
15TH INTERNATIONAL
MYELOMA WORKSHOP
ROME, SEPTEMBER 23-26, 2015

# 15th International Myeloma Workshop
## Rome, September 23-26, 2015

## Abstract Available Here:

http://www.clinical-lymphoma-myeloma-leukemia.com/issue/S2152-2650(15)X00048

## Welcome Message

Dear Colleagues and Friends,
It is my great pleasure and honor to invite you to attend the 15th International Myeloma Workshop to be held in Rome, Italy, from September 23rd to 26th, 2015.
During this important biannual event, the emerging advances in the biology and treatment of multiple myeloma, as well as debates on more controversial arguments, and consensus report will be presented.
The location of the Workshop, in the Auditorium Parco della Musica which is right in the city centre, will ensure that you all enjoy both the meeting and the fascinating city of Rome.
I am very much looking forward to welcoming you to Rome in September 2015!

Antonio Palumbo
President, 15th International Myeloma Workshop


# 15th International Myeloma Workshop
## Rome, September 23-26, 2015

### PLENARY SESSION



### POSTER SESSION



### NURSE SESSION


# 15th International Myeloma Workshop
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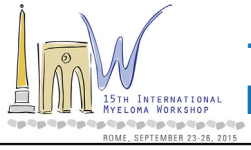
### NURSE SESSION

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## PLENARY SESSION

### Main Program

## PS-001

### Robert Kyle lecture: Access to Innovation and Quality of Care in the Context of Economic Constraints: a Challenge for Healthcare

***J.L. Harousseau***

*HAS (French High Authority for Health), Saint Denis La Plaine Cedex, France*

In oncology, the price of effective new agents, which is partly related to increasing costs of research and development, is becoming a challenging concern.

In Multiple Myeloma, although the number of patients treated is smaller than in breast, lung or colon cancer, the price of new agents already on the market and the expected price of agents in development raise two different issues

- In poor countries or in countries without universal coverage of healthcare-related costs: the issue of access to treatment and of inequity of care, since many patients cannot afford for such expensive drugs
- In rich countries or in countries with universal coverage: the issue of healthcare system sustainability, since economic constraints limit the possibility of reimbursing all diagnostic and therapeutic innovations

The introduction of novel agents (thalidomide and mostly bortezomib, lenalidomide) raised some concerns even in high-income countries. For instance, in England were cost-effectiveness evaluation has been proposed for more than 15 years by the NICE, reimbursement of bortezomib was initially limited by a risk-sharing program

But these concerns are being increased with the development of two therapeutic strategies

- combination of drugs. Triple combinations using one imid(thalidomide or lenalidomide which is more expensive) and one proteasome inhibitor (bortezomib or carfilzomib) have already been evaluated and show promising results both in newly diagnosed patients and in relapsed patients. In the near future, antibodies might be added to these backbones
- maintenance therapy: although the benefit in overall survival is not always clear, maintenance therapy studies show significant and sometimes dramatic improvements of progression free survival which might lead to prolonged treatments with expensive drugs

Therefore the question is to choose the most efficient strategies in order to offer the most effective treatment at affordable costs. There are two levels of decisions

- reimbursement and pricing decisions based on Health Technology Assessment : the objective is to provide patients with a rapid access to new active agents but to define the fair price which is compatible with national resources in the context of economic constraints. In Europe, different strategies exist. In Germany, the decision is mostly based on the assessment of therapeutic added value by comparison with existing treatments. On the opposite, in England, drug access is limited by the determination of an Incremental Cost-Effectiveness Ratio calculated in GBP per Qaly with a pre-defined threshold. To avoid the risk of rationing, patient access schemes and a specific cancer drug fund have been proposed. Other countries use some form of health-economic assessment without formal thresholds but with recommendations for payers
- good clinical practices guidelines defined by health professionals and supported by national or regional agencies for quality of care with the objectives of limit misuse and to organize efficient patient pathways.

## PS-002

### How to introduce Technology Assessment in Clinical Studies

***C. Iglesias***

*Department of Health Sciences, Hull and York Medical School, Centre for Health Economics, University of York, United Kingdom*

**Introduction/Background:** Efficient resource use is a priority for healthcare systems. Health technology assessment processes provide a platform to increase efficiency in the healthcare sector and promote informed healthcare decision making. **Materials (or patients):** Multiple Myeloma patients **Methods:** Trial and model based economic evaluation analysis in Multiple Myeloma **Results:** Economic

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evaluation analysis is an analytic tool to inform health technology assessment processes. There are three main types of economic evaluation that differ in their approach to measure and value health benefits. Cost-effectiveness analysis defines health benefits in natural units / clinical outcomes (e.g. relapse free days, remittance duration, symptom severity, complications, etc.) Preference base measures of HRQoL are measures of benefit used in costutility analysis (e.g. QALYs). Cost-benefit analysis aims to measure health benefit in monetary terms (e.g. willingness to pay estimated in discrete choice experiments).

"Piggyback" economic evaluations - i.e. those conducted alongside a clinical randomised controlled trial - allow collecting individual patient level primary economic data on resource use and preference based measures of health related quality of life (e.g. EuroQol-5D- 3L or 5L and health utility index) in parallel to clinical outcome measures. In turn, this facilitates both: investigation of the relationship between clinical and economic outcomes and development of mapping algorithms for extrapolation.

To inform healthcare decision making, trial based economic evaluations need to be complemented with model based economic evaluations. Decision models provide and analytical framework that - for any given decision problem - enables consideration of all relevant alternative competing treatments over an appropriate time horizon for different populations of interest.

Examples of the way in which different methods of EE could be implemented in the context of current healthcare interventions for Multiple Myeloma will be discussed during the presentation. **Conclusion:** The experience of health technology assessment agencies internationally indicates that trial based economic evaluation is a valuable tool to: measure the economic impact of healthcare interventions; and inform key parameters of decision analytic models. Model based economic evaluation is however increasingly recognised as the preferred tool to inform healthcare decision making.

