kappa FLC and 0 mg/L lambda FLC was identified when 1 g/L

daratumumab was diluted into saline. The kappa FLC concentration reduced in a linear, dose dependent manner. Conclusion: Daratumumab interference with Freelite assays was insignificant in patient samples containing a range of clinically relevant FLC concentrations. Freelite assays can therefore be used to monitor response in myeloma patients receiving daratumumab treatment.

PS-230
Efficacy of novel agents on soft-tissue plasmacytomas in patients with relapsed multiple myeloma

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Introduction: the frequency soft-tissue plasmacytomas (Ps) is high in patients (pts) with refractory multiple myeloma (RRMM). There are two types of Ps: 1) paraskeletal (PPs): originating from focal bone involvement and 2) extramedullary (EMPs): originating from hematogenous spread. Aim: to analyze the effectiveness of novel drugs (thalidomide, bortezomib, lenalidomide, pomalidomide, carfilzomib) in pts with RRMM and PPs or EMPs. Patients and Methods: patients with PPs or EMPs at the time of first or subsequent relapses from our database from Hospital Clínic of Barcelona who were treated with novel agents were analyzed (novel drugs in monotherapy or in combination with corticosteroids). Results: 29 pts (median age 61, M 17/F 12) with RRMM and Ps were treated with bortezomib (btz). The median number of previous therapies was one. 22 pts had PPs and 7 EMPs. Median number of cycles received:4. The serological response rate was: 4% CR, 27% PR, 7% MR, 24% SD, 17% PD, 7% early death, 14% non evaluable (NE). The response of the Ps were: 14% CR, 17% PR, 10% SD, 41% PD, 4% early death, 14% NE. The median PFS from the initiation of btz was 3.9 months. Sixteen pts (median age 49 years, M 6/F 10) were treated with lenalidomide (lenad). 13 pts had PPs and EMPs. The median number of previous therapies was two. Median number of cycles :5.5. The serological response was: 38% PR, 12% MR, 19% SD, 19% PD, 12% NE. The Ps response was: 25% PR, 19% SD, 44% PD, 12% NE. The median PFS from initiation of lenad was 8.4 months. Nine pts (median age 61 years, 3M/6F) were treated with pomalidomide. Median number of previous therapies:4. Two pts had PPs and 7 EMPs. The median number of cycles was 2. Serological response rate was: 44% PR, 11% SD, 23% PD, 11% NE. None of the patients showed response of the Ps (11% SD, 77% PD, 11% early death). The median PFS was 1.3 months. 8 pts (median age 49 years, 6M/2F) were treated with thalidomide (thald). Median number of previous therapies:one. Six pts had PPs and 2 EMPs. The median number of cycles of thald received was one. None of the pts showed serological response (25% SD, 50% PD, 25% early death) or reduction in the size of the Ps (50% SD, 50% PD). The PFS from initiation of treatment with thald was 1.6 months. Four pts (median age 62, 2M, 2F) were treated with carfilzomib (cfz). The median number of previous therapies was 3. The Ps type was PPs (1) and EMPs (3). The median number of cycles administered was one. None patient responded to cfz: serological response rate: 75% SD, 25% PD; Ps response: 100% PD. Median PFS: 0.7 months. The median survival in the overall series of pts with soft tissues masses at relapse treated with novel agents was 15.2 months. Conclusions: The efficacy of novel drugs in the treatment of Ps is limited, being the most effective bortezomib and lenalidomide. The presence of Ps at relapse is associated with poor OS even in the era of novel agents.

PS-231
Clinical features and results of

bortezomib-melphalan-prednisone (VMP) as initial treatment in elderly multiple myeloma patients received lenalidomide with dexamethasone (Len/Dex): Subgroup analysis of lenalidomide registry from Korean Multiple Myeloma Working Party (KMM151)

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Background Bortezomib-melphalan-prednisone (VMP) therapy is a well-established standard treatment for elderly patients with multiple myeloma (MM) who are ineligible for high-dose chemotherapy followed by autologous stem cell transplantation. These patients will generally experience relapsed or refractory myeloma after VMP treatment, and then lenalidomide with dexamethasone (Len/Dex) regimen can be chosen as a salvage therapy. We aimed to investigate the clinical features and results of VMP as initial treatment in MM patients received Len/Dex as a salvage therapy. Methods We analyzed the lenalidomide registry data from Korean Multiple Myeloma Working Party (KMM151). One hundred sixty-eight patients of 289 patients in lenalidomide registry data were identified as MM patients received VMP as initial treatment who aged 65 years or older with newly diagnosed MM between September 2005 and August 2015. Results Median age of the patients was 69.5 years (range, 65-84), and median body mass index (BMI) was 23.5 (range, 15.4-33.2). Fifty-one patients (30.4%) had Charlson comorbidity index 2 or more and 117 patients had 1 or less. Most patients (45.8%) had International Staging System (ISS) III. Median cycles of VMP was 6 (range, 1-9) and 54 patients (32%) finished 9 cycles of VMP. At 2nd cycles of VMP, overall response rate was 59.4% with CR rate of 6%, VGPR rate of 16.7%, and PR rate of 32.1%. Overall best response rate over VMP treatment was 67.3% with CR rate of 9.5%, VGPR rate of 25.6%, and PR rate of 32.1%. With median follow-up duration of 48.8 months in surviving patients, median progression-free survival (PFS) of VMP as initial treatment was 13.4 months. Clinical variables such as age (<70 years vs. ≥70 years), BMI (<23 vs. ≥23), and ISS were not independent prognostic factor for PFS, while Charlson comorbidity index 2 or more was significantly associated with worse PFS (hazard ratio=1.95, 95% confidence interval: 1.39-2.73, P<0.001). Conclusion Median PFS of VMP as initial treatment in MM patients received Len/Dex as a salvage therapy was relatively short, since the patient who did not experience progression after VMP treatment were excluded in lenalidomide registry data. Charlson comorbidity index was important variable for PFS in elderly MM patients received VMP as initial treatment in lenalidomide registry data.

PS-232
A phase I clinical study of autologous

dendritic cell therapy in patients with relapsed or refractory multiple myeloma

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Cellular immunotherapy is emerging as a potential immunotherapeutic modality in multiple myeloma (MM). We have developed potent immunotherapeutic agent (VAX-DC/MM) generated by dendritic cells (DCs) loaded with autologous myeloma cells irradiated with ultraviolet B. In this study, we evaluated the safety and efficacy of VAX-DC/MM in patients with relapsed or refractory MM. This trial enrolled relapsed or refractory MM patients who had received both thalidomide- and bortezomib-based therapies. Patients received the intradermal VAX-DC/MM injection every week for 4 weeks. Patients were treated with 5×106 or 10×106 cells, with nine patients treated at a higher dose. The median time from diagnosis to VAX DC/MM therapy was 56.6 months (range, 28.5–130.5). Patients had received a median of five prior treatments, and 75% had received autologous stem cell transplantation. VAX-DC therapy was well-tolerated, and the most frequent adverse events were local reactions at the injection site and infusion-related reactions. In seven of nine patients who received 10×106 cells, an immunological response (77.8%) was observed by interferon-gamma ELISPOT assay or a mixed lymphocyte reaction assay for T-cell proliferation. The clinical benefit rate was 66.7% including one (11.1%) with minor response and five (55.6%) with stable disease; three (33.3%) patients showed disease progression. In conclusion, VAX-DC/MM therapy was well-tolerated, and had disease-stabilizing activity in heavily pretreated MM cases. Further studies are needed to increase the efficacy of VAX-DC/MM in patients with MM.

PS-233
Drug response prediction in high risk multiple myeloma

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The aim of this study is to test if we could predict progression free survival (PFS) and drug response in high risk myeloma by a new method based on gene expression profiling (GEP). This may provide us with a tool for effective personalized medicine and to prevent any potential non-responders from suffering from drug induced side-effect. A specific Drug Response Predictor (DRPTM) has been developed by Medical Prognosis Institute, DK. The DRP is an assay that based on gene expression analysis of cell lines and tumor samples, can predict the response to specific drugs. High-risk myeloma patients were identified by use of the GEP of 70 genes (GEP70) which has been validated in the transplant, non-transplant, and relapse setting1. We used publically available GEP from patients at diagnosis to predict the response by DRP of drugs used in the treatment of myeloma patients2;3. We stratified patients by GEP70 and by virtual karyotyping of t(14;14) and t(14;16). Furthermore, we used DRP to test for predicted

sensitivity to a panel of B-cell active drugs. Multidimensional scaling presented high and low risk myeloma by GEP70 as a continuum pattern rather than two separate clinical populations. The median predicted sensitivity by DRP for all patients varied between 40 to 70, on a scale of 0-100 for melphalan, bortezomib, etoposide, doxorubicin, cisplatin, vincristine, lenalidomide, thalidomide and cyclophosphamide and was higher among high-risk patients. The predicted sensitivity to drugs by DRP was highest for IMiDS, vincristine, doxorubicin and bortezomib. Tumor samples with high expression levels of MMSET had lower predicted sensitivity to all drugs. Among patients with high gene expression levels of cMAF the highest predicted sensitivity was found for IMiDS, bortezomib and vincristine. Twenty-five percent of high-risk patients by GEP70 have a PFS of more than 10 years. The DRP score stratified patients further. Patients with a predicted sensitivity by DRP to melphalan, bortezomib and lenalidomide had a prolonged PFS (melphalan: HR 2.4 [1.2-4.9], P= 0.014; bortezomib: HR 5.7[1.2-27], P= 0.027; lenalidomide HR 3.8 [1.2-13], P= 0.028) and a trend was found for thalidomide HR 2.3 [0.6-8.8] (P= 0.21). Patients with predicted sensitivity to bortezomib had a better response to treatment (P= 0.022). DRP was applied to a panel of B-cell active drugs and a predicted response to treatment was found for all high-risk myeloma patients. In newly diagnosed myeloma patients we find that DRP can predict the outcome to melphalan, bortezomib and lenalidomide and also the response to bortezomib. DRP also predicted response to drugs used in treatment of other B-cell diseases. We will use the results for up-coming clinical trials. (1) Johnson SK et al. Int J Hematol 2011;94:321-333. (2) Shaughnessy JD, et al. A. Blood 2007;109:2276-2284. (3) Terragna C et al. Oncotarget 2016;7:9666-9679.

PS-234
REAL-WORLD DATA FOR THE TREATMENT OF

RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH LENALIDOMIDE AND DEXAMETHASONE IN 2ND LINE (LEGEND STUDY): THE PROGNOSTIC SIGNIFICANCE OF BIOCHEMICAL VERSUS CLINICAL RELAPSE

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Lenalidomide-dexamethasone (LenDex) is an effective combination for relapsed/refractory Multiple Myeloma (RRMM) patients. However, outside clinical trials there are limited data regarding the efficacy of LenDex in 2nd line. In addition, the efficacy of LenDex combination before evident clinical relapse i.e. at biochemical relapse compared with LenDex at clinical relapse has not been explored. In the current study, we evaluated response rates and progression-free survival (PFS) of patients with RRMM treated with LenDex in 2nd line and we compared survival parameters for patients treated with LenDex at biochemical relapse vs. those treated at clinical relapse. We studied the medical records of 220 patients with RRMM treated in 2nd line with LenDex between 2009-2014. Currently, we have analyzed data of 135 patients (M/F: 74:61, median age: 69 years, range: 31-91, ISS I: 36, ISS II: 49, ISS III: 50, high risk: 16%, standard risk: 84%). First-line treatment included: bortezomib-based therapies (68.9%), thalidomide-based therapies (40%) and conventional treatment (37.8%); 20.7% of patients underwent autologous transplantation; 2nd line therapy was administered in 63.4% of patients at biochemical relapse and in 36.6% at clinical relapse. Overall response rate (ORR) was 71.9% (very good partial response: 23.7%, complete response: 16.3%). Median time until best response was 7.2 μήνες (range: 1.2-44.4). After a median follow-up of 44.4 months, 73 patients remain alive (54.1%) and 62 (45.9%) have died; 84 patients (62.2%) have relapsed. Median PFS and 12-month PFS were 19.2 months (95% CI: 15.6-25.2) and 66.2%, respectively. Median PFS of patients treated at biochemical relapse was 24 months (95% CI: 15.6-39.6), vs. 15.6 months (95% CI: 8,4-22,8) for those treated at clinical relapse (p=0.027; HzR: 0.64, 95% CI: 0.42-0.97); median overall survival (OS) was significantly longer in patients treated at biochemical relapse vs. those

treated at clinical relapse (Not reached vs. 72.5 months, p=0.01, HzR: 0.51, 95% CI: 0.31-0.87) In conclusion, this preliminary analysis has confirmed that, outside the setting of clinical trials, 2nd line therapy with LenDex leads to high response rates and prolonged PFS. More importantly, despite the limitations arise from the retrospective fashion of our study, we have demonstrated for the first time, that patients treated for 2nd line at biochemical relapse enjoy a prolonged PFS and OS compared to those treated at clinical relapse, thus highlighting the importance of early intervention at relapse, before the development of clinical manifestations.

PS-235 (d)

Phase 2 Study of the All-Oral Combination of Ixazomib Plus Cyclophosphamide and Low-Dose Dexamethasone (ICd) in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

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Background: Ixazomib is an oral proteasome inhibitor (PI), approved by the US FDA in combination with lenalidomide-dexamethasone (Rd) for pts with MM who have received at least 1 prior therapy. This open-label, multicenter phase 2 study (NCT02046070) assessed the safety and efficacy of the all-oral ICd combination in RRMM. Methods: Adult pts with RRMM after 1–3 prior lines of therapy who were not PI-refractory and did not have grade ≥2 peripheral neuropathy (PN) or grade 1 PN with pain were eligible. Pts received ixazomib 4 mg and cyclophosphamide 300 mg/m2 on days 1, 8, and 15, plus dexamethasone 40 mg (20 mg for pts aged >75 yrs) on days 1, 8, 15, and 22 in 28-day cycles until disease progression or unacceptable toxicity. Primary endpoint was overall response rate (ORR; ≥partial response [PR]); secondary endpoints included safety, pharmacokinetics (PK), complete response (CR) plus very good PR (VGPR) rate, time to response (TTR), duration of response (DOR), and progression-free survival (PFS). Results: 78 pts were enrolled; median age 64 yrs (47% aged ≥65 yrs), median time from diagnosis 53.4 mos (range 12.9–142.7), 62% ISS stage II/III disease. 62% of pts had received 2–3 prior lines of therapy including bortezomib (58%), lenalidomide (49%), and SCT (64%); 17% were immunomodulatory-drug-naïve. At data cut-off (June 29, 2016), pts had received a median of 12 treatment cycles (range 1–24); 69% pts had discontinued treatment, primarily due to disease progression (37%) and AEs (19%). AEs were reported in 92% of pts, including 59% grade ≥3 (49%/70% in pts aged <65/≥65 yrs), and 29% serious AEs (29%/30%). AEs resulted in dose reductions of any study drug in 37% of pts (24%/51% of pts aged <65/≥65 yrs) and treatment discontinuation in 23% pts (24%/22% aged <65/≥65 yrs). Ixazomib,

cyclophosphamide, and dexamethasone doses were modified in 90%, 85%, and 86% of pts, respectively. The mean relative dose intensity of ixazomib was 89%. There were 4 on-study deaths: cardiac arrest, severe pulmonary edema, respiratory syncytial viral pneumonia, and cerebral hemorrhage secondary to thrombocytopenia, with the latter two considered treatment-related. Ixazomib exposures were comparable to those in pts treated with IRd in the TOURMALINE-MM1 study, suggesting no PK interaction with Cd. ORR was 48% including 16% CR+VGPR. Median TTR in responding pts was 1.9 mos; median DOR was not reached, with response durations of up to 17 mos. After a median follow-up of 15.2 mos, median PFS was 14.2 mos. A trend towards PFS improvement was seen in pts aged ≥65 yrs vs pts aged <65 yrs (median PFS 18.7 vs 12.0 mos, HR 0.62, p=0.14). Conclusions: ICd appears to have activity in RRMM pts, and a toxicity profile consistent with that seen with IRd (Moreau, et al; N Engl J Med 2016). Preliminary efficacy data suggest there may be a preferential benefit in elderly versus younger pts, albeit with additional toxicity.

PS-236
Copanlisib has activity as a single agent and in combination with carfilzomib and response correlates with phospho-S6 level

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Background The reversible, pan-class I PI3K inhibitor copanlisib (BAY 80-6946) has potent activity against the alpha and delta isoforms. Using a panel of 20 multiple myeloma cell lines, we show the in vitro activity of copanlisib as a single agent and in combination with carfilzomib. Sensitive cell lines had lower baseline and post-treatment levels of phospho-

S6 (p-S6) resulting in a potential biomarker of response and a potential pharmacodynamic biomarker. Methods After screening the panel of multiple myeloma cell lines, 3 sensitive: NCI-H929, MM.1S, L-363, and 3 resistant: AMO-1, JJN3, COLO-677 were selected were selected for further analysis. KMS-11, a medium range responsive cell line was included in some assays. After treatment with copanlisib at 50 and 100nM, apoptosis and cell senescence assays were done at 72 hours. FACS analysis was done for cell cycle and induction and apoptosis after propidium iodide or PI/ANX-VFITC staining. β- galactosidase activity was measured in cells treated for 96 hours for the cellular senescence assays. Copanlisib and carfilzomib combination studies utilized excess over highest single agent statistics (EOHSA) to evaluate potentiation. Pre and post treatment reverse phase protein array (RPPA) was done with confirmatory western blots. Pre and post treatment p-S6 level changes were also assessed with flow cytometry. Results Apoptosis was induced in sensitive cell lines (50-80% AN-V+ cells) but not resistant cell lines (1-5% AN-V+ cells). Increased G1 cell cycle arrested was noted in sensitive cell lines but not in the resistant cell lines. Apoptosis as a mechanism of inhibition of proliferation was confirmed with cell senescence assays. There were lower baseline p-S6 (S235/236, S240/244) protein levels noted in sensitive lines as compared with resistant lines according to RPPA analysis. This finding was confirmed with western blot analysis. There was a greater decrease in p-S6 levels in sensitive lines NCI-H929 and L363 (53-83%, 73-93% respectively) as compared to resistant lines COLO-677 and JJN3 (5-27% and 38-67%, respectively). Both of these findings were validated by western blot analysis and phospho-flow. It was also shown that copanlisib down-regulates p-S6K1, p-S6 and p-4EBP1 (pro-survival and proliferation molecules) and up-regulates PDCD4 (pro-apoptotic). The combination of copanlisib and carfilzomib showed potentiation by EOHSA statistics and resulted in a post treatment decrease of p-S6 levels in the sensitive rather than resistant cell lines. Discussion Copanlisib has single agent activity in human multiple myeloma cell lines, and this response is improved by the addition of carfilzomib. The sensitive cell lines with median IC50 values between 5 and 100nM demonstrated low base p-S6 levels and greater decrease in p-S6 levels following treatment. Further studies are in progress to confirm this finding in vivo and in primary patient patient samples.