## Genomics and Microenvironment

### PS-003

### Next Generation Sequencing in Multiple Myeloma

***N.C. Munshi, N. Bolli, S. Minvielle, K.C. Anderson, G. Parmigiani, P. Campbell, H. Avet-loiseau***

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Initial oncogenomic studies utilizing a high-resolution analysis of recurrent copy number alterations, coupled with expression analysis in primary Multiple Myeloma (MM) cells has revealed a complex disease process accompanied by numerous genetic and epigenetic alterations. Number of highly recurrent and focal copy number alterations have been identified and these regions of amplification/deletions have been evaluated for involvement in MM pathogenesis and prognosis. With the availability of massively parallel sequencing, these oncogenomic studies are now further expanded to include various genomic changes including evaluation of mutational profile to study changes that may drive the disease as well as clonal content in MM. An earlier publication in 29 patients (22 whole genomes and 17 whole exomes) used deep sequencing and identified unique recurrent mutations that may have biological importance. These genes include histone methyltransferases, transcription factor IRF4, BRAF, genes involved in protein translation, and surprisingly genes involved in blood coagulation.

Two subsequent larger studies including one from our group have identified various genomic characteristics. Myeloma cells on an average has between 50-60 mutations; there is no universal mutation that drives the disease in a large majority of patients; in fact frequency of no single mutation is greater than 15-20%, in fact most are less than 10%. Importantly, the 3 most common mutations involve MEK/ERK pathway genes namely N-Ras, K-Ras and BRAF.

An important observation from this study has been significant genomic heterogeneity in myeloma. Mutations were often present in subclonal populations, and multiple mutations within the same pathway (e.g., KRAS, NRAS, and BRAF) were observed in the same patient. In vitro modeling predicts only partial treatment efficacy of targeting subclonal mutations, and even growth promotion of mutated subclones in some cases. Interestingly, analysis of the mutational profile data have also identified a complex subclonal structure at diagnosis which evolves further over time, driven by inherent tumor characteristics and/or under the selection pressure from therapeutic intervention. Further analysis of the exome sequencing data, in serial sampling revealed diverse patterns of clonal evolution: linear evolution, differential clonal response, and branching evolution. Diverse processes contributing to the mutational repertoire including kataegis and somatic hypermutation have been identified, and their relative contribution changed over time. The analysis of the myeloma mutational profile suggest that the disease may be driven by diverse processes which may require different therapeutic intervention, raising the need and possibility of individualized therapy based on the driver mutations.

The ability to utilize massively parallel sequencing has allowed interrogation of various other genomic correlates. For example large size RNA-seq data has identified a complex but reproducible spliced isoforms patterns with differential expression between normal plasma cells and myeloma cells as well as between various myeloma subtypes. Evaluation of the expression of mutated genes in MM using RNA-seq has identified a pattern of differential and limited expression of mutant alleles. We observe that only quarter of the mutations are expressed and among mutated genes that are expressed, there are often allele-specific patterns of expression. These results highlight the important contribution of RNA-sequencing to identify clinically significant mutations and for their therapeutic applications. Moreover, sequencing of long noncoding RNA, microRNA, global UTR-sequencing and sequencing of epigenomic markers have now begun to unravel disease process as well as highlight differences in various genomic subtypes.

In summary, the early mutational analyses of clinically annotated samples have provided insight into molecular mechanism of disease

behavior, and help identify novel therapeutic targets for the development of molecularly-based therapies to improve outcome in myeloma.

## PS-004

### The Risk Classification based on Gene Expression Profiling: a Tool for Prediction of High- and Low-risk Multiple Myeloma across International Trials

***P. Sonneveld, R. Kuiper, A. Broijl, M. van Duin***

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Patients with multiple myeloma have variable survival, and require reliable prognostic and predictive scoring systems. Currently, clinical and biological risk markers are used independently. Here, ISS, FISH markers and gene expression (GEP) classifiers were combined to identify novel risk classifications in a discovery/validation setting. We used the datasets of HOVON-65/GMMG-HD4, UAMS-TT2, UAMS-TT3, MRC-IX, APEX and IFM-G (total number of patients: 4750) to test the relative prognostic impact of individual markers alone and in combination. A total of 20 risk markers were evaluated including t(4;14) and deletion of 17p (FISH), EMC92 and UAMS70 (GEP classifiers) and ISS. It was observed that ISS is a valuable partner to GEP classifiers and FISH. Ranking all novel as well as existing risk markers showed that the EMC92-ISS combination is the strongest predictor for overall survival, resulting in a four group risk classification. The median survival was 24 months for the highest risk group, 47 and 61 months for the intermediate risk groups and median not reached after 98 months for the lowest risk group. The EMC92-ISS classification is a novel prognostic tool, based on biological and clinical parameters, which is superior to current markers and offers a robust clinically relevant 4-group model. The relative value of GEP based risk classification will be discussed in the context of alternative classification models

## PS-005

### SNP/microRNA

***C. Croce***

*The Ohio State University, Ohio, USA*

Several reports and our data suggest that MDM2 overexpression in MMs, but not its gene amplification could be responsible for p53 inactivation in cells retaining functional p53 pathways. This supports the idea that induction of p53 in this setting might be a suitable treatment for MM. We studied the role of miRNAs in the p53 apoptotic pathway upon nongenotoxic activation of p53 in MM cells, using small molecular inhibitors of MDM2 (Nutlin-3a, MI-219) and identified two related microRNA clusters located in regions considered important for MM (miR-194-2-192 at 11q13.1 and miR-194-1-215 at 1q41.1). Through characterization of the miR-194-2-192 cluster promoter region and definition of a non-canonical p53 consensus site, we have shown that these miRNAs are direct p53 targets. In patient samples, the expression of these miRNAs changed during transition from normal PC, via MGUS to intramedullary MM and these miRNAs were significantly downregulated in a cohort of newly diagnosed MMs versus MGUS. We also noted, as in the case of KMS28BM cells, that their biological action could be associated with the MDM2 status in MM cells, and Luciferase assays using plasmids harboring the MDM2 30UTR sequence confirmed that MDM2 is the direct target of these miRNAs. In a subset of newly diagnosed MMs, elevated levels of MDM2 mRNA were inversely associated with miR-192 expression. We proved, in vivo and in vitro, that the combination of these miRNAs with p53 pharmacological activator (MI-219), leading to MDM2 downregulation and subsequent p53, p21, and Puma upregulation, could be a successful therapeutic strategy. In fact, it produced anti-tumor results that could not be achieved solely by increasing the drug concentration. We also found that miR-192 and miR-215 expression, by overriding MDM2 ubiquitination of IGF-1R, directly targets the IGF-1 axis in MM cells, controlling mobility and invasive properties of MM cells in vitro and in vivo. We proposed a model in which these miRNAs are (1) regulators of the autoregulatory loop, increasing the window of time between p53 apoptotic action and p53 degradation by MDM2; and (2) at the same time targeting the IGF axis, antagonizing the MDM2 ubiquitin ligase function on IGF-1R.

In summary, our results have defined a mechanism of p53 regulation through miRNAs acting on MDM2 expression, providing the basis for the development of miRNA-targeted therapies for MM.

## PS-006

### The Vk*MYC Mouse Model to study Drug and Immunotherapy Response and Resistance

***M. Chesi, P.L. Bergsagel***

*Mayo Clinic, Arizona, USA*

A genetic rearrangement of the MYC locus is among most common mutations in human MM. The genetically engineered Vk*MYC mouse model is based on dysregulation of MYC, and has been extensively validated as a clinically and biologically faithful model of untreated MM. Eleven drugs or classes of drugs – Selinexor, Pim kinase inhibitor (LGH447), DNA alkylators, Glucocorticoids, Proteasome Inhibitors, IMiDs, paclitaxel, HDACi, TACI-Ig, perifosine and SNS-032- have more than a 20% PR rate in Vk*MYC MM. Among these, eight also have greater than 10% PR rate as single agents, or increased PR rate when used in combinations in patients with MM for a positive predictive value of 73%. In contrast, 11/12 drugs that have less than 20% PR in Vk*MYC MM also have less than 20% PR in patients with MM for a NPV of 92%. Confident that drugs with activity in Vk*MYC mice will likely be effective in the treatment of MM, we have used this model to study novel drugs. We found that bromodomain inhibitors which compete with acetylated histones for the binding to BRD4, inhibiting super-enhancer activity and MYC transcription were also active in the Vk*MYC model. The histone methyltransferase EZH2 inhibitor CPI-'169 is active against Vk*MYC MM, identifying EZH2 as a promising new epigenetic target in MM. EDO-S101 is a molecular

fusion of bendamustine with vorinostat that aims to increase the efficacy of the alkylator through the HDACi-mediated chromatin relaxation to make DNA more accessible to the damaging effect of bendamustine. It induced a high rate of response in Vk*MYC MM that was sustained for more than three months in mice receiving only two doses, one week apart. The IAP antagonist LCL161 results in rapid degradation of cIAP1/2 with stabilization of NIK and constitutive activation of NFkB. In vivo this results in activation of the innate immune system, with a cytokine release syndrome the dose limiting toxicity. In Vk*MYC mice with MM LCL161 results in a phagocytic-cell dependent, NK and T-cell independent anti-tumor response that is augmented with the addition of cyclophosphamide. Inhibition of coinhibitory receptors CTLA4, PD1 or PDL1 was ineffective, however activation of the costimulatory receptor CD137 with agonist antibody resulted in NK and CD8 T-cell dependent anti-tumor responses. These preclinical studies suggest that the Vk*MYC model can be successfully used to rationally develop novel targeted and immunotherapies for the treatment of MM.

## PS-007

### Multiple Myeloma Biological Pathways

**G.J. Morgan**

*Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, USA*

Myeloma is not a single disease but is rather a collection of different disease entities all presenting as clonal expansions of plasma cells. Much of the last 20 years has been spent on ways of defining these different entities, understanding their clinical course and, more recently, at targeting therapy to their biology. Cytogenetics was the initial tool used to understand the biology of multiple myeloma and has provided the basis for our current understandings. Gene mapping improved the understanding of indels, large copy numbers abnormalities, and their impact on biology and prognosis. Further levels of complexity have been superimposed on these initial observations by the use of global gene expression profiling (GEP). GEP has allowed the subgrouping of myeloma by the TC or UAMS classifications, and we have developed these approaches further by using an extended dataset generated from the total therapy program.

In addition, the integration of both mutational analysis and other levels of epigenetic data can clarify molecular subgroups and refine prognostic subgroups. The critical challenge now is to understand and improve the outcome of high risk multiple myeloma. In order to do this we must understand the molecular lesions which underlie its behavior. We have applied the above mentioned techniques to this question and we are starting to understand how these molecular features interact to generate aggressive clinical myeloma. This knowledge pathway is providing the platform for clinical relevant targeted treatment strategies and improved survival.

## PS-008

### Multiple Myeloma and the Bone Marrow Niche

**I.M. Ghobrial**

*Dana-Farber Cancer Institute, Boston, USA*

Multiple Myeloma (MM) is a disease of plasma cells with specific localization in the bone marrow. Recent studies have shown that MM is consistently preceded by MGUS. This has given rise to the concept of a myeloma precursor disease and raised questions about the biologic events leading to progression of these precursor states to symptomatic MM. The genomic complexity in MM was recently corroborated next generation sequencing that provided resolution pictures of the genetic changes in cancer cells and heterogeneity in tumors where tumor progression proceeds in a branching rather than in a linear manner, leading to substantial clonal diversity and coexistence of wide genetic heterogeneity. Although many factors regulating tumor progression are tumor cell autonomous, they are insufficient to induce progression and metastasis, and a permissive microenvironment is required for frank malignancy to emerge[7]. Indeed, studies have shown that the tumor microenvironment is a key regulator in many steps of the invasion-metastasis cascade including tumor oncogenesis, egress, protection in the circulation, preparation of the metastatic niche, organ-specific homing, and the permissive role of the microenvironment in tumor colonization[7]. These studies provide proof of bidirectional interactions that occur between tumor cells and the nearby microenvironment that are permissive for tumor initiation and progression, establishing a positive-feedback loop that may be self-amplifying[7,8]. Although the BM microenvironment is commonly referred to as the "non-tumor" entity, it has to be kept in mind that it is a complex network including a broad range of cells and factors[9,10]. Indeed, the BM microenvironment consists of 3 components: the cellular component (hematopoietic and non-hematopoietic cells, including msenchymal stromal cells, immune cells, osteoclasts, osteoclasts and endothelial cells); the extracellular matrix component; and the soluble component (such as exosomes, cytokines, circulating free miRNA and growth factors)[11,12]. Multiple biological aspects that are affected by interactions between abnormal plasma cells and the BM microenvironment including homing to the BM, spread to secondary BM sites by the bloodstream, generation of paracrine factors, osteoclastogenesis, inhibition of osteogenesis, immune cell dysregulation, and angiogenesis lead to the progression of MM from early MGUS-like stages to overt metastatic myeloma.