PS-237
No Relationship between Delta Neutrophil Index (DNI) and Hospitalization in elderly Patients with Newly Diagnosed Multiple Myeloma

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Introduction Serum delta neutrophil index (DNI), a new inflammatory marker, reflects the fraction of circulating immature granulocytes and is elevated in cases of bacterial infection. We evaluated the predictive value of the DNI in assessing the superimposed infection in immunocompromised patients with multiple myeloma during induction therapy. Methods We retrospectively collected data on 71 patients with newly diagnosed multiple myeloma (MM) at Kyungpook National University Hospital from August 2015 to August 2016. Patients aged ≥65 years with a diagnosis of symptomatic myeloma and treated with frontline bortezomib, melphalan, and prednisone (VMP) or other regimens were included. White blood cell (WBC) and absolute neutrophil counts (ANC), C-reactive protein (CRP) level, procalcitonin and DNI were evaluated regarding their usefulness for diagnosis of infection. Results Among 71 patients, 41 were treated with a frontline VMP regimen, 19 with non-bortezomib regimens, and 11 with best supportive care. Median age was 71 years (range 65-86). International Staging System

(ISS) risk groups included 8 (11.2%), 35 (49.2%), and 28 (39.4%) in stage I, II, and III, respectively. Fifteen patients (21.1%) had creatinine ≥2 mg/dl. Twenty (28.1%) patients had Eastern Cooperative Oncology Group (ECOG) performance status ≥2. Ten patients (14%) were hospitalized to treat with antibiotics for bacterial infection. The median hospitalized days was 14 days (range, 7-28days). Median initial WBC, CRP and procalcitonin were significantly higher in the patients hospitalized with bacterial infection (5.26×109/L vs. 11.53×109/L, p=0.028, 0.43 mg/dL vs. 8.5 mg/dL, p=0.032, and 0.33 ng/mL vs. 2.2 ng/mL, p=0.019). Serum DNI was not significantly higher in the patients with bacterial infection (p=0.76). The other patients characteristics were not statistically different according to the hospitalization. Conclusions There is no evidence that the serum DNI aids in diagnosis the bacterial infection in elderly patients with newly diagnosis multiple myeloma. Further study will need to evaluate a DNI as a convenient and useful marker for early diagnosis of superimposed infection.

PS-238 (d)

Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in RRMM Based on Prior Lines and Treatment Exposure: CASTOR

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Introduction: To determine whether DVd provides superior treatment benefit vs Vd in patients who have relapsed or become refractory to established standard of care regimens, subgroup analyses were performed based on an updated analysis of CASTOR. Methods: All patients received ≥1 prior line of therapy (LOT) and were administered 8 cycles (Q3W) of Vd (Days 1, 4, 8, 11 for bortezomib 1.3 mg/m2 SC; Days 1-2, 4-5, 8-9, and 11-12 for dexamethasone 20 mg PO) ± daratumumab (16 mg/kg IV once weekly in Cycles 1-3, every three weeks for Cycles 4-8, then every 4 weeks until progression). Bortezomib-refractory patients were ineligible. High cytogenetic risk (determined using next generation sequencing) was defined as having any of t(4;14), t(14;16), or del17p abnormalities. Results: Patients received a median (range) of 2 (1-10) prior LOT. 66% were bortezomib-pretreated and 21% were refractory to lenalidomide at last prior LOT. With median follow-up of 13.0 months, PFS was significantly prolonged with DVd vs Vd (median not reached [NR] vs 7.1 mo; HR, 0.33; 95% CI, 0.26-0.43; P<0.0001). PFS benefit was observed for DVd in patients with 1 prior LOT (median NR vs 7.9 mo; HR, 0.22; 95% CI, 0.14-0.34; P<0.0001) and 2 to 3 prior LOT (median 9.8 vs 6.3 mo; HR, 0.51; 95% CI, 0.36-0.73; P=0.0002). DVd was associated with superior PFS for all patients who received study treatment regardless of time since last LOT: median PFS was NR vs 9.4 mo (HR, 0.27; 95% CI, 0.17-0.43; P<0.0001) if treated >12 months after last prior treatment; for those treated ≤12 months after last prior treatment, median PFS was 10.3 mo for DVd vs 5.2 mo for Vd (HR, 0.34; 95% CI, 0.24-0.48; P<0.0001). ORR was numerically higher for DVd vs Vd in the >12

month subgroup (91% vs 83%; P=0.0632) and significantly higher for DVd vs Vd in the ≤12 month subgroup (77% vs 49%; P<0.0001). Among bortezomib-pretreated patients, PFS was significantly prolonged with DVd vs Vd (median: 12.4 vs 6.7 months; HR, 0.37; 95% CI, 0.28-0.50; P<0.0001). In patients who received 1 prior LOT which included bortezomib, median PFS was NR in DVd and 8.0 months in Vd (HR, 0.23; 95% CI, 0.13-0.41; P<0.0001). ORR was significantly higher with DVd vs Vd in bortezomib-pretreated patients (81% vs 60%; P<0.0001), with deeper responses with higher minimal residual disease (MRD)-negative rates (6% vs 1% at 10–5 sensitivity; P=0.0056). In patients refractory to lenalidomide at last prior LOT, PFS was significantly longer in DVd vs Vd (median: 9.3 vs 4.4 mo; HR, 0.36; 95% CI, 0.22-0.58; P<0.0001). Higher ORR (81% vs 50%; P=0.0021) and MRD-negative rates (9% vs 0% at 10–5 sensitivity; P=0.0082) was observed with DVd vs Vd. Additional efficacy data, including analyses by cytogenetic risk and MRD status, will be presented at the meeting. Conclusions: DVd is superior to Vd regardless of prior LOT, time since last therapy, prior exposure to bortezomib, or refractoriness to lenalidomide.

PS-239
Real-World Treatment Patterns in Relapsed or Refractory Multiple Myeloma: Evidence from a Medical Chart Review in the United Kingdom

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INTRODUCTION: Improvement in outcomes in relapsed/refractory multiple myeloma (RRMM) remains an area of unmet need, yet there is a shortage of data describing typical management of these patients in real-world settings. Such data may inform health technology assessments and other regulatory evaluations of RRMM therapies. To help address this information gap, we analyzed data from an RRMM cohort in the United Kingdom (UK). METHODS: A retrospective medical record review was conducted in 216 patients with RRMM in the UK. All patients were ≥18 years of age at initial MM diagnosis and first diagnosed with RRMM (during or following first-line induction therapy) between 01-Jan-2009 and 31-Dec-2011. Patients were retrospectively assessed on second- and third-line treatment regimens received, treatment duration, and reasons for treatment discontinuation from date of first relapse/progression (i.e., RRMM diagnosis). RESULTS: Mean (SD) age at first relapse was 65.6 (8.7) years, with approximately half (53%) having advanced age (≥65 years). The sample was 63% male and 69% were still alive at the time of medical record review. Among all patients, 208 (97%) received ≥1 line of chemotherapy after first relapse; 94 (43%) received ≥2 lines after first relapse. The most common second-line regimen was bortezomib + dexamethasone with or without other agents (66% of second-line initiators), followed by lenalidomide + dexamethasone with or without other agents (20%). Median duration of second-line treatment was 6 cycles over a median of 5.4 months. Among the 98% of patients who discontinued second-line treatment, a majority (62%) stopped due to reaching a perceived maximal response with no additional benefit expected; 33 patients (16%) discontinued due to disease progression and 8% discontinued due to toxicities. Lenalidomide + dexamethasone with or without other agents was the predominant third-line regimen (67% of third-line initiators). Among the 94 patients receiving third-line treatment, median duration was 6 cycles over a

median of 5.7 months. The leading reason for third-line discontinuation was disease progression (48%); 30% discontinued because they reached a perceived maximal response with no anticipated additional benefit, and 20% discontinued because of loss or lack of response. CONCLUSIONS: In the RRMM cohort reviewed, bortezomib-containing regimens were the predominant second-line therapy and lenalidomide + dexamethasone was the most common third-line regimen. The most common reason for discontinuation in RRMM treatment was reaching a perceived maximal response with no additional benefit expected; disease progression was also a common discontinuation reason. With growing evidence that treatment to progression may be superior to a fixed therapy duration, the relatively short treatment duration reported here (<6 months) highlights a potential under treatment and unmet need in current RRMM therapy.

PS-240
Real-World Treatment Patterns and Health Care Resource Utilization in Relapsed or Refractory Multiple Myeloma: Evidence from a Medical Chart Review in France

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INTRODUCTION: Despite the introduction of numerous novel agents and treatment strategies leading to improved response rates and overall survival, virtually all patients with multiple myeloma (MM) eventually relapse. While relapsed/refractory multiple myeloma (RRMM) remains an area of unmet need, little data have been generated describing typical treatment patterns and resource utilization in these patients. To help address this information gap, we analyzed data from an RRMM cohort in France. METHODS: A retrospective medical record review was conducted in 200 patients with RRMM in France. All patients were ≥18 years of age at initial MM diagnosis and first diagnosed with RRMM (during or following first-line induction therapy) between 01-Jan-2009 and 31-Dec-2011. Cytogenetic risk was defined as follows: high-risk: cytogenetic abnormalities del(17p), t(4:14), or t(14;16); standard-risk: all patients with known cytogenetics not classified as high-risk. Patients were retrospectively assessed on second- and third-line treatment regimens received, treatment duration, reasons for discontinuation, and subsequent health care utilization from date of first relapse. RESULTS: Altogether, 55 cytogenetic high-risk and 113 standard-risk patients were selected; risk category was unknown for 32 patients. Among all patients, 192 (96%) received ≥1 line of chemotherapy after first relapse; 114 (57%) received ≥2 lines after first relapse. The most common second-line regimen was lenalidomide + dexamethasone (54%), followed by bortezomib + dexamethasone with or without a third agent (23%). Median second-line duration was 9 cycles over 9.4 months. Most patients (92%) discontinued second-line treatment, most often due to progression (37%), to reaching a perceived maximal response with no additional benefit expected (33%), and to lack/loss of response (13%). Among the 114 patients receiving third-line treatment, regimens were more varied, bortezomib + dexamethasone being the most common (27%). From first relapse until death or last medical record, 35% of patients had ≥1 inpatient hospitalization. High-risk patients had greater incidence than standard-risk patients of inpatient

hospitalization (34 vs. 15 admissions per 100 person-years; p<0.05) and emergency department utilization (25 vs. 15 visits per 100 person-years; p<0.05). CONCLUSIONS: Lenalidomide + dexamethasone was the most common second-line regimen in this review. Second-line duration was generally <1 year, indicating a potential unmet need in light of the primary reasons cited for discontinuation (disease progression or loss of response, no perceived additional benefit, and toxicities). Hospitalizations and emergency department visits were common after first relapse, indicating a potentially high cost burden, particularly for patients with high-risk cytogenetics in whom health care utilization was generally higher than for patients with standard-risk.

PS-241
TOXICITY AND BENEFIT OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS WITH MULTIPLE MYELOMA

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INTRODUCTION: Autologous stem cell transplantation(ASCT) is the standard treatment for multiple myeloma(MM) patients under 65 years old, but its role is doubtful for patients over this age. METHODS: Retrospective analysis from one single centre concerning MM patients who underwent ASCT between January/2010 and July/2016. Data from 65-70 years old MM patients diagnosed in this period who were not transplanted were used for comparison. RESULTS: We analyzed 160 patients, 135 of which underwent ASCT. One-hundred-and-six of the transplanted patients were aged 65 years or less (median 56, IQR 10), 29 patients were aged more than 65 years (median 67, IQR 2) and 25 patients were non transplanted (median 68, IQR 4). Regarding transplant-related myelotoxicity there were no statistical differences between patients aged ≤65 years and >65 years old, however the first group needed less days of G-CSF(p=0.04). Non-hematopoietic toxicity measured by infections and mucositis was not influenced by age. Patients >65 years conditioned with melphalan 200mg/m2(MEL200) had more days of aplasia(p=0.05), greater need of G-CSF(p=0.01) and transfusional support(p=0.04) than patients ≤65 years. There were no differences on non-hematopoietic toxicity. In the elderly group, patients conditioned with MEL200 presented more aplasia days(p<0.01), higher grade of mucositis(p=0.03) and more days of IV antibiotics(p=0.02) than those transplanted with melphalan 140mg/m2. Comorbidities had no effect on transplant-related toxicity, either by age or by dose of melphalan. Days of hospitalization and post-transplant complications did not differ according to age group. Survival after transplant in patients ≤65 years vs older patients (median follow-up time, 30 months), was not influenced by age (OS,83mo vs 59mo,p=0.17; PFS,38mo vs 37mo,p=0.59). Regarding the non-transplanted elderly group, they had more renal disease(p=0.02), poorer performance status(p=0.04) and higher cytogenetic risk(p=0.01) than the transplanted cohort. Induction regimens were similar in transplanted group and non-transplanted group >65 years old and response to treatment revealed no differences. Infections were the most common complication in both groups. Transplanted patients needed less days of hospitalization(p=0.04). Comparing the long term outcome, survival curves of the elderly patients transplanted were clearly superior to the non-transplanted (OS,62mo vs 21mo p<0.01; PFS,45mo vs 20mo,p<0.01) however the non-transplant group has worse features than the elderly transplant group.

CONCLUSION:Transplantation in the elderly is still debatable but this study shows that, globally, age does not influence transplant related toxicity. Even though higher melphalan dose in elderly patients had higher toxicity, there was no apparent benefit in survival. Therefore, age should not restrict the access to ASCT and selection must be based on individual functional status.

PS-242 (d)
Overall Survival (OS) and Progression-Free Survival (PFS) Adjusted for Treatment Crossover in the CALGB/ECOG 100104 (Alliance) Study of Lenalidomide (LEN) Versus Placebo (PBO) Maintenance After Stem Cell Transplant (SCT) for Patients With Newly Diagnosed Multiple Myeloma

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Introduction/Background: At the pre-specified interim analysis (December 17, 2009) of the phase 3 CALGB 100104 study, LEN maintenance showed significantly longer PFS vs PBO after SCT (McCarthy et al, NEJM 2012). With the primary endpoint met, the study was unblinded and patients (pts) without progressive disease (PD) in the PBO arm crossed over to LEN maintenance. In an updated OS analysis (McCarthy et al, EHA 2016; cutoff date March 1, 2015), the study showed a significantly longer OS in favor of LEN maintenance. However, crossover makes it difficult to estimate the true treatment effect of LEN for PFS and OS. Using the updated data cutoff, this analysis examines

the relative treatment effect for LEN vs PBO for OS and PFS from randomization, whilst attempting to adjust for the potential favorable effect on outcomes for pts in the PBO arm due to crossover. Methods: The rank-preserving structural failure time model (White et al, Stat Med 1999) chosen for crossover adjustment assumes the treatment effect (LEN vs PBO) is the same for pts randomized directly to LEN as for those who crossover from PBO to LEN prior PD. Two approaches were taken for partitioning survival: treatment group (TG), which assumes a residual effect of LEN treatment, even after discontinuation, and on treatment (OT) which assumes no residual treatment effect after discontinuation. Given LEN's immunomodulatory mechanism of action, the TG approach was used as the base case and the OT approach was conducted as a sensitivity analysis. Results: The intent-to-treat (ITT) population consisted of 231 pts randomized to LEN maintenance and 229 to PBO. After study unblinding, 76 pts without PD crossed over from PBO to LEN maintenance. The median time from randomization to crossover was 11.5 months. Kaplan-Meier (KM) analysis of the ITT population showed median OS not reached (NR) vs 79.0 months for LEN vs PBO (hazard ratio [HR], 0.565; 95% CI, 0.419-0.761). Following crossover adjustment using the TG approach, the median in the PBO arm decreased to 70.9 months and the relative treatment effect increased (HR, 0.479; bootstrapped 95% CI, 0.339-0.694). KM analysis of the ITT population showed median PFS of 58.4 vs 28.9 months for LEN vs PBO (HR, 0.579; 95% CI, 0.458-0.732). Following crossover adjustment using the TG approach, the median in the PBO arm decreased to 25.8 months and the relative treatment effect increased (HR, 0.496; bootstrapped 95% CI, 0.386-0.628). Sensitivity analysis, including the OT method, showed consistent results across OS and PFS. Conclusions: Adjusting for the potential diluting effects of crossover resulted in numerical improvements to the ITT analyses for OS and PFS. The statistically significant improvement

in OS and PFS with LEN vs PBO maintenance after SCT was maintained in all analyses. Support: U10CA180821, U10CA180882, and CA180820. ClinicalTrials.gov Identifier: NCT00114101

PS-243
Double autologous stem cell transplantation followed by maintenance therapy conquers the adverse cytogenetic abnormalities in newly diagnosed multiple myeloma patients

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Introduction: Even in the era of novel agents, the prognosis of myeloma patients with adverse cytogenetic abnormalities is still poor. The purpose of the study is to explore the strategies for improving the outcome of the cases with adverse cytogenetic abnormalities. We analyzed the factors associating with the prognosis in transplant eligible patients with adverse cytogenetic abnormalities. Methods: We studied 85 patients who were treated with autologous stem cell transplantation (ASCT) from May 2010 to August 2016 in National Center for Global Health and Medicine, Tokyo Japan. We defined adverse cytogenetic abnormalities (CA) as del(17p), t(4;14), t(14;16), 1q21 gain by FISH and hypodiploidy. Age, ISS, R-ISS, number of ASCT, consolidation therapy, maintenance, response after each treatment, overall survival (OS) and progression free survival(PFS) were analyzed. Factors associated with prognosis were studied using Log-rank test and Cox proportional hazards models. Results: Median age was 58 years old (33 to 68), 27 (31.8%) had adverse CA. All patients were treated with bortezomib-based remission induction therapy followed by ASCT, and 38 (42.4%) patients were received second ASCT.