# Diagnostic and Response Criteria

## PS-009

### New Diagnostic Criteria for Multiple Myeloma

**S.V. Rajkumar**

*Division of Hematology, Mayo Clinic, Rochester, USA*

Multiple myeloma (MM) has been traditionally defined by the presence of end-organ damage, specifically, hypercalcemia, renal failure, anemia, and bone lesions (CRAB features) that are felt to be a consequence of the underlying clonal plasma cell proliferation. The International Myeloma Working Group (IMWG) has updated the diagnostic criteria for MM in 2014, adding 3 specific biomarkers that can be used to make the diagnosis in patients who do not have CRAB features. These 3 biomarkers are: presence of

≥60% clonal plasma cells in the marrow, serum free light chain (FLC) ratio ≥100 (provided involved FLC level ≥100), and more than 1 focal lesion (≥5mm in size) on magnetic resonance imaging (MRI) or whole body or spine/pelvis (Table1). Each of these biomarkers has been validated in 2 or more independent studies to have a very high risk (~80%) of progression to symptomatic disease within 2 years. In addition, the update allows modern imaging methods including computed tomography (CT) and positron emission tomography-CT to diagnose MM bone disease. The new diagnostic criteria provide 3 important clarifications on requirements for bone and renal disease in the diagnosis of MM. First, the presence of osteoporosis, vertebral compression fractures, or bone densitometric changes in the absence of lytic lesions is not considered sufficient evidence of myeloma bone disease. Second, only suspected or proven light chain cast nephropathy is considered as meeting the renal component of the CRAB criteria. Renal disorders associated with M proteins such as light chain deposition disease, membranoproliferative glomerulonephritis, and AL amyloidosis, are considered unique diseases and not MM. Third, an estimated GFR less than 40 ml/ minute is preferred to the serum creatinine concentration for purposes of fulfilling the CRAB criteria.

**Table 1** International Myeloma Working Group Diagnostic Criteria for Smoldering Multiple Myeloma and Multiple Myeloma

| Disorder | Disease Definition |
|---|---|
| Smoldering multiple myeloma | Both criteria must be met:<br>• Serum monoclonal protein (IgG or IgA) ≥3gm/dL, or urinary monoclonal protein ≥500 mg per 24h and/or clonal bone marrow plasma cells 10-60%<br>• Absence of myeloma defining events or amyloidosis |
| Multiple Myeloma | Both criteria must be met:<br>• Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma<br>• Any one or more of the following myeloma defining events (MDE):<br>○ CRAB features felt attributable to the underlying plasma cell proliferative disorder, specifically:<br>■ Hypercalcemia<br>■ Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 μmol/L (>2 mg/dL)<br>■ Anemia<br>■ Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT<br>○ Clonal bone marrow plasma cell percentage ≥60%<br>○ Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)<br>○ >1 focal lesions on MRI (at least 5mm in size) |

Reproduced from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-e548.

One of the main implications of the new diagnostic criteria is that at least one advanced imaging exam (PET-CT, low-dose whole body CT, or MRI of the whole body or spine) is needed for diagnosis in patients with suspected SMM or solitary plasmacytoma. Another implication is that patients with high risk SMM and solitary plasmacytoma who develop symptoms worrisome for progression during the course of follow up can be initiated on therapy before the onset of serious end-organ damage.

## PS-010

## Flow Cytometry for Minimal Residual Disease

***B. Paiva,[1] M.B. Vidriales,[2] N. Puig,[2] M.A. Montaban,[3] L. Cordón,[4] M.V. Mateos,[2] J.J. Lahuerta,[3] J. Blade,[5] A. Orfao,[6] J.F. San Miguel[1]on behalf of the GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study group***

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Assessment of minimal residual disease (MRD) is becoming standard diagnostic care for potentially curable neoplasms such as acute lymphoblastic leukemia. In multiple myeloma (MM), the majority of patients will inevitably relapse despite achievement of progressively higher complete remission (CR) rates. Novel treatment protocols with inclusion of antibodies and small molecules might well be able to further increase remission rates and potentially also cure rates. Therefore MRD diagnostics becomes essential to assess treatment effectiveness. Large evidence from different cooperative groups has been generated during the last two decades demonstrating that persistent MRD by multiparameter-flow-cytometry (MFC), polymerase-chain-reaction (PCR), next-generation-sequencing (NGS), and positron-emission-tomography (PET/CT), predicts significantly inferior survival among CR patients. Extensive data also indicates that MRD information can potentially be used as biomarker to evaluate the efficacy of different treatment strategies, help on treatment decisions, and act as surrogate for overall survival. Accordingly, the time has come to address within clinical trials, the exact role of baseline risk factors and MRD monitoring for tailored therapy in MM, which implies systematic usage of highly sensitive cost-effective, readily available and standardized MRD techniques. Consequently, highly-sensitive and automated flow-MRD represents a particularly attractive approach to determine BM response because of its wide availability, independence of diagnostic sample, turn-around time, cost-effectiveness, and the inclusion of internal quality controls to identify non-representative BM samples.

## PS-011

### Next Generation Sequencing for Minimal Residual Disease

**H. Avet-Loiseau**

*IUC-Oncopole, Toulouse, France*

It has been shown for a long time that achievement of complete remission (CR) was correlated with longer survival in patients with multiple myeloma (MM). However, even in CR patients, relapses are observed. Furthermore, with current drug combinations used for transplant-eligible patients, the CR rates are in the 70-80% range. Assuming that the tumor burden at diagnosis of MM is in the range of $10^{12}$ plasma cells, CR corresponds to a 2-log reduction. Thus, techniques enabling to further measure the residual tumor plasma cells below this "conventional" CR threshold are warranted.

Myeloma cells are characterized by a unique molecular signature corresponding to the clonal Ig rearrangements. Since these rearrangements occur mostly within the early bone marrow B-cell maturation, they are supposed to be identical in all the plasma cells, independently of any potential sub-clonal variability. Thus, it is theoretically possible to take advantage of this phenomenon to design molecular tests enable to measure the minimal residual disease (MRD) with a great sensitivity.

Several academic laboratories are currently developing specific tests, but no result has been published or presented yet. The few available published results are coming from Sequenta/Adaptive Inc., using the LymphoSight™ platform. They designed primers to amplify most of the *IGH* and *IGLκ* rearrangements. The first step is to identify these clonal rearrangements at diagnosis. Then, the MRD measurements are performed on bone marrow samples obtained at the time of response. An aspirate of at least $10^7$ cells is sent to the laboratory, where DNA is extracted. A known sequence is added to the sample, and PCR amplification of the sample is performed, and then sequenced with a large depth. Then, using bio-informatic tools, the patient-specific sequence is searched in the millions of reads. This technique enables to detect MM-specific sequences at the $10^{-6}$ level.

So far, only one publication has reported results using this approach.[1] In this study, 133 patients who achieved at least a very good partial response (VGPR) were analyzed. The time to progression was 80 vs 31 months in patients with a MRD level below $10^{-5}$ or $>10^{-5}$. When restricted to patients who were in CR, the time to progression was not reached vs 35 months, with the same cutoff.

Recently, we used the same platform for patients treated in the IFM 2009 trial. This trial enrolled 700 patients < 66 years of age, and randomized the use of high-dose melphalan frontline versus at relapse after a RVD induction/consolidation followed by a 1-year lenalidomide maintenance. A subset of 235 patients who achieved at least a VGPR was analyzed for MRD at pre-maintenance and/or post-maintenance. Using the most sensitive cutoff, i.e., $10^{-6}$, at the end of treatment, the 4-year PFS was 83% for patients below this cutoff vs 30% for others.

In conclusion, NGS is the most sensitive technique currently available to measure MRD. Even though all the patients are not analyzable (8% of failure in identification of the clonal rearrangement), this very standardized technique enables to clearly identify the patients with a long disease-free survival, some of them being probably cured of the disease.

## PS-012

### Imaging Techniques

**E. Zamagni, C. Nanni, M. Cavo**

*Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy*

Bone disease is the most frequent feature of multiple myeloma (MM), occurring in approximately 2/3 of the patients (pts) at diagnosis and in nearly all the pts during the course of their disease. Imaging plays an important role in the diagnosis and management of MM. Various techniques are to date available to assess bone disease, to evaluate bone marrow plasma cell infiltration, to detect spinal cord and/or nerve root compression and to reveal the presence of soft tissue masses. Optimal use of these techniques is warranted in all disease phases.

At diagnosis, imaging is essential for the correct identification of bone disease as myeloma-related organ damage, requiring the start of therapy and of eventual sites of extra-medullary disease (EMD). Due to the low sensitivity and inability to detect "early" bone involvement, whole body X ray is considered nowadays sub-optimal and in the recent revised IMWG diagnostic criteria whole body low dose multi-detector computed tomography (WB-LDCT) or FDG PET/CT are recommended to stage the disease. Functional techniques, such as PET/CT and MRI, either whole body (WB) or axial (spine and pelvis), are adding prognostic information as well; the presence and number of focal lesions (FLs), as well as EMD, goes along with an adverse prognosis in all stages of monoclonal plasma cell disease. In smoldering MM, the progression into symptomatic disease occurs earlier if more than one FL is identified at MRI or PET/CT; due to a risk of progression to active MM > 80% in 2 years, the presence of > 1 FL on MRI leads to the definition of symptomatic MM.

For assessing and monitoring response to therapy, both MRI and PET/CT are gold standard techniques, although PET/CT is likely to provide more careful information than MRI. Pts with residual lesions after therapy suffer from earlier relapse and have a shorter OS. This is probably due to the persistence of plasma cell sub-clones, displaying different genetic profile, which are responsible for the relapse. Moreover, PET/CT can provide a more accurate definition of CR, allowing to stratify patients in conventional CR after up-front therapy into different prognostic subgroups regarding PFS and OS, according to the persistence or absence of FDG metabolic activity.

PET/CT may usefully be employed during the follow-up phase to monitor the small sub-group of patients with persistent high glucose metabolism after first-line treatment, in order to detect otherwise unidentifiable skeletal progression.

Integrating newer imaging techniques into the algorithm of MM staging and follow-up after treatment may improve disease management.

## PS-013

### Risk Assessment and Stratification

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Multiple myeloma (MM) is a malignancy for which great progress has occurred. The biologic understanding of the disease has allowed for

more precise estimates of survival and a more targeted therapeutic approach. Since a small fraction of patients can be cured it follows that complete eradication of all genetic subclones is possible. Many classifications of the disease, predominantly based on genomic markers, have identified different subgroups of MM, with dissimilar clinical outcomes. These classifications have been based on the presence of primary genetic aberrations (*e.g.* translocations), progression events (*e.g.* del17p13), GEP markers of disease aggressiveness (*e.g.* SKY-92, UAMS-70, UAMS-17, UAMS-80, MRCIX-6) or other markers such as genomic instability or genomic complexity (*e.g.* aCGH, centrosomes, etc.). These markers confer intrinsic characteristics to clonal cells that allow them to overcome therapeutic effects of drugs (such as decreased apoptosis for -17p13 deleted clones) or promote clonal diversity and allows for resistant clones to emerge (evolutionary medicine). The recent detailed confirmation of the existence of genetic subclones highlights the importance of understanding genomic instability (genotype) and genomic complexity (genotype) as perhaps the main drivers of clinical outcomes. Prognostic and predictive markers are inexorably linked to the specific therapeutic agents used. In the recent past the advent of proteasome inhibitors greatly improved the outlook for patients with high-risk MM. Paradoxically some recent reports suggest that these same agents may not be as effective in patients who traditionally were thought to have better outcomes such as those with t(11;14). Perhaps the scant cytoplasm observed in t(11;14) clones precludes ER stress mediated apoptosis. Assuming biology has not changed one can only conclude that mechanisms of action or resistance need to be considered for each unique patient and that the overall prognosis can only be estimated in the context of planned therapies. The advent of new markers of resistance such as CRBN mutations holds the potential not only to allow treatment selection, but also has paved the way to better understand resistance and mechanisms to overcome it.