Consolidation therapy after ASCT was performed in 64.7%, and 65.9% were treated with maintenance therapy. Complete response(CR) was obtained in 56.5%, and 42.4% of patients achieved stringent CR(sCR). Univariate analysis showed significant factors which improve the OS in patients with adverse CA were double ASCT, maintenance therapy, and CR or better. Also, double ASCT, maintenance therapy, consolidation therapy, and CR or better improved PFS, significantly. Cox proportional hazard model revealed that double ASCT(p=0.019), maintenance therapy (p=0.031) and achievement of sCR(p=0.029) were significant factors for improvement of PFS in patients with adverse CA. Conclusion: The strategy including double ASCT followed by maintenance therapy and the achievement of sCR may overcome the adverse CA.

PS-244
Impact of Early Reduction in Paraprotein on Survival in Transplant Ineligible Myeloma : Lesson from a tertiary centre in rural India

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Introduction: The impact of rapid reduction in paraprotein levels , with induction chemotherapy in myeloma, on treatment outcomes is less clear. There are very few studies in transplant ineligible patients treated with novel agents, correlating early reduction in paraprotein levels with survival duration. With this background we decided to analyse our cohort of patients treated with novel agent based chemotherapy and the treatment outcomes with respect to rapidity of response. Methods This is a retrospective analysis of all cases of newly diagnosed multiple myeloma ,ineligible for stem cell transplant , registered at our center between January 2011 to June 2016. Paraprotein levels at baseline and at 3 months were noted with

percentage reduction. Survival analysis was performed with Kaplan-Meier (KM) curves and Cox proportional hazard (CPH) model. Univariate analysis was performed for variables like paraprotein percentage reduction at 3 months from baseline(100% Vs < 100 , ≥ 90% Vs < 90 %) , response at the end of induction treatment(CR Vs < CR, ≥VGPR Vs < VGPR), International staging system(ISS) , ECOG Performance Status (<2 versus ⩾ 2),and age (< 65 versus ⩾65). Analysis was performed with R v 3.2.2 (http://cran.r-project.org.) Results Median follow up was 27 months(95% CI : 25-34). Estimated 3 year overall survival(OS) was 71% (95 % CI : 62-83). Median progression free survival(PFS)was 24 months (95 % CI: 21-36) . Among a total of 121 patients, 42 (35%) , 29(24%) and 50 (41%) had paraprotein reduction of 100%, 90-99%,and less than 90 % respectively from baseline levels at 3 months .Patients with complete disappearance of paraprotein (100 % reduction) at 3 months had a trend towards higher OS , even though it was not statistically significant(3 year OS of 81 % Vs 69 %, HR= 0.54, p=0.182). But the PFS was significantly higher when these two groups were compared (median PFS of 51 Vs 17 months, HR= 0.33, p= < 0.001). When patients with ≥ 90 % reduction were compared with < 90 % reduction at three months, there was significant improvement in both OS and PFS(3 year OS of 80 % Vs 48 %, HR= 0.24, p=0.001, median PFS of 38 Vs 14 months, HR= 0.13, p < 0.001). Patients with CR at the end of treatment compared with those not in CR had significant improvement in both PFS and OS (median PFS 36 Vs 22 months, HR=0.27,p=0.01, median OS not reached in either group,p=0.002) . Similarly achieving VGPR or more was associated with improved PFS , although OS benefit could not be demonstrated(Median PFS 35 Vs 12 months, HR=0.19, p<0.001, 3 yr OS of 74 % Vs 66 %, HR=0.53, p=0.12) Conclusions Achieving a faster and deeper reduction in paraprotein as early as 3 months could lead to significant improvement in PFS. With a number of newer drugs in the field of myeloma, one should be aiming for better early response and consequently better survival.

PS-245
VALIDATION OF FRAILTY ASSESSMENT IN MULTIPLE MYELOMA (MM) PATIENTS

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The frailty score, combining ADL, IADL and CCI indexes, identifies 3 patients' groups: the fit, intermediate fitness and frail ones, with distinct outcomes. It was shown to be important for making treatment decisions but very few studies validated it in clinical practice. AIM: To retrospectively apply frailty score in a series of symptomatic MM patients, to study its prognostic impact and to eventually evaluate the most suitable treatment for frail patients. PATIENTS AND METHODS: We studied 349 symptomatic MM patients, diagnosed and followed –up in our department, treated within clinical indications over the last 15 years. Median age was 69 years (31-90) while 55% were males. Twenty-three percent, 30% and 47% were ISS staged I, II and III respectively. MM type was IgG in 66%, IgA in 22% and light-chain in 11% of the population, while 4 patients (1%) were biclonal. Frailty score was estimated following the Geriatric Assessment formula described by Palumbo et al. Statistical analysis was performed conventionally with SPSS v22.0 software. RESULTS: 45% were fit (frailty score 0), 32% were of intermediate fitness (frailty score 1) and 23% (=79 patients) were frail. Median overall survival was 95, 41

and 20 months in fit, intermediate fitness and frail patients respectively (p<0,00001). Frail patients' median age was 70 years (44-90). ISS stage was not of prognostic value in this group while it was in the whole cohort. Twenty percent of them, with a median survival of 19 months, received at first line bortexomib-dexamethasone, 44% received melphalan-prednisone (median survival: 24 months),10% a melphalan-prednisone-containing regimen (median survival: 24 months), while 10 % received lenalidomide-dexamethazone but their follow-up is too short to evaluate results because the indication at first line is recent; the rest of the patients received other various regimens. Thirty-two percent of frail patients succumbed during first line treatment while the other patients received further lines. Patients that were conventionally treated at first line received new agents in next lines (lenalidomide was in general well tolerated and dexamethasone or bertezomib usually dose reduced). In conclusion, frailty score is highly predictive of outcome; however fail patients benefit from treatment.

PS-246
RVD is a superior induction regimen compared to VCD among transplant-eligible myeloma patients

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Background: Transplant-eligible myeloma patients derive a significant survival benefit with a triplet induction therapy followed by transplant. The triplet induction regimen, VTD (bortezomib, thalidomide and dexamethasone) was demonstrated to be superior to VCD (bortezomib, cyclophosphamide and dexamethasone) prior to transplant. While lenalidomide is the most commonly used IMiD in the induction regimens in the US, to date, no comparative data is available comparing its efficacy vs VCD. Methods: We performed a case-control study among myeloma patients that underwent VCD or RVD induction therapy followed by ASCT. The VCD cohort for this analysis consisted of myeloma patients diagnosed at the University of Calgary, Canada from September 2010 until May 2015. The RVD cohort was identified from the myeloma database at the Winship Cancer Institute of Emory University Hospital, US. 1:1 matching was performed by period of diagnosis, age (±5 years), sex, race and risk stratification. The endpoints of interest were complete response (CR) rates post-induction therapy and post-transplant, PFS and OS. Chi square test, Mann-Whitney U test and log-rank tests compared the cohorts. Survival curves generated from CoMMpass data was also used as comparator. Results: Eighty-eight patients that received VCD and a similar number of patients that received RVD were included in the analysis. The median age at diagnosis was 58.51 years and 58 years for VCD vs RVD cohorts, respectively. VCD (59M, 29F) and RVD (58M, 30F) cohort characteristics were well-balanced. The overall response rate (ORR) was 90.9% in VCD cohort, including a 6.8 % CR rate and ≥VGPR rate of 56.8%, while in RVD cohort the ORR was 100%, with a 38.6% CR and a 69.3 % ≥VGPR rate. The CR (p=0.000), ≥VGPR (p=0.059) and PR rates (p=0.003) were significantly higher in the RVD arm post-induction. Post-transplant augmentation of responses in the VCD cohort: 37.5 % CR rate, 70.5% ≥VGPR rate and RVD cohort: 69.3 % CR (p=0.000), 89.3 ≥VGPR (p=0.001) strongly favored the RVD cohort. The benefit was seen across higher ISS stages, as well as high risk patients. PFS was 43 months vs 46 months for VCD and RVD cohorts (median f/u 19 and 24 months, respectively, p=0.399). OS was not reached for both cohorts (median f/u of 19 months and 26 months, respectively p=0.075).

Next we evaluated the CoMMpass data for comparison of OS. OS favored the patients treated with RVD as initial therapy compared to VCD (Hazards ratio 0.4549, p=0.0002). Conclusion: This trial is the first comparison of VCD versus RVD administered as induction therapy for myeloma patients. RVD was shown to be significantly superior to VCD in terms of CR and VGPR both as post-induction and post-transplant responses and favoring OS benefit. Similar results were observed in the CoMMpass trial and emphasizes the rationale for the preferential use of RVD as induction regimen vs VCD prior to ASCT.

PS-247
To Treat or not to Treat: Hyperelderly Multiple Myeloma

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With demographics shifting in the developed world, Haematologists are often called upon to treat myeloma patients at advanced age. Representation of this age group in clinical trials or cohort studies is almost non-existent. We aimed to explore real world treatment paradigms and survival outcomes of hyper elderly (≥85 years) MM patients in the novel agents era. We retrospectively estimated Overall Survival (OS), Event Free Survival (EFS: next treatment or death), cumulative incidence (CI) of next line with death competing and CI of death before next line. We retrieved treatment data from the ARIA database and survival status from the SPINE database from 2009 through October 2016. Relative survival (RS) was estimated from observed OS and expected OS calculated from UK population death rates obtained from the Human Mortality Database (www.mortality.org). Between 2009 and 2016 1328 patients were treated for MM in our Cancer Network. Of these, 102 were treated at the age of ≥85 and 89 have been followed-up from start of first line for a median of 37 months. Median age was 87 (85-96). Fifty-six per cent were men. Only 2 patients were enrolled in clinical trials. First line regimens were Thalidomide based (Thal Dex, CTD, MPT) in 50.6%, Bortezomib based (VD, VCD, MPV) in 16.1% and alkylator based (melphalan prednisolone or cyclophosphamide prednisolone) in 33.3%. Thirty three patients had second line treatment (VD or VCD in 50%) and 16 had third line treatment (LenDex in 13/16 patients). Median number of treatment lines of patients observed until death was 1 (1-5) in the ≥85 group, 2 (1-5) in the 75-84 group, 3 (1-7) in the 65-74 group and 3 (1-9) in the younger patients (<65 years). Median OS from start of first line was 22.2 months, significantly shorter than younger groups (75-84: 30.3 months). Early mortality in the ≥ 85 cohort was 17.3% (10.8-27%) at 6 months vs 10.1% (7.4-13.8%) in the 75-84 group. No difference in OS between men and women was observed. Patients ≥85 who received alkylator-only treatment had significantly poorer OS (median 14 months vs 35 months) and shorter EFS (208 days vs 351 days) after first line. Maximum CI of second line treatment was only 35.5% (24.4-46.8%), much lower compared to younger groups (65.8% in 75-84 group). Death CI before second line was 52.9% (40.4-64%) vs 24.6% in the 75-84 group. RS of patients ≥85 at 2 years after starting treatment was 0.92 (0.88-0.96) for males and 0.88 (0.84-0.91) for females versus 0.7 (0.67-0.73) in the youngest age group (<65 years). Patients ≥85 are considered too frail or have significant comorbidities and are often treated without novel agents. Our data shows significantly higher early mortality rate in the hyperelderly. RS is only marginally shortened, in contrast to younger MM patients. Offering

treatment to hyperelderly MM patients with more effective and less toxic regimens will improve clinical outcomes and RS.

PS-248
Randomized Phase II Trial of Combination Idiotype Vaccine and Anti-CD3/Anti-CD28 Costimulated Autologous T Cells in Patients with Multiple Myeloma Post-Autotransplantation

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Background: Despite major advances in the treatment of multiple myeloma (MM) only a minority of patients achieve long-term disease control. Immunotherapy combined with autologous hematopoietic stem cell transplantation (auto-HCT) may reduce relapse rates. Immunoglobulin idiotype (Id) conjugated with a carrier protein, Keyhole limpet hemocyanin (KLH), is a tumor-specific antigen in MM. Vaccine-primed, anti-CD3/anti-CD28 costimulated adoptive T-cell transfer can augment humoral and cellular immune responses to vaccination despite cytotoxic therapy. We hypothesized that Id-KLH vaccine + the vaccine-primed costimulated T cells will result in a robust Id-specific humoral and cellular response, compared to a control vaccine (KLH only). Methods: In this randomized, phase II trial, the primary objective was to determine if Id-KLH primed, costimulated T cells will induce a more robust Id-specific immunity than KLH-primed T cells. Eligible patients had IgG monoclonal protein. Patients were randomized 1:1 to receive either Id-KLH vaccine or KLH-only vaccine, followed by auto-HCT, and then vaccine- primed costimulated T cells followed by two booster doses of the vaccine they were randomized to. Results: A total of 36 patients were enrolled between 1/2013 and 5/2015. Sixteen (44%) were randomized to Id-KLH and 20 (55%) to KLH-only. There was no significant difference between the two groups in terms of age, cytogenetic risk status, ISS stage, renal function, induction therapy or disease status at transplant. No treatment-related mortality, infusion reactions or dose-limiting toxicity was seen in either arm. Five (31%) and 3 (15%) patients achieved complete remission (CR) by day+180 in the Id-KLH and KLH arms, respectively (p=0.42). Initial analysis for idiotype-specific immune response in a subgroup of patients revealed a significantly higher mRNA expression of immune activation genes IL-2, CCR6 and CD40 by NanoString nCounter in the Id-KLH group compared with the KLH only group. Sixteen (100%) and 19 (95%) went on to receive maintenance therapy with lenalidomide, lenalidomide + ixazomib or lenalidomide + Elotuzumab in the Id-KLH and KLH arms, respectively (p=0.42). After a median follow up of 27.4 months, 2-year PFS was 64% and 84% in Id-KLH and KLH arms, respectively (p=0.10). Conclusion: Id-KLH vaccine and vaccine-primed costimulated T cells can be safely administered in the setting of auto-HCT. As hypothesized, there was a more robust immune response in the Id-KLH group.

PS-249
A PHASE 3 RANDOMIZED, OPEN-LABEL STUDY OF ISATUXIMAB

(SAR650984) PLUS POMALIDOMIDE (POM) AND DEXAMETHASONE (DEX) VERSUS POM AND DEX IN RRMM

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Trial in Progress Treatment for refractory or relapsed and refractory multiple myeloma (MM) remain an unmet need. Isatuximab (ISA), an anti-CD38 monoclonal antibody with multiple mechanisms of tumor killing has shown efficacy and an acceptable tolerability profile in Phase 1/2 studies in patients with refractory or relapsed refractory MM (RRMM). This phase 3 prospective, multicenter, randomized, open-label study (NCT02990338; ICARIA-MM) is being conducted to evaluate the clinical benefit of ISA in combination with pomalidomide and low-dose dexamethasone (Pom/Dex) versus Pom/Dex for the treatment of adult patients with RRMM with demonstrated disease progression within 60 days of the last therapy, and who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination. Patients will be randomly assigned in a 1:1 ratio to either ISA (10 mg/kg IV on Days 1, 8, 15, and 22 in the 1st cycle; Days 1 and 15 in subsequent cycles) plus Pom (4 mg on Days 1 to 21) and Dex (at 40 mg for patients <75 years of age and at 20 mg for patients ≥75 years of age, on Days 1, 8, 15 and 22) or Pom and Dex. Treatment cycles will be 28 days each. Patients will continue therapy until disease progression, occurrence of unacceptable adverse events or their decision to discontinue the study, whichever comes first. The primary endpoint is progression-free survival (PFS), i.e. time from randomization to progressive disease or death from any cause. Response will be determined by IMWG criteria (2016). Key secondary endpoints include overall response rate and overall survival (OS). Safety evaluations include treatment-emergent AEs/serious AEs (including infusion-associated reactions), laboratory parameters, vital signs and assessment of physical examination, and second primary malignancies. Statistical analyses will be conducted according to a pre-specified plan; approximately 300 patients (150 in each arm) are expected to be adequate to achieve the targeted number of events for both PFS and OS. The study was launched in December 2016. Funding: Sanofi

PS-250
Influence of obesity on outcomes of patients with relapsed refractory multiple myeloma

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The prevalence of obesity is increasing worldwide. It has been associated with increased risk of some malignancies, including multiple myeloma (MM). However, its influence on the outcomes of patients with MM remains to be defined. We investigated the association between BMI and outcomes of patients with relapsed and/or refractory MM treated on a prospective clinical trial (MC0789) which treated patients in different cohorts of

Pomalidomide (2 vs. 4 mg; 21 vs. 28 days cycle) with fixed dose dexamethasome (dex) (40 mg oral weekly). Patients were divided in 2 groups, BMI less than 30 (non-obese; NO) or BMI 30 or more (obese; O). Responses were assessed according to established criteria. Continuous and categorical variables were compared between the two groups using two-sample t-test, Fisher's exact test or Chi squared test. Kaplan-Meier method was used to estimate overall survival and progression free survival. Results from the MC0789 clinical trial have been reported previously. Data on 331 patients was analyzed for this study, 101 were obese (O) and 229 non-obese (NO). 27% and 39% respectively were female, . Median weight (range) of O vs.NO was 97.9 (69-147) vs. 73.4 (36-105) kg; and BMI 32.4 (30-50) vs 25.7(14.6-29.9). Only 2 patients were underweight (BMI <18.5). 93% and 82% of O and NO had ECOG performance status of 0–1. Disease characteristics were similar in the 2 groups. 32% were ISS stage III in both. O and NO patients had received median of 3 (1-10) vs. 3 (1-14) prior regimens. 91%, 69% and 66% of O were previously treated with lenalidomide, bortezomib, or both vs 94%, 71% and 66% of NO. Cytogenetic information was available only for a subset of patients; 17% of both cohorts had 17p deletion. Median number of treatment cycles received by O and NO were 6 (1-74) and 4 (1-74). Grade > 2 hyperglycemia occurred in 25% and 10% (p=0.001) and dex dose reduction was done in 45% and 59% of O and NO patients,(p=NS). Partial response or better occurred in 41% of O vs 36% of NO (p=NS). Kaplan-Meier estimate of median PFS of O vs. NO was 47.9(14.6-NR)m vs. 9.2(6.6-12.8)m (p=0.006) and median OS was 47.9 (26.8-NR) vs. 20.5(13.9-31.7)m (p=0.007). Conclusion: In patients with heavily pretreated multiple myeloma obesity (BMI 30 or more) was associated with better outcomes compared to BMI < 30. Response rate was similar in the 2 groups but progression free and overall survival was significantly better in the obese group. The exact cause of this is unknown. Obesity has a number of physiologic consequences that may influence disease biology or effect of drug metabolism. Whether obesity also affects newly diagnosed MM patients is unknown. Future studies to confirm this finding in other cohorts and also study the role of obesity in newly diagnosed myeloma should be considered. Understanding the biologic basis of this phenomenon may provide useful insights for treatment.