## PS-014

### Geriatric Assessment and Stratification

***A. Larocca***

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Multiple myeloma (MM) is a disease of older adults, with a median age at diagnosis of 70 years. A consistent and continuous increase in life expectancy is recorded worldwide and the global population is rapidly aging. Consequently, the number of MM is expected to considerably increase in the next future.

Highly effective novel agents and supportive care have substantially improved survival in MM. However, different trials showed an inferior survival in patients ≥75 years of age.

The aging process is very complex. Aging is commonly associated with the concomitant occurrence of multiple diseases (comorbidity), and an increased risk of developing physical and cognitive decline (disability). Older people are at high risk of developing frailty, a state of increased vulnerability, with cumulative deficits in several physiological systems, which results into a diminished resistance to stressors, such as MM and its treatment.

Elderly patients with MM are highly heterogeneous; chronological age, performance status or clinician judgment are not sufficient to properly stratify them. Usually the term "frail" is used synonymously with a person over 75 years of age, which sometimes leads to an improper under-treatment of patients based only on age.

The geriatric assessment (GA) is a sensitive predictor of frailty. It is a systematic procedure used to objectively appraise the health status of older people, focusing on somatic, functional and psychosocial domains, which enables the categorization of patients according to frailty. A simplified GA that includes Katz's Activity of Daily Living (ADL) and Lawton's Instrumental Activity of DaiIy Living (IADL) to assess self-care activities, tasks of household management and independence status, and Charlson Comorbity Index (CCI) to estimate the number and severity of comorbidities should be adopted.

Age and GA are the fundamental determinants of patient stratification. The cut-off age that define frail patients is 80 years. However, irrespective of age, the presence of either a functional decline on ADL and IADL, or the presence of comorbidities, may identify frail patients. Frail patients are at high risk of non-hematologic adverse events and treatment discontinuation, regardless of other prognostic factors, and should be appropriately evaluated to determine their ability to tolerate treatment.

An appropriate definition of frailty is fundamental to better assess patients and provide them with effective, tailored treatments.

## Novartis Oncology Sponsored Symposium: Understanding the Role of Epigenetics in the Pathogenesis and Treatment of Multiple Myeloma

## PS-015

### Opening remarks

***J.F. San Miguel***

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Outcomes for patients with multiple myeloma have improved significantly in the era following the introduction of proteasome inhibitors and immunomodulatory agents. Despite these improvements, multiple myeloma remains incurable, and there is an unmet need for patients who progress on or following treatment with these agents. Continued research into the biology of multiple myeloma has led to the discovery of additional novel targets to help overcome therapeutic resistance. Epigenetic mechanisms have been shown to contribute to pathogenesis and therapeutic resistance in many hematologic malignancies, including multiple myeloma. In this symposium, the latest developments in the understanding of the role of epigenetics in the pathogenesis of multiple myeloma will be discussed along with recent clinical advances with agents targeting histone deacetylases.

## PS-016

### Introduction to Epigenetics and its Role in the Pathogenesis of Hematologic Malignancies

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Therapy of hematological malignancies is undergoing a paradigm shift from traditional chemotherapy toward the targeting of proteins driving the cancer phenotype (Helin, *Nature*, 2013). One novel therapeutic approach relies on the use of epigenetic drugs which aim to reverse epigenetic events underlying cancer pathogenesis, particularly abnormalities in DNA methylation and histone modification (Arrowsmith, *Nat Rev Drg Discov*, 2012). Besides approved epigenetic drugs, namely the DNA methyltransferases inhibitors azacitidine and decitabine and the histone deacetylase inhibitors vorinostat and panobinostat (Lane, *J Clin Oncol*, 2009; Issa, *Clin Cancer Res*, 2009), novel epigenetic drugs targeting histone lysine methylation are being developed (McGrath, *Pharmacol Ther*, 2015).

This talk will focus on the role of epigenetic changes in the pathogenesis of multiple myeloma (MM). We compared the DNA methylome of normal plasma cells with those from patients with MM and MGUS and observed a highly heterogeneous pattern characterized by regional DNA hypermethylation embedded in extensive hypomethylation. In contrast to DNA hypermethylation of promoter-associated CpG islands in many cancers, hypermethylated sites in MM are located outside CpG islands and associated with intronic enhancer regions defined in normal B cells and plasma cells. DNA hypermethylation in these regions is related to enhancer decommissioning and the degree of enhancer methylation inversely correlates with expression of transcription factors involved in B-cell differentiation. This suggests that DNA hypermethylation of developmentally-regulated enhancers is a novel epigenetic modification associated with MM pathogenesis.

There is also interest in developing small molecules against epigenetic targets. We designed and synthesized novel chemical probes that simultaneously inhibit the epigenetic targets G9a and DNMT and explored their activity in hematological tumors. In vitro, our lead compound CM-272 induced inhibition of tumor cell proliferation and apoptosis at nM concentrations, at least in part by induction of interferon stimulated genes and immunogenic cell death. In vivo, CM-272 significantly prolonged survival of xenogeneic models of AML, ALL, and DLBCL. Our results represent the discovery of first-in-class dual reversible inhibitors of G9a and DNMT and establish this new chemical series as a promising therapeutic strategy in hematological tumors, to address unmet needs of an aging population.