PS-251

Improvement of Response for Multiple Myeloma patients on Lenalidomide Maintenance after Autologous Hematopoietic Stem Cell Transplantation (Auto HCT).

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Introduction: Lenalidomide maintenance (LM) starting between 2-3 months after auto HCT until progression is our standard of care for multiple myeloma (MM) patients. We aimed to determine the time to best response and the progression free survival (PFS) impact of improving response on LM. Methods: We retrospectively identified MM patients from the institutional registry who received their first Auto HCT within one year of diagnosis (excluding planned tandem HCT), were transplanted from 2012-2014, and were started on LM. Responses were determined using the IMWG criteria. After a landmark of 6 months on LM, a 12-month PFS was estimated by Kaplan-Meier methods. Results: With a median age of 61 (range 32-76), 76 patients met our inclusion criteria, with 55% male, 78% Caucasian, 28% stage 3 disease by the international staging system, and 17% with

high-risk cytogenetics. The majority of patients received lenalidomide, bortezomib, and dexamethasone (RVD) induction (72%), with the rest having doublet or triplet combinations including either agent and 14% having additional RVD after Auto HCT prior to LM. The median duration of LM was 21.5 months (range 1-49). Prior to Auto HCT, 13% achieved a complete remission (CR), 38% very good partial remission (VGPR), 26% partial remission (PR), 7% stable disease, and 3% progressive disease. After Auto HCT, this improved to 38% CR, 45% VGPR, and 17% PR, and further improved on LM to 60% CR, 30% VGPR, and 10% PR. Of the 47 patients not in CR after the Auto HCT, 21 (45%) deepened their response on LM with 19% going from PR to VGPR, 10% from PR to CR, and 71% from VGPR to CR. The time to best response on LM for the 21 responders was a median of 132 days (range 28-870). By 6 months on LM, 71 patients were alive and progression-free; the 12-month PFS (18-months from initiation of LM) was 72% (95% CI 56-92%) for patients starting LM in a CR, 93% (95% CI 80-100%) for patients whose response deepened by 6 months of LM, and 63% (95% CI 47-83%) for patients whose response did not change by 6 months of LM (p=0.11). Conclusion: Our data suggests that major responses on lenalidomide maintenance are unlikely to occur after 6 months of therapy. Therefore, clinical trials aimed at deepening response with other therapeutic strategies should be explored in patients with stable disease after 6 months of lenalidomide maintenance.

PS-252 (d)
Bortezomib Versus Non-Bortezomib Based Initial Treatment for Transplant Ineligible Patients with Light Chain Amyloidosis

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Introduction: Chemotherapeutic options for patients (pts) with light chain amyloidosis (AL) who are not transplant candidates include bortezomib (BTZ) based therapy, melphalan + steroids, & less commonly, IMiDs. This study aims to compare efficacy of BTZ based treatment to other therapies. Methods: Pts with AL seen within 90 days of diagnosis at our institution over a 10-year period (2006 to 2015) who did not undergo a stem cell transplant as initial treatment were identified. Data pertaining to demographics, treatment & follow-up was collected from electronic medical records. Results: Initial therapy was BTZ based in 38% (n=275) pts including BTZ + steroids in 24% (n=67) & BTZ + others (commonly cyclophosphamide) in 76% (n=208). Non-BTZ based treatment (62%; n=450) was melphalan-based in the majority (92%, n=414) followed by IMiDs & other drugs (8%, n=36). Median age (66.3 years, range 32.2 to 93.6), involved light chain (lambda 73%, n=523) & median bone marrow plasma cells (10%, range 0 to 91) were similar in both groups. Median dFLC was higher in the BTZ group (29 mg/dL vs. 23 mg/dL; p=0.017). There was no difference in organ involvement. In the BTZ group, organ involvement was as follows: cardiac (81%, n=219), renal (62%, n=168) & hepatic (18%, n=48). In the non-BTZ group: cardiac (78%, n=346), renal (57%, n=247) & hepatic (19%, n=85). Median duration of first line treatment was similar in the 2 groups, BTZ cohort: 5.9 months (3.3 – 9.3) & non-BTZ cohort: 6.2 months (3.6 – 10.4). Rates of very good partial response (VGPR) or better were higher in the BTZ group (64 % vs. 54%, p=0.0002) & pts achieved VGPR faster with higher rates of

VGPR or better seen at 3 months (48% vs. 27%, p <0.0001) & 6 months (57% vs. 34%, p < 0.0001) after initiation of therapy compared to non-BTZ treatment. In a multivariable model, BTZ based treatment & dFLC at diagnosis were predictors of VGPR. Rates of organ response were similar amongst the 2 groups, cardiac response 43% in BTZ vs. 46% in non-BTZ (p=0.61), renal response 64% vs. 62% (p=0.71) and liver response 26% vs. 46% (p=0.1). However, median time taken to achieve a cardiac response was shorter in the BTZ group (23 vs. 38 weeks, p=0.0026). Relapse or progression requiring change in therapy was more common in the non-BTZ group (38%, n=143/372) compared to BTZ based treatment (28%, n=67/236); p =0.01. However, no difference in overall survival was observed in pts treated with BTZ (2.2 years; 95% confidence interval (CI): 1.7 to 3.3) vs. non-BTZ therapies (1.7 years; 95% CI: 1.3 to 2.5); p=0.34. Conclusion: Treatment with BTZ based regimens resulted in a deeper response including higher rates of early VGPR at 3 & 6 months. Moreover, these pts achieved cardiac response faster & had lower rate of relapse. However, no difference in overall survival was seen, which may be explained by subsequent use of BTZ based therapies in this population.

PS-253

Phase 2 Study of Pomalidomide (POM) + Low-Dose Dexamethasone (LoDEX) Following Second-Line Lenalidomide (LEN)-Based Treatment (Tx) in Patients (Pts) With Relapsed or Refractory Multiple Myeloma (RRMM): An Updated Analysis of Efficacy and Safety

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Background: POM + LoDEX is approved for the Tx of pts with RRMM who had ≥ 2 prior Tx lines, including LEN and a proteasome inhibitor. In clinical trials, POM + LoDEX had comparable efficacy in pts refractory to their last prior Tx with LEN and in the overall pt population (San Miguel Lancet Oncol 2013; Richardson Blood 2014). This is an updated analysis of cohort A of the MM-014 trial, in which pts received POM + LoDEX immediately after relapsing or being refractory to LEN-based second-line Tx. The study was amended to include a cohort (B) of pts treated with POM + LoDEX + daratumumab. Methods: Pts were ≥ 18 yrs with documented MM, measurable disease, 2 prior lines of Tx, and progressive disease (PD) after ≥ 2 cycles of second-line LEN-based Tx. Pts received 28-day cycles of POM 4 mg/d on d1-21 + LoDEX 40 mg/d (20 mg/d if > 75 yrs) on d1, 8, 15, and 22; mandatory thromboprophylaxis. The primary endpoint was overall response rate (ORR; ≥ partial response [PR]) assessed by modified IMWG criteria. Other key endpoints included time to response (TTR), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), secondary primary malignancies (SPMs), and biomarkers. Results: Of 51 enrolled pts in cohort A, 39 (76.5%) discontinued Tx, mostly due to PD. A total of 45 pts (88.2%) were refractory to their last Tx with LEN, 37 (72.5%)

had prior Tx with bortezomib, and 33 (64.7%) had prior stem cell transplant. Median duration of prior LEN-containing Tx was 24.6 mos. With a median follow-up of 13.6 mos, ORR was 29.4% (1 [2.0%] complete response, 5 [9.8%] very good PRs, and 9 [17.6%] PRs) and median TTR was 1.9 mos; 66% had ongoing response at 1 year. Median PFS was 13.8 mos. The 1-year OS and TTP rates were 88.2% and 60.9%, respectively. Common grade 3/4 AEs included anemia (25.5%), neutropenia (11.8%), and infections (19.6%; including pneumonia [9.8%]). Any-grade pulmonary embolism (3.9%), deep vein thrombosis (2.0%), and peripheral sensory neuropathy (3.9%) were infrequent; no SPMs observed. In the immune subset analysis, the proportions of CD3+ and CD3+/CD8+ T cells after Tx (cycle 3, 5, d1) were significantly elevated vs baseline (72.6% vs 67.8% and 36.9% vs 32.1%, respectively; P<.05). Pts with response also had significantly elevated proportions of these T-cell populations, but pts with no response did not. The differences in changes from baseline for CD3+ and CD3+/CD4+ T-cell populations were significantly greater in pts with response vs no response (10.4 vs −0.8 and 4.2 vs −3.5, respectively; P<.05). Conclusions: This updated analysis of the MM-014 trial shows POM + LoDEX is safe and effective and can be used immediately after LEN-based Tx in pts with RRMM. Of note, median PFS was longer than previously seen in trials of pts with more prior Tx. Rates of hematologic AEs were lower compared with previous studies evaluating POM + LoDEX in pts with RRMM.

PS-254 (d)
Updated Results from ASPIRE and ENDEAVOR, Randomized, Open-Label, Multicenter Phase 3 Studies of Carfilzomib in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: In RRMM, carfilzomib, lenalidomide, and dexamethasone (KRd) was superior to Rd in ASPIRE (Stewart, N Engl J Med. 2015), and carfilzomib and dexamethasone (Kd) was superior to bortezomib and dexamethasone (Vd) in ENDEAVOR (Dimopoulos, Lancet Oncol. 2016) for the primary endpoint of progression-free survival (PFS) by independent review. We report safety and efficacy data after 6–7 months (mo) of additional follow-up. Methods: Adults with RRMM who received 1–3 prior regimens were randomized 1:1. In ASPIRE, pts received lenalidomide (25 mg) on days 1–21 and dexamethasone (40 mg) on days 1, 8, 15, and 22 (28-day cycle). KRd pts received carfilzomib on days 1, 2, 8, 9, 15, and 16 during cycles 1–12 (20 mg/m2 [days 1 and 2 of cycle 1]; 27 mg/m2 thereafter); carfilzomib was omitted on days 8 and 9 in cycles 13–18. In ENDEAVOR, Kd pts received carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² thereafter) on days 1, 2, 8, 9, 15, and 16 and dexamethasone (20 mg) on days 1, 2, 8, 9, 15, 16, 22, and 23 (28-day cycle). In the Vd group, bortezomib was given (1.3 mg/m²; IV or SC) on days 1, 4, 8, and 11, and dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12 (21-day cycle). Comparisons were per stratified log-rank test; data presented

here are per investigator assessment. Results: In ASPIRE, 792 pts were randomized. Baseline characteristics were balanced between arms. At a median follow-up of 37.8 mo (KRd) and 37.0 mo (Rd), median PFS was 26.1 mo (KRd) and 16.6 mo (Rd) (HR=0.67; 95% CI:0.56–0.80; P<.0001); 18-mo PFS rates were 64.5% (KRd) and 46.6% (Rd). Median time to progression (TTP) was 30.5 mo (KRd) and 18.9 mo (Rd) (HR=0.62; 95% CI:0.51–0.76; P<.0001). Median time to next treatment (TTNT) was not estimable (KRd) and 24.3 mo (Rd) (HR=0.62; 95% CI:0.50–0.77; P<.0001). 16.8% (KRd) and 19.0% (Rd) of pts discontinued due to AEs. Grade ≥3 AE rates were 5.9% and 2.2% for hypertension, 3.9% and 1.8% for cardiac failure, and 4.6% and 5.4% for peripheral neuropathy for KRd and Rd, respectively. In ENDEAVOR, 929 pts were randomized. Baseline characteristics were balanced between arms. At a median follow-up of 19.4 mo (Kd) and 17.7 mo (Vd), median PFS was 17.6 mo (Kd) and 9.4 mo (Vd) (HR=0.53; 95% CI:0.44–0.63; P<.0001); 18-mo PFS rates were 48.7% (Kd) and 23.9% (Vd). Median TTP was 19.4 mo (Kd) and 10.2 mo (Vd) (HR=0.50; 95% CI:0.42–0.60; P<.0001). Median TTNT was 26.1 mo (Kd) and 14.5 mo (Vd) (HR=0.49; 95% CI:0.40–0.60; P<.0001). 15.8% (Kd) and 14.9% (Vd) of pts discontinued due to AEs. Grade ≥3 AE rates were 13.8% and 3.3% for hypertension, 5.2% and 2.0% for cardiac failure, and 2.4% and 8.6% for peripheral neuropathy for Kd and Vd, respectively. Conclusion: Consistent with the primary analyses, these results show that incorporation of carfilzomib into treatment regimens in pts with RRMM results in clinically meaningful improvements in PFS and a favorable benefit–risk profile.

PS-255
Efficacy and Safety of Weekly Bortezomib Containing VMP Followed By Bortezomib Maintenance Therapy in Unfit or Frail Multiple Myeloma Patients

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Back ground: According to VISTA study, the prognosis of elderly multiple myeloma (MM) patients has been improved with VMP therapy. However, intensive chemotherapy has induced severe adverse events (AEs), resulting in highly discontinued rate, especially often seen in unfit or frail patients. We designed phase 2 clinical study, BoRtezomib-based Optimized therapy Aiming Disease control in Japan (BROAD-J study), based on a weekly VMP as induction therapy followed by maintenance therapy with bortezomib (Bor-MT) with every two weeks administration for newly-diagnosed (ND) symptomatic non-transplant eligible MM patients. (UMIN 00007335) Method: From August 2011 to June 2016, according to IMWG criteria, 87 patients older than 65 years with symptomatic MM were eligible for this trial . The primary objectives were included maximum response and time to progression duration. Secondary objective was the continued treatment duration and adverse event rate. The induction phase consisted of VMP treatment: Melpharan: on days 1-4 , every 35-day cycle; prednisolone: on days 1-4 , every 35-day cycle; Bortezomib: 1.3mg/m2, d1, 8, 15, 22 every 35-day cycle. After 9 cycles of VMP therapy, the maintenance therapy starts. The maintenance phase was consisted of twice a month bortezomib administration (1.3 mg/m2) without dexamethasone until progressive disease. Dose reductions of bortezomib were allowed according to instructor• fs recommendation. Patients could receive supportive therapy including bisphosphonates and transfusions as necessary. AEs were graded according to NCI-CTCAE v4.0. Results: Mean age was 75 years (66-88), sex ratio was 44:43 (M: F), and ISS stage was I 12%, II 43%, III 43%. High risk cytogenetics abnormalities were observed in 13 patients (15%). Overall response rate was 87%

and complete response was obtained in 22 patients (25%) . Median progression free survival (PFS) was 36 months and median overall survival was 57 months. Median PFS was significantly higher with patients who obtained CR or VGPR than PR or SD (P<0.0001). Significantly higher ORR, rate of VGPR or better, and rate of CR or better were achieved in patients with revised ISS I stage, respectively. In induction phase, 32% of patients were suffered from greater than grade 3 AEs, whereas only 3% had grade 3 or 4 AEs in maintenance phase. Discussion: This trial reveals that VMP regimen with weekly bortezomib administration is effective and tolerable for unfit or frail elderly MM patients. In addition, maintenance therapy of twice a month bortezomib administration was effective in patients who obtained VGPR or more better. These results are no way inferior to results of VISTA trial. However, high R-ISS stage patients or poor treatment responders did not obtain the benefit of this setting, so, another setting with anti-myeloma antibody (i.e. elotuzumab or daratumumab) may be warranted in the future for such patients.

PS-256
RAD Regimen Increases Bone Formation and Reduces Bone Resorption and Angiogenesis in Patients with Newly Diagnosed Myeloma: Results of a Phase 2 Study

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Introduction/Background: There is limited data for the efficacy of RAD combination (lenalidomide, adriamycin and dexamethasone) on newly-diagnosed myeloma (NDMM) patients. The primary endpoint of this phase 2 study was the assessment of overall response rate (ORR) after 4 cycles of RAD induction in NDMM patients who are eligible for ASCT. Exploratory endpoints included: i) the yield of stem cell collection after RAD; ii) the effects of RAD on biochemical markers of bone metabolism: CTX, TRACP-5b, bone-alkaline phosphatase (bALP), P1NP, osteocalcin, soluble RANKL, osteoprotegerin (OPG) and dickkopf-1 (Dkk-1) and iii) the effects of RAD on angiogenic cytokines: angiopoietin- (Angp) 1 & -2, angiogenin (Ang), VEGF and bFGF. Methods: Lenalidomide was administered at a dose of 25 mg, po, daily, on days 1-21 of a 28-day cycle; dexamethasone was given at a dose of 40 mg, po, on days 1, 8, 15, and 22, while adriamycin was administered as IV bolus infusion at a dose of 9 mg/m2, on days 1-4 of each cycle. Serum levels of the above markers of bone remodeling and angiogenesis were measured before and after 4 cycles of RAD, using ELISA methodology. Results: Between November 2014 and February 2016, 45 patients (median age: 56 years) were enrolled. Osteolytic lesions were present in 33 (73%) patients, while 3 (6.6%) had hypercalcemia (>11 mg/dl). All but one patient completed 4 cycles of RAD. Best response included one (2.2%) CR, 8 (17.8%) VGPRs, 21 (46.7%) PRs, for an ORR of 66.7%, while 14 (31%) patients had stable

disease and one progressed during the 4th cycle of treatment. Adverse events of grade 3 or 4 included mainly anemia (4 patients, 9%), neutropenia (3, 6.6%) and febrile neutropenia (one patient). Forty (89%) patients had adequate stem cell collection post-RAD induction (mean±SD: 8.94±6.50 x106/kg CD34+ cells). Patients at baseline had elevated levels of CTX, TRACP-5b, sRANKL/OPG, Dkk-1, Ang, VEGF, VEGF-A, bFGF and reduced levels of Angp-1/Angp-2, bALP and P1NP compared to 30 healthy subjects of similar age and gender (p<0.01 for all comparisons). RAD therapy resulted in a reduction of circulating CTX (p=0.03), TRACP-5b (p<0.01), Ang (p=0.02), VEGF (p=0.01) and bFGF (p<0.01). Moreover, RAD increased serum levels of bALP (p=0.036), P1NP (p=0.028) and Ang-1/Ang-2 ratio (p=0.022). These alterations occurred irrespective of response, although patients who achieved at least VGPR tended to have more profound differences in the above parameters. Conclusions: RAD resulted in successful induction for NDMM patients and produced an ORR of approximately 67%. RAD reduced bone resorption and increased bone formation; the latter has not been previously described with lenalidomide-based regimens. Furthermore, RAD reduced angiogenic cytokines and this supports the action of the regimen also through the disruption of the interactions between myeloma and stromal cells.

PS-257
Bortezomib and Lenalidomide (VR) Consolidation Post-ASCT without Dexamethasone and Bisphosphonates: Final Analysis of a Prospective Study

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Introduction/Background: Bortezomib, lenalidomide and dexamethasone (VRD) consolidation is an effective therapy for patients with multiple myeloma (MM) post-ASCT. The primary endpoint of the study was to explore the efficacy of VR consolidation, without dexamethasone, on newly-diagnosed MM patients who received bortezomib-based induction and underwent ASCT. Secondary endpoints included: safety, TTP, TtNT, OS and effects of VR on bone metabolism, in the absence of bisphosphonates (BPs). Methods: Patients who achieved at least stable disease post-ASCT were eligible for participation in the study. Consolidation consisted of 4 cycles of VR, which started on day 100 post-ASCT. Bortezomib was given at a dose of 1.3 mg/m2, on days 1, 4, 8 and 11 of a 21-day cycle; lenalidomide was given at a dose of 25 mg, on days 1-14. Patients did not receive any BP during or post-ASCT and during VR consolidation. The following bone remodeling markers were measured on the day of SC collection, before and after VR consolidation: i) osteoclast regulators RANKL and OPG, ii) osteoblast inhibitors Dkk-1 and sclerostin, iii) bone resorption markers CTX and TRACP-5b and iv) bone formation markers bALP and osteocalcin (OC). Results: Fifty-nine patients (30M/29F, median age 54 years) participated in the study. After induction, one (1.7%) patient achieved sCR, one (1.7%) CR, 30 (50.8%) vgPR, 22 (37.3%) PR, while 5 (8.5%) patients had SD. After ASCT, 34 (57.6%) patients improved their status of response; in total, 14 (23.7%) achieved sCR, one (1.7%) CR, 35 (59.3%) vgPR and 9 (15.3%) PR. After VR consolidation, 23/59 (39%) patients further

improved their response; overall, 30 (50.8%) patients achieved sCR, one (1.7%) CR, 26 (44.1%) vgPR and two (3.4%) PR. The most common adverse events included neutropenia (68%, grade 3/4 23%), thrombocytopenia (59%, grade 3/4 7%), and peripheral neuropathy (56%, grade 3/4 2%). Post-VR consolidation there was a reduction of sRANKL/OPG ratio and sclerostin (p<0.001) in all patients. Patients who achieved at least vgPR showed higher reductions of sRANKL/OPG and sclerostin compared to all others (p<0.01). There was no reduction of bone resorption markers, possibly due to the dramatic reduction of these markers during induction therapy, when zoledronic acid was given. No skeletal-related events (SREs) were observed during the study period. The median follow-up after ASCT was 35 months and 54% of patients have progressed. The median TTP after ASCT was 42 months (95% CI 29-54 months). There was a trend for longer TTP in patients achieving sCR (48 vs. 35 months, p=0.145). The median TtNT has not been reached yet. Conclusion: Four cycles of VR consolidation without dexamethasone improves the quality of response in approximately 40% of patients and produces long TTP. In the absence of bisphosphonates, VR consolidation has beneficial effects on bone metabolism and is related with no SREs.

PS-258
Systematic Literature Review and Network Meta-Analysis of Treatments for Relapsed/Refractory Multiple Myeloma Patients

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INTRODUCTION Many new treatment options recently became available for relapsed/refractory myeloma (R/RMM) patients. Direct comparisons are, however, lacking which makes it extremely difficult to evaluate the relative added value of each drug. Our aim was to synthesize all efficacy evidence enabling a comparison of all treatments. METHODS We performed a systematic literature review to identify all phase 3 randomized controlled trials (RCTs) using EMBASE®, MEDLINE®, MEDLINE® in-process, Cochrane Central Register of Controlled Clinical Trials and the website www.clinical-trials.gov. A conventional network meta-analysis (NMA) based on progression-free survival (PFS) outcomes allowed a comparison of all available treatment options using a Bayesian fixed effect NMA. The oldest treatment, dexamethasone, was used as reference treatment. RESULTS Seventeen RCTs were identified including sixteen treatment options: dexamethasone (Dex), oblimersen-dexamethasone (OblDex), thalidomide/thalidomide-dexamethasone (Thal/ThalDex), bortezomib/bortezomib-dexamethasone (Bor/BorDex), lenalidomide-dexamethasone (LenDex), pegylated doxorubicin-bortezomib (PeglDoxBor), bortezomib-thalidomide-dexamethasone (BorThalDex), vorinostat-bortezomib (VorinoBor), panobinostat-bortezomib-dexamethasone (PanoBorDex), carfilzomib-lenalidomide-dexamethasone (CarLenDex), pomalidomide-dexamethasone (PomDex), elotuzumab-lenalidomide-dexamethasone (EloLenDex), carfilzomib-dexamethasone (CarDex), ixazomib-lenalidomide-dexamethasone (IxaLenDex), daratumumab-lenalidomide-dexamethasone (DaraLenDex) and daratumumab-bortezomib-dexamethasone (DaraBorDex). To include all trials within one framework, we assumed: i) the relative efficacy of Bor versus Dex and BorDex versus Dex is the same, ii) the relative efficacy of Thal versus Dex and ThalDex versus Dex is the same, iii) time to progression (TTP) can be used as proxy for PFS in case of missing hazard ratios (HRs) and 95% confidence intervals of PFS, and iv) no difference in efficacy due to dosage scheme

(100 versus 200 versus 400 mg Thal) and administration method (intravenous versus subcutaneous Bor). Fourteen out of sixteen treatments were significantly better than Dex (HRs ranged from 0.13 to 0.75). Only OblDex ranked lower; the HR was, however, not significantly different (HR: 1.08; 95% CrI: 0.79 - 1.45). Eleven treatments reduced the risk of progression or death with more than 50%. DaraLenDex was identified as the best treatment because it was the most favorable in terms of i) HR (0.13; 95% CrI: 0.09 - 0.19), and ii) probability of being best (99% of the simulations). CONCLUSIONS Our NMA included all available R/RMM treatments and identified DaraLenDex as being most effective. NMAs become increasingly important because they provide a complete overview of each treatment's relative efficacy in case of missing head-to-head comparisons.

PS-259

Phase 2 Multicenter Study of Pomalidomide (POM) Plus Low-Dose Dexamethasone (LoDEX) in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM) and Renal Impairment (RI): An Updated Safety Analysis

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Background: Renal failure, a common complication for pts with MM, increases in incidence throughout the disease and is associated with poor prognosis. Here, we report updated safety results of the European MM-013 trial, in which pts with RRMM and moderate or severe RI, including pts on hemodialysis, were treated with POM + LoDEX. Methods: This phase 2 study enrolled 3 cohorts of pts with RRMM and RI: cohort A included pts with moderate RI (eGFR between 30 and 45 mL/min/1.73m^2), cohort B included pts with severe RI (eGFR ≤ 30 mL/min/1.73m^2) not requiring hemodialysis, and cohort C included pts with severe RI requiring hemodialysis. Pts received 28-day cycles of POM 4 mg/day and DEX 40 mg/day (20 mg/day if > 75 years old) until disease progression or unacceptable toxicity. Supportive care, such as hematopoietic growth factors, was allowed; thromboembolic prophylaxis was required for all pts not on hemodialysis. Adverse events (AEs) were graded according to the CTCAE v4.03. Results: At the data cutoff date of November 15, 2016, 81 pts (33 in cohort A, 34 in cohort B, 14 in cohort C) were enrolled, of which 16 (19.8%) were still on Tx. A total of 65 pts (80.2%) discontinued Tx, mostly due to progressive disease (45.7%). There were 23 (28.4%) reported deaths during the Tx period (6 in cohort A, 10 in cohort B, and 7 in cohort C). Median number of cycles on study medication was 5.0 (range, 1-21) overall (7.0 [range, 1-21], 5.5 [range, 1-16], and 3.0 [range, 1-10] in cohorts A, B, and C, respectively). Median average daily POM dose was 4 mg/day for all cohorts. POM dose reductions were reported in 15 pts (18.5%) overall (21.2% [n = 7], 17.6% [n = 6], and 14.3% [n = 2] in cohorts A, B, and C, respectively). POM dose reductions due to

treatment-emergent AEs occurred in 13 pts (16.0%), mostly due to thrombocytopenia (7.4%) and neutropenia (3.7%). At least 1 POM dose interruption was noted in 50 pts (61.7%) overall (60.6% [n = 20], 70.6% [n = 24], and 42.9% [n = 6] in cohorts A, B, and C, respectively). Incidence of grade 3/4 AEs was similar between cohorts (87.9%, 88.2%, and 92.9% in cohorts A, B, and C, respectively). The most common grade 3/4 hematologic AEs were neutropenia (60.6%, 44.1%, and 57.1% in cohorts A, B, and C, respectively) and anemia (21.2%, 32.4%, and 57.1%). Grade 3/4 febrile neutropenia was 3.0%, 2.9% and 0% in cohorts A, B, and C, respectively. Grade 3/4 infections were reported in 25 (30.9%) pts (36.4%, 26.5%, and 28.6% in cohorts A, B, and C, respectively), of which 7 pts (8.6%) had pneumonia (12.1%, 5.9%, and 7.1%). Conclusions: Results of this study investigating POM in combination with LoDEX in pts with RRMM and RI show a similar safety profile as previously reported in pts without renal insufficiency (San Miguel et al, Lancet Oncol, 2013; Richardson et al, Blood, 2014). POM + LoDEX can be safely administered in pts with moderate or severe RI, including those on hemodialysis.

PS-260
Use of the Hevylite™ assay as an early predictive tool in MGUS and smoldering myeloma transformation, as well as myeloma relapse: Results from the EU FP7 project OPTATIO

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Introduction: in the framework of the EU FP7 project OPTATIO longitudinal measurements of the Hevylite™ assay defined hevylite ratios HLRi/u (involved/uninvolved heavy chain) and differences HLD i/u , were performed in 3 major hematological centers in Austria, Hungary and the Czech Republic to address the usefulness of this parameter as an early predictive marker of MGUS or smoldering (SMMM) myeloma transformation and myeloma relapse. Methods: the Hevylite™ assay was provided by project partner The Binding Site Ltd. (Schwetzingen, Germany). Measurements were run on SPA PLUS™ plattforms and quality control assured by regular cooperative test. Clinical follow up data were retrieved from the Czech and Austrian Myeloma Registries. Results: 124 pts. with MGUS, 42 pts. with SMMM and 226 pts. with MM were judged to be informative (having at least 2 sequential measurements and a minmum of 2 years of follow up). The 124 pts. with MGUS (female 42%, male 58%) with a median age of 63 years showed a median HLRi/u of 3.33 and a median HLD i/u of 3.87 g/l. The median Freelite ratio (FLC i/u) was determined to be 3.33. The 226 pts. with MM (female 34%, male 66%) with a median age of 68 years showed a median HLRi/u of 3.55 and the median Freelite ratio (FLC i/u) was determined to be 3.55. Out of the 124 pts. with MGUS 9 transformed during the relatively short observation period (3 to indolent NHL, 1 to AL-Amyloidosis and 5 to frank MM). Most of the pts. had shown pathological HLRi/u and HLD i/u in the upper quartile of all measurements. The putative predictive power rof highly pathological HLRi/u and HLD i/u was much more pronounced than the predictive power of the corresponding FLC analysis. We will present further data on the effect of Hevylite™ on treatment effectivity and durability of responses (time to next treatment, etc.) in MM, as well as a comparison with conventional risk factors and risk models like ISS, Mayo-score, PETHEMA score and cytogenetics. Discussion: In the framework of a tri-national multicentre effort we found the Hevylite™ assay to be a

promising predictive tool to identify high risk MGUS, SMMM and MM. In our hands the assay seems to be superior to conventional Freelite tests (obviously excluding LC MM) and integration of the HLR in scoring systems seems to be warranted. As even much more informative invasive marrow based MRD technologies can not be performed with higher frequencies indefinitively HLRi/u and HLDi/u may be used as „gatekeeper assays" to trigger MRD analysis and subsequent therapeutic interventions.

PS-261
Autologous stem cell transplant in Multiple Myeloma: 15 year data from cancer hospital

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Introduction: Novel agent based induction therapy followed by consolidation with high dose therapy and autologous stem cell transplant (ASCT) with maintenance is considered standard of care for Myeloma patient management. We, hereby present our 15 yr data of ASCT in myeloma. Material and methods: This is a retrospective study, where records of all patients who underwent ASCT at our centre from the yr 2002 to 2016 were analysed. Results: A total of 141 patients (90 males and 51 females) with median age 55yr (23-68), underwent ASCT. At presentation, 109 (77.3%) of patients had bone disease; 85 (60.2%) had anemia; 14 (9.9%) patients had renal failure and 15 (10.6%) patients had hypercalcemia. 27 (19.1%) patients were ISS 1; 34 (24.1%) patients were ISS 2; 42 (29.7%) patients were ISS 3 and stage unknown in 38 (26.9%) patients. 58 (41.1%) of patients were IgG class, 18 (12.7%) IgA and 21 (14.8%) had light chain myeloma. Class could not be ascertained in 43 (30.4%) of cases. Bortezomib, dexamethasone with thalidomide/cyclophosphamide or Lenalidomide- dexamethasone were most common therapy regimens used for a median of 4 cycles (3-26) prior to transplant and 9 patients (6.4%) received only chemotherapy based regimens. Median time from diagnosis to transplant was 7 months (3-79 months), with 68 (48.2%) undergoing early transplant (< 6 months in first remission), 56 (39.7%) undergoing late transplant (>6 months in first remission) and 17 (12.0%) patients undergoing delayed transplant beyond first remission. Median dose of Melphalan was 200mg/m2 (140-200 mg/m2) and CD 34 dose was 3.81 x 106cells/kg (1.41-9.34 x 106cells/kg). Median grade of maximum mucositis during peri-transplant period was 3, packed cell transfusion was 2 (0-20) and platelet transfusion was 9 (3-68). Neutrophil and platelet engraftment was achieved at median of 10 and 11 days respectively. 90% patients experienced febrile neutropenia, with documented bacterial/fungal infections in 21% patients. Two patients expired before engraftment (1.41 %). Best response post transplant was equal or more than VGPR in 82.9% (n=117), PR 12.0% (n=17) and progressive disease in 3.5% (n=5) and not assessed in 2 (1.4%) patients (one lost to follow up and other not yet completed 100 days post ASCT). 65 (46.09%) and 48 (34.04%) of patients were on Lenalidomide and Thalidomide maintenance respectively. Median duration of follow-up was 35 months. Median progression free survival was 19.5 months (1-88 months), 62 (43.9%) patients relapsed. Overall survival was 85.10%. Delay in transplant may confer a higher risk of relapse (p= 0.025). Poor correlation was seen between PFS and age, ISS stage or Melphalan dose. Conclusion: ASCT is a feasible option in Indian settings with low mortality and significantly improve PFS if performed early. Relapse rate correlate with delay in transplant. Post transplant response also showed a trend of correlation with relapse risk.

PS-262
Synergistic antitumor immunity by dendritic cells in combination with pomalidomide and dexamethasone in a murine myeloma model

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Background: Pomalidomide (Pom) plus dexamethasone (Dex) could be considered one of the new treatment options in patients with relapsed and/or refractory multiple myeloma (MM). Recently, several diverse agents would be combined to improve the therapeutic efficacy. In this study, we investigated the preclinical efficacy of combined therapy with dendritic cells (DCs) and Pom-Dex in a murine myeloma model. Materials and Methods: After establishing myeloma-bearing mice, four treatment groups were designed to be a mimic protocol as like treatment in clinics as following: 1) PBS control, 2) DCs, 3) Pom + Dex, and 4) DCs + Pom + Dex. After vaccination, preclinical and in vitro immunological responses were evaluated. Results: Treatment of DCs combined with Pom-Dex strongly inhibited tumor growth compared with other groups. In vitro immunological analyses revealed that these enhanced anti-tumor effects were closely associated with the decrease of immune-regulatory cell populations, such as regulatory T cells (Tregs) and type 2 macrophages (M2), and the increase of effector immune cell populations, including activated CD4+ T cells and type 1 macrophages (M1), accompanied with the activation of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells in the splenocytes from the treated mice. Conclusion: This study suggests that DC vaccination strongly enhances the anti-tumor immunity when combined with Pom and Dex, by skewing immuno-suppressive status toward immuno-supportive status in tumor microenvironment, in a murine myeloma model.

ELECTRONIC POSTERS

1. Disease Biology and Related Disorders

E-263
Lymphocytes Characterization in Patients with IgM Monoclonal Gammopathy

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Abstract INTRODUCTION: In 15-20% of patients with monoclonal gammopathy the IgM type that is produced either by clonal B-cells or plasma cells can be identified. The MYD88 (L265P) mutation is found in lymphoplasmacytic lymphoma and in 47–87% of IgM monoclonal gammopathy patients. Flow cytometry and molecular analysis of MYD88 might facilitate the identification of the underlying clone of monoclonal IgM, i.e. B-cell or plasma cell origin, linking the MYD88 (L265P) mutation to an immunophenotype. METHODS: Twelve patients with IgM monoclonal gammopathy were included and evaluated with regard to gender, age, serum IgM level and serum immunofixation. For characterization of the lymphatic clone cytology, molecular analysis of MYD88 (L265P) mutation and multicolor flow cytometry of bone marrow aspirates were

performed. RESULTS: In five patients a clonal plasma cell population (CD38+, CD138+, SLAMF7+, κ/λ restricted) was found, among them two patients were positive for the MYD88 (L265P) mutation. In four patients, we identified a B-cell clone (CD19+, κ/λ restricted) and all of these patients showed a MYD88 (L265P) mutation. In three patients a transitional B-/plasma cell immunophenotype (CD19+, CD38+, SLAMF7+, CD138+, κ/λ restricted) was found, two patients were positive for MYD88 (L265P) mutation. CONLUSION: In patients with IgM monoclonal gammopathy a B-cell, plasma cell or a transitional B-/plasma cell phenotype population could be identified by multicolor flow cytometry as the underlying lymphatic clone. The MYD88 (L265P) mutation was therefore not strictly associated with a certain immunophenotype.