## PS-017

### Rationale for Targeting Epigenetic Mechanisms in Multiple Myeloma

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Epigenetic dysregulation is a common hallmark of a number of human cancers, including multiple myeloma (MM), promoting tumor cell proliferation and survival through aberrant protein expression. A number of recent studies using next-generation sequencing platforms have expanded our knowledge of the MM epigenome, supporting the development of therapeutic agents targeting specific abnormal epigenetic processes. For instance, hypermethylation of a number of genes, particularly tumor suppressor genes, and overexpression of histone deacetylases (HDACs) have both been correlated with a poorer prognosis in MM. In particular, overall survival of patients with MM is significantly reduced in patients with higher expression of class I HDACs, and preclinical data have shown that pan-deacetylase inhibitors preferentially targeting class I HDACs induce greater MM-cell killing than those preferentially targeting other HDAC classes. The combination of pan-deacetylase and proteasome inhibition induces synergistic anti-MM effects partially through inhibition of HDAC6 and blockade of aggresome formation, an alternative mechanism for protein degradation in the absence of a functional proteasome. However, recent evidence also suggests the presence of proteasome inhibitor—induced class 1 HDAC transcriptional repression, implying both epigenetic and nonepigenetic mechanisms may cooperate in the synergy between pan-deacetylase and proteasome inhibitors. Additionally, recent work has identified anti-MM synergism between pan-deacetylase inhibitors and inhibitors of pathways integral to the regulation of the actin cytoskeleton, offering a potential new direction in the treatment of MM. Future studies will be aimed at discovering novel deacetylase inhibitor combinations to potently and specifically disrupt pathways integral to the survival of MM.

## PS-018

### Clinical Update on Pan-Deacetylase Inhibitors in Multiple Myeloma

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Increasing evidence suggests that epigenetic mechanisms play a pivotal role in the pathogenesis of multiple myeloma (MM). Pan-deacetylase inhibitors (DACi) have been developed in an effort to target aberrant gene expression in MM cells. When used as monotherapy, DACi have shown only modest clinical benefit in patients with MM. However, recent evidence from clinical trials using a combination of the novel DACi panobinostat with bortezomib (BTZ) and dexamethasone in patients with relapsed or relapsed and refractory MM has shown significant clinical benefit. In a subanalysis from the phase 3 PANORAMA 1 trial, this clinical benefit was further enhanced in patients who had prior treatment with BTZ and an immunomodulatory drug (IMiD), leading to US Food and Drug Administration accelerated approval of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed or relapsed and refractory MM who have had $\geq 2$ prior regimens that include bortezomib and an IMiD. The positive results with panobinostat have set the stage for the clinical development of other DACi, such as ricolinostat, which have differential potency against the various deacetylase enzyme subtypes; these varying potency profiles may be associated with alternative efficacy and safety outcomes in combination with various agents. Additionally, the success of DACi with proteasome inhibitors has provided the impetus to assess the efficacy and safety of DACi in combination with other standard-of-care agents, including IMiDs such as lenalidomide, and in multidrug combinations with bortezomib,

thalidomide, and dexamethasone. The latest data from these trials will be discussed in the context of providing novel therapeutic strategies in a patient population with a significant unmet need.

## PS-019

### Opportunities for Novel Combinations with Agents Targeting Epigenetic Mechanisms

***H. Einsele***

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Over the past decade, patients with multiple myeloma have experienced increases in overall survival. These increases can be attributed to the development of new agents, including the proteasome inhibitors bortezomib and carfilzomib and the immunomodulatory agents (IMiDs) thalidomide, lenalidomide, and pomalidomide. Despite these advancements, multiple myeloma remains incurable; thus new agents with novel mechanisms of action are urgently needed. Deacetylase inhibitors, which activate expression of genes that are epigenetically silenced, have recently emerged as a novel class of agents for the treatment of multiple myeloma. The pan-deacetylase inhibitor panobinostat was recently approved by the US Food and Drug Administration for use in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received $\geq$ 2 prior regimens that include bortezomib and an IMiD. Based on the mechanism of action of agents targeting epigenetic pathways, such as deacetylase inhibitors, there is interest in the potential for combining them with other "next-generation" therapies, including carfilzomib and pomalidomide. Additionally, monoclonal antibodies targeting myeloma cell surface receptors are emerging as another class of agents with clear potential as a new treatment option. Evidence suggests that resistance to these agents may be mediated through epigenetic downregulation of receptor gene expression. Future studies should evaluate the potential for combinations of deacetylase inhibitors and monoclonal antibodies. Taken together, agents targeting epigenetic mechanisms have clear potential to increase treatment options and novel combinations for patients with multiple myeloma. Ongoing studies will help shape the role of these agents in the treatment landscape for this disease.

## Newly Diagnosed Multiple Myeloma Young Patients

## PS-020

### Single-tandem Transplantation

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Currently different transplantation strategies are used to intensify treatment of patients with multiple myeloma and to consolidate response quality after a first transplantation.

The IFM 94 trial has revealed a doubling of the PFS and OS in patients who received a tandem SCT when compared to a single SCT. A non-planned subgroup analysis showed that especially patients not achieving a VGPR or CR after the first SCT benefitted from a second SCT. In the era of the novel agents how randomized trial has been analyzed yet which compares single vs tandem SCT. Data from the Hovon/GMMG group as well as a retrospective analysis of 3 European trials all using novel agents for induction demonstrated a PFS and OS advantage for tandem SCT especially in patients with a suboptimal response to induction therapy and a high risk features of their MM.

In patients at an ultrahigh risk (17pdel, e.g.) the administration of auto/allo transplantation was shown to be superior to a tandem auto SCT in patients who did not receive novel agents for induction and/or consolidation.