E-264
A CLINICO PATHOLOGICAL PROFILE ANALYSIS OF POEMS SYNDROME A SERIES OF 5 CASES

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Introduction: POEMS syndrome is rare multisystem disorder of plasma cell origin. As the syndrome manifests as conglomeration of symptoms of different organ dysfunction, misdiagnosis is common. Here we are reporting 5 cases of POEMS syndrome diagnosed in our centre and their clinical profiles. Patient & Method: 5 consecutive patients diagnosed as POEMS syndrome from August 2012 to February 2016 are included in this study. We analyzed their general information, symptoms and signs, laboratory tests. Results: The average age of patients was 61.8 years. The patients were referred from different departments, because of different initial presenting symptoms. The time delay from onset of symptom to accurate diagnosis was 5 to 36 months. The patients had peripheral neuropathy (100%), Hepato-splenomegaly (80%), lymphadenopathy (40%), hypothyroidism (80%), hypogonadism (20%), pigmentary skin changes (100%), and sclerotic bony lesion (40%). The serum Cortisol level was normal in all of them. All patients had monoclonal protein with lambda restriction (100%). IgA was more common (80%). Discussion: POEMS syndrome is one of the rare disorders which is commonly misdiagnosed. The misdiagnosis varied from congestive cardiac failure, chronic liver disease, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) to carcinoma of unknown origin. Presence of constellation of symptoms and sign and a high clinical suspicion may help in early diagnosis of such case. The rapid and proper diagnosis helps in early initiation of early treatment and may limit morbidity and organ dysfunction in these patients. Conclusion: This study provides a clinic-pathological profile of POEMS syndrome and raises awareness for keeping a high clinical suspicion for diagnosis of such multi system disorder. The early recognition of clinical constellation and properly directed specific investigation may help in early diagnosis of POEMS syndrome and help in avoiding misdiagnosis.

E-265
18F-FDG PET/CT findings and baseline clinical parameters in multiple myeloma

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Background: In a recent study, a positive correlation was reported between baseline fluorodeoxyglucose (FDG) positron emission tomography (PET) findings and clinical parameters in patients with multiple myeloma (MM). FDG-PET findings were associated with disease outcomes. Aims: We aimed to investigate the correlation between baseline FDG-PET findings and clinical parameters in our MM patients. Methods: We conducted a

retrospective analysis in a total of 385 patients that were followed up between January 2005 and December 2013. Forty-eight chemotherapy naïve patients were found to have baseline FDG-PET evaluation. We compared the initial clinical characteristics of these patients with their PET findings: the number of focal bone lesions (FLs) and the maximum standardized uptake value (SUVmax).   Results: Twenty-three out of 48 patients were male. The median age was 62 years. Among patients with secretory disease (97.9%), IgA, IgG, and light chain only disease were evident in 8.3%, 62.5%, and 27.1%, respectively. The median percentage of bone marrow plasma cells was 40% (range 25-60). Median serum beta-2 microglobulin was 3.5 mg/L (range: 2.5-5.0) and 20% of patients had international staging system (ISS) stage 3. Durie-Salmon (DS) stage III disease was detected in 43.8%. Forty-one (85.4%) had bone lesions on FDG-PET imaging. Of those, 17 (54.8%) had more than three FLs. The median SUVmax for those FLs was 6.5 (range: 4.9-10). The number of FLs on PET correlated only with DS stage III disease. Summary / Conclusion: Baseline FDG-PET findings predicts advanced stage in MM patients.

E-266

Use of 18-F FDG PET / CT scanning into the first follow up of patients with multiple myeloma and association with biochemical response

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The positron emission tomography with computed tomography (PET/CT) using glucose labeled with 18F fluorodeoxyglucose (FDG) is a reliable technique for assessing skeletal involvement and recent studies propose for predicting outcomes at the response of Multiple Myeloma (MM) The primary endpoint was the correlation of the biochemical response with the FDG PET/CT in a second evaluation after six cycles of first line treatment. Eighteen patients (8 males and 10 females) with untreated MM entered this retrospective study at the Universitary Hospital of Vall d´Hebrón. FDG-PET/CT was performed baseline and after six cycles of first line treatment. The median age was 58 years (range 44-74), seven patients were classified with stage ISS III, 16% had hypercalcemia, none presented creatinine >2 mg/dL and 66% showed immunoparesis. A positive PET-CT was defined as radiologist interpretation of increased uptake in one or more focal areas. The results from FDG-PET/CT were evaluated and categorized by a team of radiologists into positive or negative disease according to the criteria proposed by Zamangni, et al. PET/CT was positive in all the patients pre treatment (15 focal lesions, 2 diffuse bone marrow involvement with focal lesions and 1 bone marrow involvement), 11 patients had more than 3 focal lesions, and in 83% SUV max was > 4.2; extramedullary disease was present in two patients. After six cycles of first line treatment, PET/CT negativity was achieved in 61% of patients and the complete response in 67%. The patients that had a PET/CT negative, all showed flow minimal residual disease (MRD) negative. Three patients had PET/CT with progression disease and corresponded with a progression according to the standard IMWG response criteria, and both of them had del (17 p). The correlation between PET/CT and response obtained before six cycles of treatment was positive as well as PET/CT and Flow MRD, but are necessary more long term studies that include greater number of patients to confirm that the PET/CT negative is associated with the bioquimical response and to establish the mandatory scanning after first line of treatment.

E-267

Impact of chromosomal aberrations detected by FISH on benefits of autologous stem cell transplantation in multiple myeloma patients

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With rapid increment in its incidence and changes in treatment paradigms, multiple myeloma (MM) represents a considerable challenge. The introduction of potent novel therapeutic agents challenged the role of autologous stem cell transplantation (autoSCT), a more traditional front-line treatment. Since there are no established guidelines on who should still undergo autoSCT in this era of novel drugs, we conducted this study to identify those who can benefit from autoSCT and those who can avoid unnecessary transplantation. This was a retrospective single center study. During the period between January 2005 and June 2015, 177 newly diagnosed MM patients with complete set of molecular data and undergoing autoSCT were evaluated for their demographic, laboratory and clinical data. Adult patients, defined as 18 years old or older were included, while cases with smoldering myeloma, monoclonal gammopathy, solitary plasmacytoma and plasmablastic lymphoma were excluded. Since there are no standard MM FISH probes used in Korea, 7 commercially available FISH probe sets were used: IgH dual color, break-apart rearrangement probe; TP53 SpectrumOrange probe; D13S25 (13q14.3) SpectrumOrange probe; IgH/MAF dual color, dual fusion translocation probe; IgH/FGFR3 dual color, dual fusion translocation probe; 1q21/8p21 dual color probe; and CDKN2A (9p21, p16) SpectrumOrange/CEP9 SpectrumGreen probe (Abbott Diagnostics, Abbott Park, IL, USA). The median age was 57 years (18-69 years), and there were 89 males (50.3%). The proportion of patients at International Staging System stage III was 28.2%. Overall, 71.2% of the patients had bone involvement at initial MM diagnosis, and 26.9% were associated with azotemia (defined as serum creatinine>2mg/dL). The most common

induction therapy used was thalidomide based (92/177, 52.0%), followed by cytotoxic chemotherapy based (60/177, 33.9%). Bortezomib based induction was used in 25 patients (14.1%) and none received lenalidomide as induction for autoSCT. Maintenance after autoSCT was carried out in 50 patients (28.2%), and all but 1 received thalidomide with dexamethasone. FISH results showed del(17p13) in 7.3% (7/96), del(13q14) in 36.8% (63/171), t(14;16) in 4.5% (8/95), t(4;14) in 18.9% (18/95), IgH rearrangement in 45.2% (80/168), +1q21 in 38.7% (65/168) and del(9p21) in 3.7% (6/162) of cases. Univariate statistical analyses revealed that the presence of del(17p13) and t(14;16) was associated with worse overall survival (OS), while the presence of IgH rearrangement, +1q21 t(14;16) and t(4;14) was associated with adverse progression free survival (PFS) after autoSCT. Multivariate analyses showed that only the presence of t(14;16) retained prognostic value for OS and PFS, regardless of induction therapy regimen. In conclusion, MM patients at various risks benefits differently from autoSCT. Better risk-adaptive therapeutic approaches based on FISH data are needed.

E-268
Gamma heavy chain disease-two new cases with distinct clinical features

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Introduction. Gamma heavy chain disease (γ-HCD) is a rare B-cell neoplasm with up to 130 cases reported by now and no standardized treatment recommendation. We describe two

new cases with different patterns of disease. Case report. Case 1. A 65-year woman with no relevant medical history complained about weakness and frequent respiratory infections within the last months prior referral to our department in 11/2014. Her physical examination was normal. Laboratory tests showed normal blood counts and normal chemistry. Serum protein electrophoresis (SPEP) and immunfixation (IFE) of serum and urine detected a monoclonal γ HC without associated light chain (LC). Total IgG was 38g/l, free IgG was 34.5 g/l IgGk 2.3 g/l and IgGλ 1,2 g/l respectively (Hevylite®). Testing for antinuclear antibodies (ANA) was negative. Renal biopsy detected a chronic tubulointerstitial nephropathy comprising 50% of the parenchyma with γ HC excretion and negative staining for k and λ LC. The findings were consistent with γ-HCD. We decided that there was no need for immediate therapy. In 03/2016 she was admitted with acute renal failure and pneumonia. Creatinine was 680 μmol/l, Hb 11 g/dl and HSV 1 and Candida albicans were identified in the bronchoalveolar lavage. Renal dialysis and chemotherapy with bortezomib, dexamethasone and cyclophosphamide were initiated. In addition, acyclovir and caspofungin were instituted. After 2 weeks, renal function improved and dialysis was discontinued. Subsequently she received 5 cycles of bendamustine and bortezomib. The patient is now doing well, her creatinine is 125 μmol/l total IgG 11.8 g/l, free IgG 9.6 g/l, IgGk 1.35 g/l and IgGλ 0.78 g/I. Stem cell apheresis and autologous stem cell transplant are planned. Case 2. A 28-year women presented to our ambulatory in 04/2016 due to a newly IgG increase (39g/l). She has a history of systemic lupus erythematosus (SLE) diagnosed 06/2006 and receives immunosuppression with methotrexate. The SPEP/IFE of serum and urine revealed a monoclonal γ HC with absent LC. She had moderate anemia (Hb 9g/dl), normal leucocytes and platelets counts and a creatinine of 126 μmol/l. Bone marrow histology showed a slight erythroid hyperplasia and elevated CD 38 positive plasma cells (12%) with γ HC secretion without associated LC. Renal histology detected minimal mesangial lupus glomerulonephritis type I without renal damage related to γ HC

excretion. Bone CT scan was normal. We interpreted the case as γ-HCD associated with SLE and decided to monitor the patient. On last follow up (09/2016) her laboratory values were stable

E-269

Incorporation of a nurse Case Manager for the diagnosis and follow up of patients with multiple myeloma

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Introduction: An early diagnosis and management, in suspected MM cases, is essential to prevent secondary complications. For this reason, it is important to reduce the timing of diagnostic tests availability. However, in frail patients the management of these procedures can be troublesome. The nurse case manager (CM) might help by reducing the time needed both for the completion of the tests and for treatment initiation. Furthermore, it might also improve the follow up of patients by reducing admissions and random visits, leading to decreasing costs. Objectives: To evaluate the incorporation of a CM in relation to the time to diagnosis and time to treatment initiation, and to evaluate the effectiveness during follow up period. Likewise, to analyse patient satisfaction degree, and potential costs and savings associated to NCM management. Material and methods: From September 2014 to November 2016 we implemented a prospective, single centre study in patients with MM (interventional group) (IG). Results were been compared with a control group (CG) of MM patients diagnosed in 2012-2014. Variables measured were: - Time from referral to first visit in the Hematologic Unit; -Time from referral to completion of diagnostic tests; -Time from referral to therapy initiation; -Attendances to the Emergency Department and hospital admissions. We collected a patient satisfaction survey and a

phone call registry. A cost analysis was also performed. Results: Sixteen patients were included in the IG group and 27 patients were included in the CG group. In the IG group, a reduction >10% in median time was observed for all time-related variables, although those differences were not statistically significant. Also, attendance rate to the Emergency Department and hospital admissions rate were reduced by 75% (p=0,003) and 37% respectively (NS). Phone calls were managed and solved in more than 60% of the cases by the CM herself. The cost analysis of the Emergency Department attendance demonstrated a significant reduction in IG compared with CG (p=0, 0006). The degree of patient satisfaction in IG was of 94%. Conclusions: The incorporation of a NCM for the diagnosis and follow up of patients with MM has allowed to reduce the median time for all time-related variables. It has also improved the follow up and quality of care, significantly decreasing the number of visits to the Emergency Department. Our data suggest that an early intervention may reduce costs resulting in significant savings for the healthcare system. Further follow-up is needed to confirm these results.

E-270

Synchronous Presentation of Smoldering Multiple Myeloma (SMM) and PolycythemiaVera (PV)-A Rare Case Report

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INTRODUCTION- Secondary acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) due to the cytotoxic chemotherapy for multiple myeloma (MM) is well known. On the other hand, population based studies have shown the increased incidence of coexistence of plasma cell neoplasms (PCN) and AML/MDS.

However, reports of cases with simultaneous presentation of PCN and myeloproliferative neoplasms (MPN) are extremely rare. There are only two reports with 17 cases. We present a rare case of polycythaemia vera (PV) with asymptomatic PCN diagnosed in Tata Memorial Centre. METHODS- We discussedthe clinical, morphological, immunophenotypic, genetic and other laboratory features of a patient presented withPV with coexisting asymptomatic PCN. RESULTS-A 74 year-old-man was incidentally detected for having consistent high haemoglobin (> 19g/dl) and WBC counts (>16000 x 109/L). Erythropoietin levels were subnormal (15.66 mU/ml) and molecular studies revealed JAK2 V617F mutation meeting the diagnostic WHO criteria for PV. Bone marrow analysis showed hypercellular marrow with 22% plasma cells. Immunophenotyping analysis revealed 3% plasma cells positivefor strong CD38, strong CD138, weak to negative CD200, and weak CD45 with lambda chain restriction but negative for remaining markers.Serum electrophoresis revealed M-protein (1.2 g/dl) with IgA-lambda type. No features of CRAB criteria noted. Thus, the diagnosis of synchronous presentation of SMM and PV was confirmed. CONCLUSION- We report a rare case of synchronous presentation of PCN with MPN. As the incidence of myeloid neoplasms like AML/MDS in PCN is high, it can be also true for MPN. However, the frequency of MPN with PCN is inadequately recorded, probably due to low index of suspicion. This case highlights the need for upfront evaluation of coexistence of monoclonal gammopathies with MPN and vice-a-versa in elderly patients. It is important to detect such a coexistence to avoid the misdiagnosis of therapy-related neoplasms after few years of follow-up.

E-271
Case Report: 2 Cases of Rare And Aggressive Plasma Cell Leukemia

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Plasma cell Leukaemia is a rare disease and is the least common variant of multiple myeloma accounting for 2-3% of all plasma cell dyscrasias. Primary plasma cell leukaemia is defined by the presence of >2×109/L peripheral blood plasma cells or plasmacytosis accounting for >20% of the differential white cell count, and does not arise from preexisting multiple myeloma. Secondary plasma cell leukaemia is a leukaemic transformation of end-stage multiple myeloma. Case 1 61 yr old gentleman presenting with low grade fever, weight loss, fatigue and generalized bone pain. Physical examination reveals multiple cervical and inguinal lymphadenopathy and moderate splenomegaly. Laboratory evaluation showed haemoglobin of 5.3g%, White blood cell count of 104×109/L, platelet count of 60×109/L, Creatinine of 189 µmol/L and serum calcium 3.8 mmol/L. Peripheral blood plasma cell of 50% and immunophenotypic analysis demonstrated the presence of circulating clonal plasma cells with expression of CD38/CD138 without expression of CD45/Cd19/ CD27/ CD81. This abnormal population appears to be positive for kappa light chain both surface and intracytoplasmic. CD20/Cd117/ CD56/ HLA DR/CD123/ CD4/CD8/ CD5/CD7/ CD3/ CD16 are negative. Additional investigation reveals IgA kappa monoclonal gammopathy and β2 microglobulin of 5.8mg/L. Total protein 65.9g/L, albumin 33g/L and globulin 33g/L. Bone marrow biopsy reveals hypercellular marrow with 60-70% atypical plasma cells. Treatment with bortezomib combined with dexamethasone and thalidomide was initiated. Supportive therapy with hydration, pamidronate, allopurinol were given. Despite the effort, patient was expired 15 days after admission. Case 2 79 yr old lady admitted for fever and confusion. Physical examination reveals moderate splenomegaly. Laboratory evaluation showed haemoglobin of 4.3g%, total white cell count of 45.3×109/L, platelet count of 108×109/L and peripheral blood plasma cells of 40%. Lactate dehydrogenase of 444 U/L, creatinine of 178µmol/L and serum calcium of 9.4mg/dl, total protein of 83.8 g/L, albumin 31.0g/L and globulin of 52.8 g/L. peripheral blood immunophenotypic analysis reveals presence of circulating clonal plasma cells with

strong positivity of CD 38 and CD 138, lambda light chain restriction and CD5, CD10, CD 23, CD45, CD19, CD20 and CD56 negative. Immunofixation electrophoresis reveals IgG lambda and β2 microglobulin 21.48 µg/L. Bone marrow biopsy demonstrated hypercellular marrow with diffuse infiltration with 80% of plasma cells. Multiple small osteolytic lesions were noted on skeletal survey. Supportive management with bortezomib, thalidomide and dexamethasone . Despite treatment, patient was expired after 10 days of admission. Plasma cell leukaemia is an aggressive and rare variant of multiple myeloma with poor outcome.

E-272
MULTIPLE MYELOMA (MM) AND PURE RED CELL APLASIA (PRCA): INTERESTING DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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INTRODUCTION Pure red cell aplasia (PRCA) is a rare entity that presents with severe anemia with marked reticulocytopenia and absence of erythroblast / erythroid precursors in the bone marrow. The acquired variant is the most common. The most frequent cause in adults is idiopathic, although it has been associated with infections (HCV, HIV, EBV, Parvovirus B19), autoimmune diseases, drugs and neoplasias (thymoma, PFS, carcinomas ...) CLINICAL CASE A 79-year-old man with a past history of hypertension, asthma, pneumonia, and inguinal herniorrhaphy. Initial consultation for a two-month course of asthenia, hyporexia and unquantified weight loss with musculoskeletal pain, guide to perform a full study of normochromic normocytic anemia. Physical Exploration was anodyne. At admission he had arregenerative, normocytic-normochromic

anemia with (Hb = 7.7 g / dL, reticulocytes 0.2%). Biochemistry, with ferric profile, B12 vitamin, folic acid and thyroid hormones were normal. Autoimmunity study was also negative. IgG-kappa Monoclonal Band (MB) of 1.77 g/dL was detected in the serum proteinogram. The IgG dosage was slightly high but IgA and IgM dosages were normal. The FLC-ratio was also normal. No MB was detected in urine and there were no lytic lesions in conventional radiology. In the Bone marrow aspirate there were a 21% of plasma cells with absence of red cell hematopoietic precursors and normality of the rest of series. Flow cytometry detected a 3.6% of plasma cells (PC), with a 95% pathological phenotype (PPC). FISH (in purified PC) was normal. Viral serologies (inc. Parvovirus-B19) were negative. At one month, Hb was 12 g / dL, initiating a descending steroid regimen. At 3 months, treatment was discontinued after complete resolution of anemia. The patient continues periodic reviews (+ 42m) with no need to start MM treatment. DISCUSSION Association of PRCA and MM or plasma cell dyscrasias is anecdotal. A study involving 50 patients with idiopathic PRCA found significant fibrosis and plasmacytosis findings in 20% of patients (9 MM and 1 MGUS). It is postulated that MB can play a key role in the pathogenesis of PRCA, inhibiting erythropoiesis at an early stage, a finding that has been previously reported in other classic studies with in vitro studies. In the case of other pathologies associated with PRCA, mechanisms mediated by T-lymphocytes have been found. In the available literature, with few reported cases, there are a great variety of treatments: from intensive (antiMM treatment), Rituximab (MM-CD20+) or corticoids, with variable responses. CONCLUSIONS Anemia is a defining event of initiation of anti-MM treatment ONLY if it is caused by the MM itself. The association of MM and PRCA is extremely rare and could be explained by the inhibitory effect of MB on early erythropoiesis. The treatment must be individualized taking into account the origin of anemia.

2. Treatment and Outcomes

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Cost- effective Autologous Stem-Cell Transplantation in Plasma cell disorder: Single Institution Experience. Dr Shailesh Bamborde Dr Chandrakala S Dr Farah Jijina

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Background: Multiple myeloma accounts for 10% of hematologic malignancies. It is well established that high dose therapy (HDT) combined with autologous stem cell transplantation (ASCT) produces superior response rates and progression-free survival compared to conventional chemotherapy in patients with multiple myeloma. We present our experience of eleven patients of plasma cell disorder who underwent autologous stem cell transplant between Jan 2013 and Nov 2016, in a resource poor tertiary care hospital in Mumbai. Patients and Method: We performed 11 transplants from Jan 2013 till date. All patients were treated in non- hepa-filtered isolation rooms. There were 5 male and 6 female patients. Patient's age ranged from 21 to 57 years (median 39 years). Out of 11 patients, 10 patients had multiple myeloma and 1 was of POEMS syndrome. International staging system was 1 for 3 patients and 3 for 7 patients. Patient with POEMS syndrome presented to us with advanced disease. FISH studies were not done in any of the patients. Before transplant, patients had received induction therapy using Bortezomib, Cyclophosphamide and Dexamethasone combination. The number of cycles ranged from 6 to 12. Post induction, 2 patients were in VGPR and 9 were in complete remission. All Patients had ECOG-1 performance status with no co-morbidities. High-dose Melphalan (200mg/m2) was given to 6 patients. 5 Patients who had renal insufficiency at the time of transplant received 140mg/m2 of Melphalan. For all patients, granulocyte colony stimulating factor mobilised peripheral blood stem cells were collected without cryopreservation which reduced the cost of transplant.4 patients received Plerixafor.

Median follow up for all patients was 8 months (range, 0.5 to 44 months). Result: Post-ASCT, 8 (73%) patients achieved complete response (day 100). Response at day 100 is yet to be defined in 2 patients. One patient expired on Day 10 of transplant due to sepsis and another one relapsed and died within 11 months post transplant after achieving CR. 2 of the 9 patients received maintenance therapy for 12 months with thalidomide post-transplant and both are in CR till date. Another 6 patients are still on thalidomide maintenance therapy. None of our patients had developed engraftment syndrome. The Total Cost of treatment ranged from Rs. 75000 to Rs. 1.3 lakhs. Conclusion: Induction therapy followed by autologous stem cell transplant (ASCT) is the standard of care in transplant-eligible patients. Our institute has started Transplant programme from Jan 2013. We have done total 11 autologous transplants in plasma cell disorders using peripheral blood stem cell without cryopreservation in non- hepa-filtered isolation room. Average cost of transplant was Rs. 1.0 lakh at our center.

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Myanmar Experience of Clinical Response of Patients With Newly Diagnosed Symptomatic Multiple Myeloma Treated with Bortezomib Based or Non-Bordezomib Based Therapy

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Introduction Multiple myeloma is not uncommon haematological disease in Myanmar. There is increasing incidence of myeloma patients because of increasing awareness of diagnosis and proper referral system. With introduction of novel therapeutic agents, like proteosome inhibitor and thalidomide combined with autologus stem cell transplant, the outcome of myeloma patients become more favourable. Aim The aim of the present study is to treat the newly diagnosed myeloma patients using bortezomib based or non-bortezomib based regimens and to compare the clinical response. Methods Sixty one patients under 75 year of age with various stages of multiple myeloma are included in this study. They were divided to two groups with mutual decision between researcher and the patients according to patient's preference after taking informed consent. Thirty eight patients were treated with bortezomib based therapy and twenty three patients were treated with non-bortezomib based therapy. Presenting symptoms, myeloma related organ and tissue involvement (ROTI) according to CRAB criteria, their staging according to Durie Salmon and International Staging Systems, monoclonal immunoglobulin type by immunofixation electrophoresis were recorded. Their outcomes according to International Myeloma Working Group (IMWG) Uniform Response Criteria and adverse events of therapy were monitored and analyzed. Results Pallor and bone pain were the commonest presentations. Hypercalcemia, renal impairment, anemia and lytic bone lesions were found in 29.8%, 27.9%, 81.9% and 83.6% respectively. On immunofixation electrophoresis, 63.9% had IgG, 29.5% had IgA, 3% had light chain and only one patient had IgM subtype. Regarding the staging by International Staging System, majority of patients in bortezomib group were in stage II 63.2%, whereas 47.8% in non-bortezomib group were in stage III. Regarding the treatment response, in non-bortezomib group CR=13%, VGPR=4.3%, PR=47.9%, >PR=65.2% and ORR=93.8%. In bortezomib group, CR=44.8%, VGPR=10.5%, PR=18.4%, >PR=73.7% and ORR= 96.6%. In respect to CR and >PR, bortezomib base regimen was 3.4 times more superior to non-bortezomib regimen as an induction therapy for newly diagnosed multiple myeloma. Response rate was 3.43 (1.13-10-44) at 95% CI. IgA subtype and light chain disease were associated with better response to treatment. Neuropathy, gastrointestinal and infections are most common adverse events associated with treatment. There was no significant difference in adverse events between two treatment groups apart from diarrhea and hyperglycaemia. Mortality was 18.5% in bortezomib group and 21.8% in non bortezomib group. Conclusion In conclusion bortezomib based therapy is superior to non-bortezomib based therapy in achieving remission bu

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ASSESSMENT OF QUALITY OF LIFE IN MYELOMA PATIENTS POST AUTOLOGOUS STEM CELL TRANSPLANT- A SINGLE CENTRE EXPERIENCE IN SOUTH INDIA

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Background-In this study, we report the overall Quality of life [QoL] in myeloma, post autologous stem cell transplantation, and impact of various factors like age, sex, stage of disease, remission status of disease at time of transplant, conditioning regimens, and stem cell dose, on QoL. Patients and methods- 26 patients who had undergone autologous stem cell transplantation at our centre from June 2014 to June 2016 were included in the study. FACT-BMT(Version4) questionnaire was used as assessment tool of QoL and individual scores were recorded on day of transplant and day 100 post transplant. The influence of factors such as sex, age, stage of disease, remission status of disease at time of transplant, conditioning regimens, and stem cell dose on QoL was determined using dispersion analysis. Results-Out of 26 patients interviewed 13 were male and 13 female patients, with an average age of 56.6years.13(50%) patients had IgG kappa, 3 patients had IgG lambda, 4 patients had kappa light chain, 5 patients expressed IgA lambda and one patient had IgA kappa disease. Six patients had normal cytogenetics, nine patients had hyperdiploidy, four patients had t(4;14), three patients had del 1q of which two had hyperdiploidy and remaining had normal cytogenetics ,two patients had tp53 deletion of which one had hyperdiploidy and other had normal cytogenetics and one patient each had t(14;16) and t(14;20) respectively. Three patients were stage 1, eight patients were stage 2 and fifteen patients were stage 3 as per ISS staging. Stage of disease did not have any significant impact on overall QoL in our study (p value=0.369). Fifteen patients were in CR, Eight patients had attained VGPR and three patients were in PR at time of transplantation. Overall remission status prior to transplantation did not have a major impact on QoL(p=0.76). Fourteen patients received Mel 200mg/m2, six patients received Mel 140mg/m2, five patients received 180mg/m2 and one patient received 160mg/ m2. Overall conditioning regimen did not have any impact on QoL (p=0.148). Stem cell dose ranged from 2.34 to 10.35x106 cells per kg. Stem cell dose did not have any influence on overall QoL. Finally there was significant improvement of QoL on day 100 post autologous stem cell transplant in this study (p value-<0.001) Conclusions-Stage of disease at presentation, remission status at time of transplant, conditioning regimen, nor stem cell dose had any influence on QoL. However there was significant improvement in QoL [Day100] post autologous stem cell transplantation.

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Isolated Gastrointestinal Graft versus Host Disease after Autologous Hematopoietic Stem Cell Transplantation in a patient of Multiple Myeloma

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Introduction: A syndrome similar to acute graft versus host disease (GVHD) has been reported after autologous HSCT, and has been termed autologous GVHD (auto GVHD). We report a case of multiple myeloma who developed isolated gastrointestinal GVHD (GI GVHD), following an autologous HSCT. Case report: A 60 year old male with IgG-lambda multiple myeloma in complete remission, underwent autologous HSCT in December 2013 at our centre. The patient engrafted successfully on day +14. On day +16 post transplant he developed intense nausea, few vomiting and severe diarrhoea. The frequency of diarrhoea ranged from 14 to 21/day. The stools were watery with an average volume of about 200

ml/stool. The possibilities considered were drug related diarrhoea (Melphalantibiotic induced) or infective diarrhoea. There was no fever and no skin rash. Blood cultures were sterile. Repeated stool examinations showed no pus cells/RBCs, no ova/cyst, no opportunistic pathogens, negativity for giardia antigen and bacterial and fungal cultures were negative. The PCR for CMV was negative; serology for EBV and hepatitis A, E, B and C viruses was negative. The Clostridium difficile toxin assay was negative. LFTs were normal. Despite administration of systemic antimicrobials, anti-motility drugs, anti secretory drugs and probiotics, the diarrhoea was persistent. Hence a procto-sigmoidoscopy was done on day +19 which was normal but a rectal biopsy was taken. The rectal biopsy showed features of GVHD, and was negative for CMV, fungi and acid fast bacilli. The patient was started on methylprednisolone @ 2mg/kg/day in two divided doses. There was a dramatic improvement in the nausea and diarrhoea and the anti motility and anti secretory agents could be stopped. The methylprednisolone was later changed to oral prednisolone and prednisolone was gradually tapered and stopped over a period of 3 months. The patient has been in follow-up for past 2.5 yrs, with no recurrence in the GI symptoms and disease is in remission.
Discussion: GVHD following autologous HSCT is uncommon, with only case reports or reports of small case series. Of the cases reported, it is more common in patients of multiple myeloma than in other haematological malignancies. In particular, the risk for auto GVHD is higher in multiple myeloma patients undergoing tandem transplantation than in those undergoing a single transplant. Isolated GI GVHD is rare, with only few reports in literature and is associated with a very high mortality if not treated early.
Conclusion: Our case highlights that GI GVHD should be considered in the differential diagnosis of severe unexplained diarrhoea following autologous HSCT in multiple myeloma when other causes have been ruled out. Appropriate investigations including endoscopy and biopsy are essential for a prompt diagnosis and initiation of early therapy with steroids to prevent mortality in this potentially treatable condition

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Monoclonal Gammopathy Triggering C3 Glomerulopathy: A Rare Association

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Introduction C3 glomerulopathy (C3GP) has been described as a distinct entity in the last few years and represents glomerular injury due to alternate complement pathway (ACP) dysregulation. Monoclonal proteins have been shown to activate ACP leading to C3GP. Herein, we describe two cases of C3GP triggered by monoclonal gammopathy. Material and Methods In a retrospective study, cases of C3GP from 2010 to 2016 with monoclonal gammopathy were retrieved from Histopathology Department, PGIMER, Chandigarh. Light microscopy, direct immunofluorescence (DIF), electron microscopy (EM), ACP was performed, and clinical details were analysed. Results Amongst these 150 cases, only two cases of C3GP triggered by monoclonal gammopathy were identified (incidence 0.02%) as described below: Case-1 Fifty-three year old male, a known hypertensive for past 2 years, presented with RPRF, cola colored urine and proteinuria (3.5gm/day). Kidney biopsy was performed with a provisional diagnosis of hypertensive nephropathy? The biopsy revealed membrano-proliferative pattern of injury. DIF showed presence of fine granular 3+ C3 deposition along the glomerular capillary loops. On EM, organized deposits representing cryoglobulins were seen. A diagnosis of C3GP with cryoglobulins and hypertensive arteriosclerosis was made. Further investigation into its cause was advised. Biochemical examination showed low C3 and normal C4 with abnormal ACP functional assay. Factor H & B levels were normal and C3Nef was present. Cryoglobulins and M band was present, IFE showed IgG kappa

restriction. Bone marrow examination revealed 5% plasma cells. The patient was started on chemotherapy in the presence of MGRS and thereby improved. Case-2 Forty-five year male, a known hypertensive (2 years) was presented with RPRF. Serum creatinine was 2.62 mg/dl, No urine proteins, anemia (8.5 gm/dl), and hypercalcemia (13.1 mg/dl) was noted. No bone lesions were present, and No M band was identified on SEEP. Therefore, a possibility of MGRS was kept, and serum free light chain assay was performed which showed lambda restriction (kappa:lambda=5.7:15000). A kidney biopsy was performed with a provisional diagnosis of RPRF?MGRS. The kidney biopsy revealed 14 unremarkable glomeruli. On DIF, there was fine granular 3+ C3 positivity in the mesangium and lambda restriction was noted along the GCL and TBM. EM showed the presence of dense osmiophilic deposits in the mesangium and intramembranous location indicating DDD and Randall type powdery deposits were noted along the TBM signifying LCDD. Further, C3 levels were low and C4 levels were normal. Conclusion C3GP triggered by monoclonal gammopathy is very rare. pathologists should be aware of such association and alert the clinicians for a complete evaluation of monoclonal disorders/ACP workup.

NURSE SYMPOSIUM

1. Oral Presentations

NS-278
Common Adverse Effects of Novel Therapies for Multiple Myeloma (MM) and their Management Strategies: A Need for Clinical Research Priority

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This integrative literature review (ILR) aimed to describe the common adverse effects that patients reported while on novel therapies. A secondary goal of this ILR was to appraise the strength of evidence of management strategies that have been reported to ameliorate these adverse effects. PubMed and CINAHL Complete databases search was performed. The following Medical Subject Heading (MeSH) terms and search details were used and the Boolean operator AND was utilized to get a highly relevant search yield: Multiple Myeloma AND novel therapy AND adverse effects AND management. CINAHL Complete search was completed using the following search terms: Multiple Myeloma AND adverse effects AND management. The search yielded 66 and 101 articles for PubMed and CINAHL Complete, respectively. Articles were included in the final analysis if they focused on MM, novel therapies, and reported adverse effects and management strategies. Year limit was between 2003 and 2016, and articles that focused on adverse effects of supportive therapies such as bisphosphonates or growth factors were excluded. The final 28 articles used were categorized by level of evidence according to Melnyk and Fineout-Overholt's (2011) hierarchy of evidence to appraise the strength of evidence for reported management strategies. Whittemore and Knafl (2005) updated ILR methodology was strictly followed during the conduct of this review. This ILR included 28 articles that revealed novel treatment regimens utilized to treat MM have resulted in several common adverse effects reported by the patients. They include peripheral neuropathy, GI adverse effects (e.g., nausea, vomiting, constipation, and diarrhea), steroid-related adverse effects (e.g., mood alterations, insomnia, hyperactivity, heartburn, hiccups, and high blood glucose), sedation, thrombocytopenia, thromboembolism, anemia, neutropenia, myelosuppression, cutaneous rash, fatigue, infusion drug reactions (e.g., nasal congestion, cough, chills, rhinitis allergic, throat irritation, dyspnea, nausea), renal and cardiopulmonary complications. Serious adverse events were also reported, which include development of secondary malignancy, pneumonia, embryonic or fetal toxicity, sepsis, severe and fatal cardiac events, and pulmonary embolism. There are many management strategies that correspond to the specific adverse events listed above. Most (26 out of 28 articles) of the management strategies reported to ameliorate the common adverse effects is based

on one or two descriptive studies, review papers, or expert opinions in the form of a consensus statement from myeloma specialists, which are in the lowest levels in Melnyk and Fineout-Overholt's hierarchy of evidence at Level 6 and 7, respectively. RCTs of adverse effects interventions should be a top clinical research priority to enhance evidence-based practice in myeloma patient care.

NS-279
A life in limbo: findings from a study into the experience of caring for myeloma patients

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This study conducted by Myeloma UK and the Picker Institute, provides insight into the experiences of individuals who provide care and support to myeloma patients. The research builds on our current knowledge of caring in cancer and highlights the more specific perspectives of those who provide informal care and support to relatives and friends with myeloma. The research was designed with the input of myeloma carers. The research comprised of three fieldwork stages: initial in-depth interviews with carers to determine survey themes; the resulting survey involving 374 carers; a qualitative interview phase to explore issues of importance arising from the survey in more depth involving 20 carers. Findings suggest that the most common aspects of caring are: providing emotional support (98%); accompanying myeloma patients to appointments (89%); running errands (81%); and sourcing information (78%). In addition to being the most common aspect of caring, our survey indicated that emotional support was the most difficult to provide. Qualitative interviews provided further insights into the experience of caring. Interview data suggest that caring had an impact on children's lives and that caring shifted dynamics and relationships within family systems. Additionally, a loss of work or income, was found to increase the likelihood of social

isolation, stress, and anxiety as a result of caring. Our research highlights for the first time the roles, needs, and perspectives of myeloma carers. Findings also highlight the support and information needs of carers and strategies for supporting individuals and families in their caring roles are discussed.