## PS-021

### Optimal Consolidation Therapy

***M. Cavo***

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The role of autologous stem-cell transplantation (ASCT) in the treatment of multiple myeloma (MM) has continued to evolve in recent years. The choice of induction therapy has shifted from conventional chemotherapy to newer regimens incorporating the immunomodulatory derivatives (IMiDs) thalidomide or lenalidomide and/or proteasome inhibitors (PIs), including the first-in-class agent bortezomib. Novel agent-based induction therapies have affected unprecedented rates of CR that rival those previously seen with conventional chemotherapy and subsequent ASCT. Excellent activity shown by IMiDs and/or PIs before ASCT has lead to their investigational use as consolidation and maintenance therapy after autotransplantation. Although the terms consolidation and maintenance are often used synonymously in the transplant setting, the rationale supporting these two strategies is different. Consolidation treatment is generally short-term and aims to increase the frequency and depth of response obtained with the previous treatment phases, including high-dose melphalan and ASCT. For this purpose, either bortezomib or lenalidomide as single agents or triplet regimens incorporating bortezomib-dexamethasone combined with an IMiD have been explored in phase 2 and 3 clinical studies. Overall, in all of them consolidation therapy enhanced the frequency and depth of response achieved after a single or double ASCT, even when this latter was preceded by a novel agent-based induction therapy. In several trials, the depth of response was improved up to the molecular level negativity, a finding previously seen only after allogeneic stem-cell transplantation. In other studies, enhanced rates and quality of responses offered by consolidation therapy translated into an extended PFS, a finding suggesting that the consolidation phase contributed to the improved clinical outcomes registered on an intention-to-treat basis following the entire ASCT sequence. Notably, in several trials the superior activity of a particular induction regimen was retained despite re-administration of the same therapy as post-ASCT consolidation, suggesting that no switch from one class to another class of novel agents is warranted moving from induction to consolidation therapy. As previously demonstrated in the induction phase, it is likely that combining two different agents with different mechanisms of action, like a PI with an IMiD, may help to

maximize the efficacy of consolidation therapy. Consolidation treatment appears to be generally safe, with a substantial reduction of toxic events in comparison with those frequently seen in the induction phase, a finding sometime related to a reduction in treatment intensity and/or changes in the schedule of the drug(s). Recent availability of subcutaneous bortezomib, as well as of second generation PIs that are avoid of neurological toxicity would allow a higher dose-intensity and/or a higher number of cycles of therapy. Whether more intensive regimens might ultimately result in improved activity and lesser toxicity compared with previous ones remains an open issue. Additional, not yet addressed, issues are the need, if any, to use consolidation therapy in all patients and the interface of consolidation with subsequent maintenance therapy. All these issues might be properly addressed in the context of prospective randomized trials designed to improve long-term outcomes, while retaining a good quality of life.

## PS-022

### Transplant Eligible Maintenance

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The treatment of young or transplant-eligible MM patients usually consists of autologous transplant after induction therapy or at first relapse. Consolidation therapy may be given after induction therapy or transplant. Most patients will relapse or progress after initial therapy. Therefore, maintenance therapy is given with the goal of prolonging and maintaining disease response while maintaining quality-of-life. Maintenance therapy should improve overall survival (OS) when compared to re-treatment at relapse/progression. Another endpoint for determining maintenance effectiveness is prolongation of the time to progression after first salvage therapy: progression-free survival-2 (PFS-2). Maintenance therapies have included glucocorticoids, interferon-alpha or thalidomide. The latter demonstrated improved PFS and in some studies OS. However it is not well tolerated so there is a high discontinuation rate due to adverse events. More recent maintenance treatments tested in Phase III studies include: lenalidomide (McCarthy et al NEJM 2012, Attal et al NEJM 2012, Palumbo et al NEJM 2014) or lenalidomide plus glucocorticoids (Palumbo et al ASH 2013) or bortezomib (Sonneveld et al JCO 2013). All have demonstrated a prolonged PFS; lenalidomide improved OS in one trial and bortezomib improved PFS/OS in patients with del17. Lenalidomide maintenance is associated with development of second primary malignancies (SPMs). In CALGB 100104, the cumulative incidence risk (CIR) of SPMs is higher for lenalidomide while the CIR of progression and death is higher for placebo. Combined maintenance therapy with lenalidomide, bortezomib and glucocorticoids has been studied in high risk patients in a Phase II trial (Nooka et al Leukemia 2014). Maintaining response without disease progression, identifying patients who benefit from prolonged maintenance and determining the optimal length of maintenance are goals for the future. Newer agents including oral proteasome inhibitors: ixazomib and oprozomib, antibodies: elotuzumab and the anti-CD38 antibodies, and agents targeting other molecular pathways may improve PFS and OS by extending control of MM.

## PS-023

### Ongoing Studies/Open Questions in America

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**Background:** As part of its mission the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) through its Myeloma Intergroup Committee meets to develop a Myeloma Transplant Research Agenda that allows for prioritization and development of national trials that will establish new standards of care and further our knowledge of myeloma biology.

During the last State of the Science Meeting held in Dallas in 2014 identified the following questions as the ones most important to address over the next 5 years in the context of ongoing studies summarized in Table 1.

Most Compelling Questions for Myeloma SCT

Early versus late autologous SCT.

A) The IFM/DFCI randomized trial and the European Myeloma Network trial are addressing this issue. The results of those trials will be important in optimizing frontline therapy for all SCT eligible myeloma patients.

B) Risk Adapted Therapy

Two factors are emerging as important determinants of long-term outcome in patients with myeloma.(2)

1. Identification of high risk myeloma by cytogenetics and molecular profiling.

2. Depth of response to therapy.

Two strategies have been shown to be effective in detecting minimal residual disease in patients who have achieved a CR by standard IMWG criteria. Polymerase chain reaction (PCR) and flow cytometry. In myeloma PCR with allele-specific oligonucleotide (ASO) primers complementary to the immunoglobulin heavy chain variable sequence (ASO PCR) is the most sensitive approach for the detection of malignant plasma cells. However, the need for patient specific primers and the high sensitivity of this assay has limited it's clinical value. Multiparameter flow cytometry (MFC) can detect residual myeloma cells by the aberrant expression of cell surface markers in approximately 90% of patients.(3)

The Myeloma Subcommittee agreed that one of the most compelling questions to answer over the next 5 years was whether risk adapted therapy (Prognostic index + Response) could be used to inform modern therapy. The obvious corollaries to this question were

1) Are there patients with such a "good risk" profile (i.e. those having achieved a CR to induction with low risk clinical, cytogenetic and molecular profiles) in which high dose melphalan with auto SCT is NOT warranted as consolidation of a first remission? Alternatively can these patients be cured with an auto SCT.