NS-280
Patient Perception of being involved in a clinical trial for Multiple Myeloma Ceri Bygrave, Tanya Burton*, Patricia Carter, Sarah Richard, Eric Low, Charlotte Bloodworth

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Multiple myeloma is an incurable malignancy which has undergone rapid therapeutic advances recently, aided by patients who take part in clinical trials to test new therapies. The myeloma team at the University Hospital of Wales in partnership with Myeloma UK carried out a qualitative study investigating the views of people affected by myeloma and their experience in trials. We involved past and current trial patients and canvassed their opinion via a professionally led qualitative study. A questionnaire was designed iteratively between the myeloma team, Myeloma UK and also it was reviewed by a selected panel of myeloma patients to ensure the style and content were acceptable, understandable and directed towards relevant areas. The aim was to identify how well patient experience met their expectations prior to the study, whether they felt informed and well supported by the study team and whether they felt fully involved in the trial process. The patients taking part in this study were involved in two national trials: NCRi Myeloma XI study and Myeloma UK CTN MUK 5. 47 questionnaires were distributed of which 31 were returned. Patients varied in their level of understanding of the study protocol in particular

whether they were still on active follow up after the end of treatment. Despite this most patients were satisfied with the amount of information they received prior to informed consent and felt they had ample time to engage with relevant members of the study team. Most patients were motivated by altruism in terms of their reasons for taking part, they are aware that myeloma is not curable and wanted to improve outcomes for themselves and others. They also felt that taking part in the study would provide access to more modern treatments, and potentially increased monitoring by the medical team. Hope was a common theme in many of the responses, it contrasts sharply with the framework of hypothesis testing and evidence based medicine that underpins clinical trial design. The majority of patients were satisfied with their decision to take part and would recommend a trial to other patients. Some negative aspects that were raised were the costs of travelling, car parking and additional clinic visits associated with being part in the study. Also 100% patients stated that they would like to receive feedback on the results of the study, something which is not frequently distributed by the trial authors directly to participants. In summary two main themes were identified by this study: patients are motivated by altruism and they suffer with logistical challenges. Taking part in a trial can be inconvenient, costly and physically demanding for cancer patients. Investment and thought is required to make improvements. Also, most people are altruistic, they understand that trials are important because myeloma is rare and therapeutic breakthroughs are required.

NS-281
Real World Data of the Impact of first cycle Daratumumab on Multiple Myeloma and Amyloidosis Services

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Introduction: Daratumumab (Dara) is a monoclonal antibody targeting CD38 indicated for patients with relapsed multiple myeloma (MM) both as monotherapy and in combination with Lenalidomide or Bortezomib. Due to the risk of infusion related reactions (IRRs) the first dose is given at a slow rate. If well tolerated, subsequent doses may be given faster. As Dara is not yet routinely available within the UK National Health Service (NHS), we sought to assess our initial experience investigating infusion times, incidence of IRRs, and requirements for in-patient admissions during the first cycle. Methods: This was a retrospective review of the first cycle of treatment with Dara. Patients with MM received Dara 16mg/kg weekly for the first cycle whereas those with amyloidosis received 8mg/kg with a gradual increase to 16mg/kg within 4 weeks. All patients received pre-medication with paracetamol, chlorphenamine and steroids; amyloidosis patients additionally received Montelukast. A further dose of steroids was given the day after the Dara infusion. Toxicities were graded by CTCAE v4.03 criteria. Results: Between November 2014 to December 2016 26 patients received their 1st cycle of Dara. 22 were treated for MM and 4 for amyloidosis. The median age was 67 years (49-77 years), median ISS 2 and patients had a median of 2 (0-5) prior lines of therapy. 18 (69%) had prior bortezomib, 17 (65%) had prior immunomodulatory agent and 13 (50%) had prior autologous stem cell transplant. 12 (46%) had co-morbidities including respiratory disease in 2 (8%, COPD and asthma). 15 (58%) patients received Dara monotherapy and 11 (42%) received a combination with Lenalidomide or Pomalidomide. The median infusion times for myeloma patients were: 1st dose 9.72 hours (5.5–17.3 hours); 2nd dose 4.2 hours (2.8–10.8 hours); 3rd dose 4 hours (2.3–7.2 hours); 4th dose 3.5 hours (3.3–7.3 hours). For amyloidosis patients: 1st dose 12 hours (12-12.5hours); 2nd dose 7 hours (6-12 hours) 3rd and 4th dose 6 hours. 10 (39%) patients experienced an IRR at grade 1-2 (grade 1: (19%); grade 2: (8%)) during the 1st dose, typically dyspnoea and flu-like symptoms. No IRRs were reported for subsequent doses. All patients received their

first infusion as an in-patient, 6 (23%) patients completed the first cycle as an inpatient and 14 (54%) received all subsequent doses as day cases. 21 (81%) received all 4 planned doses, 4 (15%) missed doses due to adverse events (grades 2-4). Conclusions: Dara was well tolerated with a low incidence of grade 1-2 IRRs associated with the first dose only. In-patient admission was required for all first doses; however 54% were able to receive all subsequent doses as a day case. Patients with poor performance status and/or amyloidosis required inpatient dosing. With optimisation of the patient treatment pathway, some 1st doses may be given as day cases relieving the burden on in-patient services.

NS-282
MyeNURSE: development and use of an e-portal for nurses to share best practice and information resources at the point of service

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Background: The Haematology Society of Australia and New Zealand (HSANZ) Nurses Group recently formed a Myeloma Special Practice Network (M-SPN). The M-SPN provides members with opportunities to share knowledge, information and clinical expertise. The objective is to improve nursing care quality and outcomes for individuals with Multiple Myeloma (MM). Aim: This paper describes the first project undertaken by the M-SPN, to develop an e-portal application (App) to store, share and deliver MM relevant clinical references, patient information resources and manage group events. Method: A mapping exercise was undertaken to identify existing MM relevant resources. Australian and international sources were reviewed including consensus statements, clinical practice guidelines, health policies, professional group resources, and patient organisations. Content for inclusion in the myeNURSE App were identified by group consensus. Results: MyINTERACT technology was chosen to

manage content - an existing healthcare e-platform, enabling groups to connect and securely share information. The M-SPN 'group' was established within myINTERACT, named 'myeNURSE'. myeNURSE hosts MM resources including clinical guidelines, assessment tools, patient resources, third party websites, M-SPN group events. Quick Response (QR) code capabilities are incorporated allowing targeted information delivery. Full content access is by invitation only to M-SPN members, accessible on personal computer or hand held devices, largely without wifi access. Targeted content delivery can facilitate myeNURSE access for non-member participants at educational meetings including access to meeting slides and in-meeting voting. Recent evaluation by members found 95% rated myeNURSE as good/very good. User management of content and membership is provided via web browser access allowing for control and access to user data including voting results. Conclusion: myeNURSE has fulfilled information gaps and enabled quick and easy access to current and pertinent MM resources at the point of care; enabling nurses to remain current to best practice in a rapidly evolving clinical environment.

NS-283
Patient Reported Symptoms, Concerns and Provider Intervention in Patients with Multiple Myeloma

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BACKGROUND: Numerous approved and investigational agents are available to treat multiple myeloma. Thus, it is paramount that

providers develop a systematic method of symptom assessment and intervention. The Carevive Care Planning System (CPS™) captures electronic patient-reported outcomes (ePRO) and clinical data to generate tailored, evidence-based symptom management and supportive care plans and open the lines of communication between patients and providers. This study explored the value of the CPS in assessing common symptoms and concerns among patients with MM on active therapy, as well as its value in opening and streamlining communication between patients and provider(s).

METHODS: Ninety patients were included in this prospective, multi-site pilot. Consented participants rated the frequency and severity of common symptoms, including, fatigue, shortness of breath (SOB), peripheral neuropathy, and diarrhea, using the Carevive CPS portal. EPRO data were collected at baseline (V1) and again at follow-up (V2). Patient concerns were also investigated. After questionnaire completion, a trained clinician reviewed the patient's symptoms and generated a care plan with evidenced-based supportive care recommendations prior to delivering to each patient at V1 and V2.

RESULTS: To date, a total of 90 MM patients across 3 sites have participated in 1 or 2 study visits. On average participants are 63 years old (Range: 34-82), majority (51%) male, and 77% white (race data available at 2 sites), with 41% on 2 treatments at V1. Table 1 reports common symptoms and concerns at each time-point.

CONCLUSION: This study provides a real-world perspective on symptoms and concerns in MM patients on active treatment. Despite a high prevalence of fatigue, SOB, and other physical symptoms, treatment decision-making and understanding were consistently the top concerns. The use of the CPS platform to proactively screen for common symptoms and concerns and provide evidenced-based care plans based on symptom scores, may improve patient-provider communication and efficiency of office visits. Analysis is underway to determine impact on these processes, and future

projects will evaluate the validity and reliability of the ePRO tool.

2. Poster Presentations

NP-284
CREATING A QUALITY OF LIFE CLINIC FOR MYELOMA PATIENTS

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Aims: Quality of life (QOL) for people with myeloma is a very important issue. As more and more drugs are becoming available and people with myeloma are surviving longer. However they are also experiencing more drug side effects as well as living with pain or disabled from pathological fractures, peripheral neuropathy or even dialysis. Obtaining and maintaining a good quality of life is therefore paramount. In 2015 two audits were undertaken in order to improve the assessment of QOL in the myeloma clinic. Method: One audit looked retrospectively at the results of 6 months worth of QOL questionnaire returns and the other audit involved patient feedback regarding their views on completing the QOL forms. Results: It became apparent that the results of the QOL surveys were very subjective and added little or no solid evidence to the treatment discussions being made, performance status and social history were much more useful factors. However, patients themselves were overwhelmingly in favour of them in the audit that asked patients about the importance and practicalities of doing the QOL questionnaires. Conclusion: These audits lead to the decision to create a CNS led QOL clinic where patients had more time to go through the questionnaires (QOL, fatigue management, pain assessments, Holistic Needs Assessments) and the CNS had more time to support patients and signpost them on to other support services/ courses. As the CNS is still heavily involved in the ongoing myeloma clinic, information could also be fed back into discussions on treatment decisions.

NP-285
Decision Aids Utilized by Patients and Clinicians During Treatment Decision Making for Multiple Myeloma: An Integrative Review

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Study Objectives: Currently, no published literature compiling or evaluating multiple myeloma treatment decision aids exists. This integrative review aims to synthesize and evaluate decision aids (DAs) utilizing Melnyk and Fineout-Overholt's (2011) Hierarchy of Evidence. Methods/Data Sources: DePaul WorldCat Local, PubMed, and Google Scholar databases search was performed. The following Medical Subject Heading (MeSH) terms and search details were used and the Boolean operator AND was utilized to get a highly relevant search yield: multiple myeloma AND decision aid. Google Scholar search was completed using the following search terms: decision aid for myeloma. The search yielded 65, 236, and 5,760 articles for PubMed, DePaul WorldCat Local, and Google Scholar, respectively. All abstracts were reviewed one by one independently by two researchers. Articles were included in the final analysis if they reported on decision aid, clinical practice guidelines for patients with multiple myeloma. Year limit was between 2011 and 2016. Articles that focused on supportive care issues were excluded. The final 29 articles used in this integrative literature review (ILR) were categorized by level of evidence according to Melnyk and Fineout-Overholt's hierarchy of evidence (2011) to appraise the strength of evidence of the decision aid. Whittemore and Knafl (2005) updated ILR methodology was strictly followed during the conduct of this review. Results: A total of 29 DAs met the inclusion criteria and were analyzed and appraised independently by two reviewers. Data were analyzed using SPSS version 21. Of the 29 DAs, 17 DAs (58.6%) were available as a peer reviewed journal article, 11 DAs (37.9 %) were developed as an online, web-based document, and only 1 DA was based on commercially

available laboratory genomic profile. Most DAs (N=23; 79.3%) were intended for clinicians use only and all of them are available electronically; 4 DAs (13.8%) were developed as an online PDF format intended for patients and their caregivers use, and 2 DAs (6.9%) were intended for both clinicians and patients and their caregivers use. A table was created to evaluate the strength of evidence for the 29 DAs. The strength of evidence is strong based on Melnyk-Fineout-Overholt's (2011) hierarchy of evidence. Fourteen DAs (49.4%) were based on systematic reviews of randomized controlled trials (RCTs) or clinical practice guidelines developed by myeloma experts, 4 DAs (13.8%) were based on controlled, but not randomized, and 3 DAs (10.3%) were based on case control or cohort studies. Only 5 DAs (17.2%) were based on an expert opinion and were intended for patients and caregivers use. Conclusion: The findings in this integrative review underscore the importance of developing effective decision aids that address the values and preferences of patients with myeloma. RCT to test the effectiveness of patient decision aid is lacking.

NP-286
Nursing implications for patients with relapsed and/or refractory multiple myeloma receiving combination therapy with daratumumab (Darzalex™) and lenalidomide.

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Significance and background: November 21, 2016, the United States Food and Drug Administration (FDA) approved DARA in combination with lenalidomide and dexamethasone (DRd). The POLLUX clinical trial has demonstrated an increase in overall response rate from 76% to 93% and an increase in the percentage of patients who experienced a complete response from 19% to 43% when DARA was added to lenalidomide and dexamethasone, versus lenalidomide and dexamethasone alone. Purpose: Discuss and

educate nurses on specific considerations for DARA in combination with lenalidomide and dexamethasone including prophylactic measures, infusion monitoring, toxicity evaluation, and patient education. Evaluation: Prior to initiation: Prior to receiving the first dose of DARA, patients must have their blood typed and crossmatched for associated false-positive indirect Coombs tests. Approximately half of patients will experience an infusion reaction. The majority of infusion reactions occur during the first infusion or within 4 hours post completion of infusion. There is no increased incidence of infusion reactions when given in combination with lenalidomide. The most common type of infusion reactions are respiratory symptoms such as cough, wheezing, larynx/ and throat tightness or irritation, laryngeal edema, nasal congestion, and allergic rhinitis. Patients must be premedicated with an antihistamine, antipyretics, corticosteroids, as well as a leukotriene to minimize these reactions. Prior to lenalidomide, patients must begin an anticoagulant such as low dose aspirin for deep vein thrombosis prophylaxis. Administration: DRd: DARA 16mg/kg IV weekly x 8, every 2 weeks x 16, every 4 weeks thereafter; lenalidomide 25mg orally Days 1-21 of each 28-day cycle; dexamethasone 40mg weekly Monitoring: There is a higher incidence of neutropenia, diarrhea, fatigue, upper respiratory infection, constipation, cough, and muscle spasms with DRd. Education: Patient counseling should include discussion of the most common adverse events. Nurses should instruct patients to inform the care team if fever, chills, rigors, chest pain, shortness of breath, or cough develop during DARA infusion, as well as side-effect management post infusion. Discussion: Because nurses are involved in administration, assessment, management of side-effects, and patient education, it is imperative that oncology nurses are knowledgeable of current and emerging MM therapies.

NP-287
Physical exercise habits of patients with multiple myeloma

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Background: One of the main symptoms of multiple myeloma (MM) is bone impairment, which is present in about 80% of patients at first diagnosis. The fear of fractures has therefore led caretakers to withhold MM patients from physical exercise. However, the Center for Disease Control (CDC) recommends at least 2.5 hours of moderate intense physical activity every week.
Aim: To investigate how physically active MM patients were before and directly after their diagnosis and how they desire to be physically active in the future.
Methods: Every new MM patient presenting in our clinic for the first time received a questionnaire about their regular physical activity. Questions were the following: How many hours of physical exercise have you performed per week before the diagnosis; how many hours at time of questionnaire and how many hours do you want to be active in the future (0=0; 1=-2h; 2= 2-4h; 3=4-6h; 4= more than 6h)? The current analysis reports the results of 300 consecutive patients who had completed the whole questionnaire and for whom information on stage of disease and treatment status was available. The cohort consisted of 82 asymptomatic, 46 symptomatic patients in remission (inactive) and 172 patients either at first diagnosis or in relapse (active).
Results: Patients reporting more than 2 hours per week per recommendation of the CDC were before diagnosis 63% in the asymptomatic and 65% of the inactive and active MM group, respectively. At time of questionnaire the percentage was 55%, 30% and 23%. The percentage of patients desiring more than 2 hours

per week of physical exercise in the future were 79%, 80% and 71%, respectively.

Conclusion: Regarding physical exercise, patients with active MM are restrained the most but even if the disease is in remission very few of them achieve the desired time of exercise per week.

NP-288
Symptom Management and Adherence in Multiple Myeloma (MM): A Plan to Disseminate Best- Practice Guidelines for Nurses

Faiman, B., Moran, D., Gleason, C., Richards, T., Catamero, D., King, T., Rome, S., Miceli, T., Brigle, K., Noonan, K., Tariman, J. D and the International Myeloma Foundation Nurse Leadership Board

Background: Treatment of multiple myeloma (MM) continues to undergo a rapid transformation. Each regimen potentiates unique side effects which require effective symptom management. Patients with MM are living with uncontrolled or inadequately managed symptoms. Nurses caring for these patients provide a vital link to side effect prevention and identification, symptom management and education. As the science of MM rapidly changes, it is critical to maintain nursing specific guidelines to educate those who educate the patients and caregivers to promote adherence to treatment and quality of life.

Methods: Members of the International Myeloma Foundation Nurse Leadership Board (NLB), committed to nursing and patient education, convened a series of teleconferences and face-to-face meetings to determine: 1) critical disease – and treatment – related symptoms to be addressed, 2) whether or not existing guidelines were appropriate for MM patient care, and 3) whether existing guidelines were sufficient to meet the educational needs of nurses caring for MM patients. Members divided into topics of interest and conducted independent literature reviews.

Results: Due to ongoing advances in treatment and supportive care strategies for MM, it was observed that previously written guidelines by the IMF NLB from 2008 (myelosuppression, venous thromboembolic events, peripheral neuropathy, peripheral neuropathy, steroids and gastrointestinal issues) and 2011 (renal, bone health, functional mobility, sexuality) needed updating. Additional nursing guidelines for management of acute oncologic emergencies, fatigue, depression and anxiety in the care of MM patients were lacking.

Conclusion: Nurses can improve the outcomes of MM patients through education, side effect prevention and management, and adherence strategies. Current nursing-focused guidelines in the care of MM patients are outdated in light of newly approved drugs, combinations and clinical indications. Based on this unmet need, the NLB will update existing guidelines as they relate to best practices, and create new guidelines to manage symptoms not previously addressed.

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