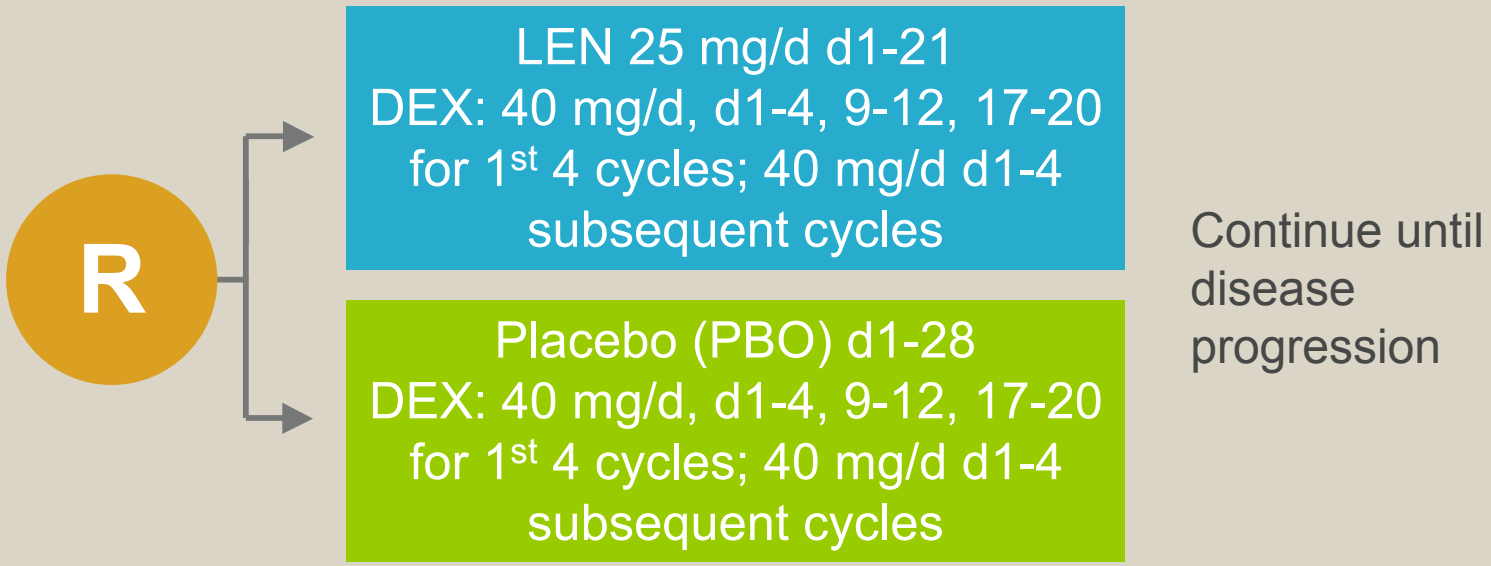
Lenalidomide and Dexamethasone (LEN plus DEX) Treatment in Relapsed/Refractory Multiple Myeloma Patients (Pts) and Risk of Secondary Primary Malignancies (SPM): Analysis of MM-009/010

Dimopoulos MA et al.

Proc ASCO 2011;Abstract 8009.

MM-009/010 Phase III Trial Schemas

Analysis of pooled data from patients with relapsed/refractory multiple myeloma (RRMM) treated in 2 Phase III studies (MM-009 and MM-010)



Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

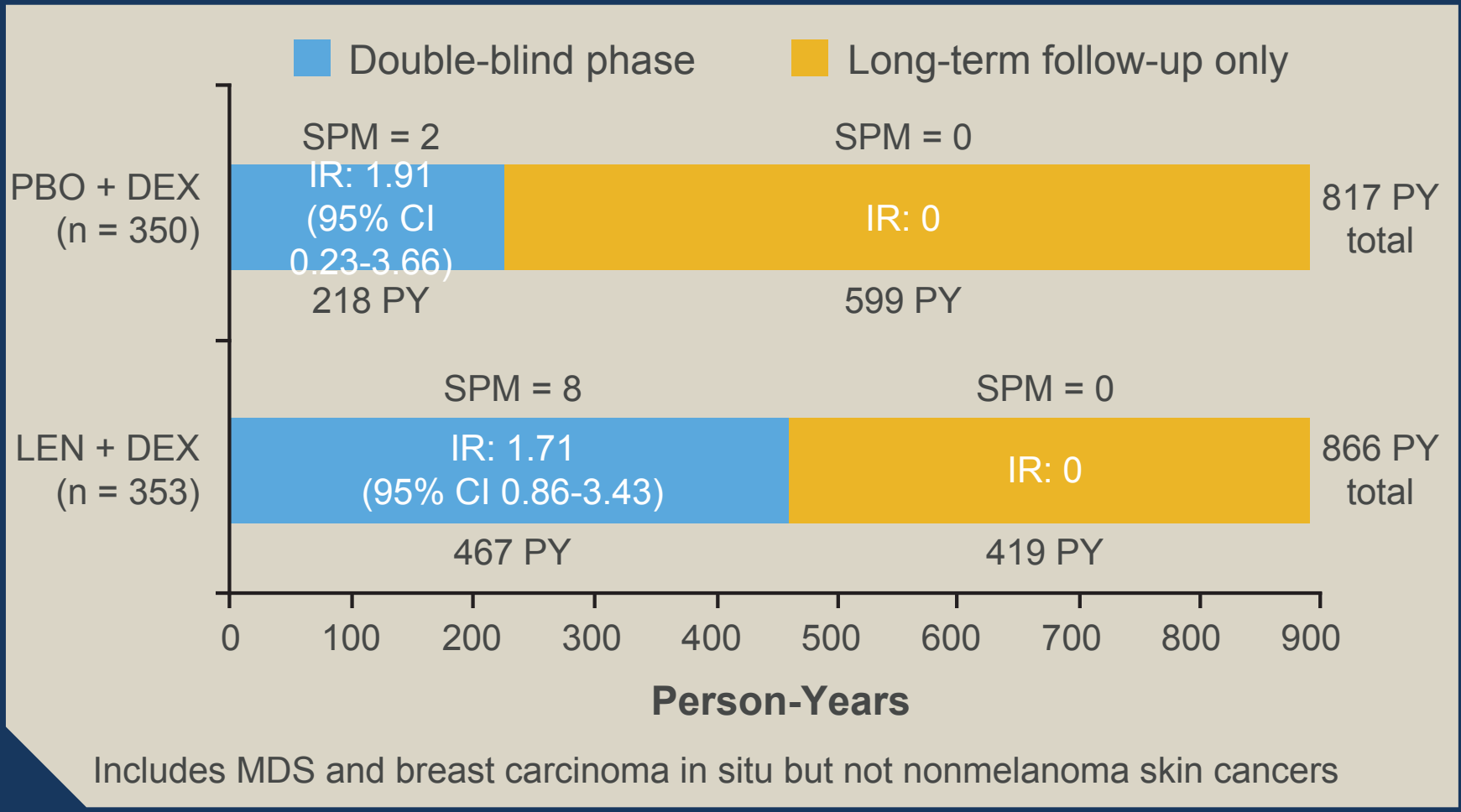
SPM Incidence Rates — Active Treatment Phase (Safety Population)

Invasive SPM	Incidence*	
	LEN + DEX (n = 353)	PBO + DEX (n = 350)
Hemtologic	0.42	0
AML/MDS	0.42	0
B-cell malignancies	0	0
Solid tumors	1.28	0.91
Noninvasive SPM		
Nonmelanoma skin cancer	2.40	0.91
Total SPM	3.98	1.38

* Incidence rate (IR) reported per 100 person-years (PY)

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Invasive SPM Incidence Rates — Treatment and Follow-Up



Includes MDS and breast carcinoma in situ but not nonmelanoma skin cancers

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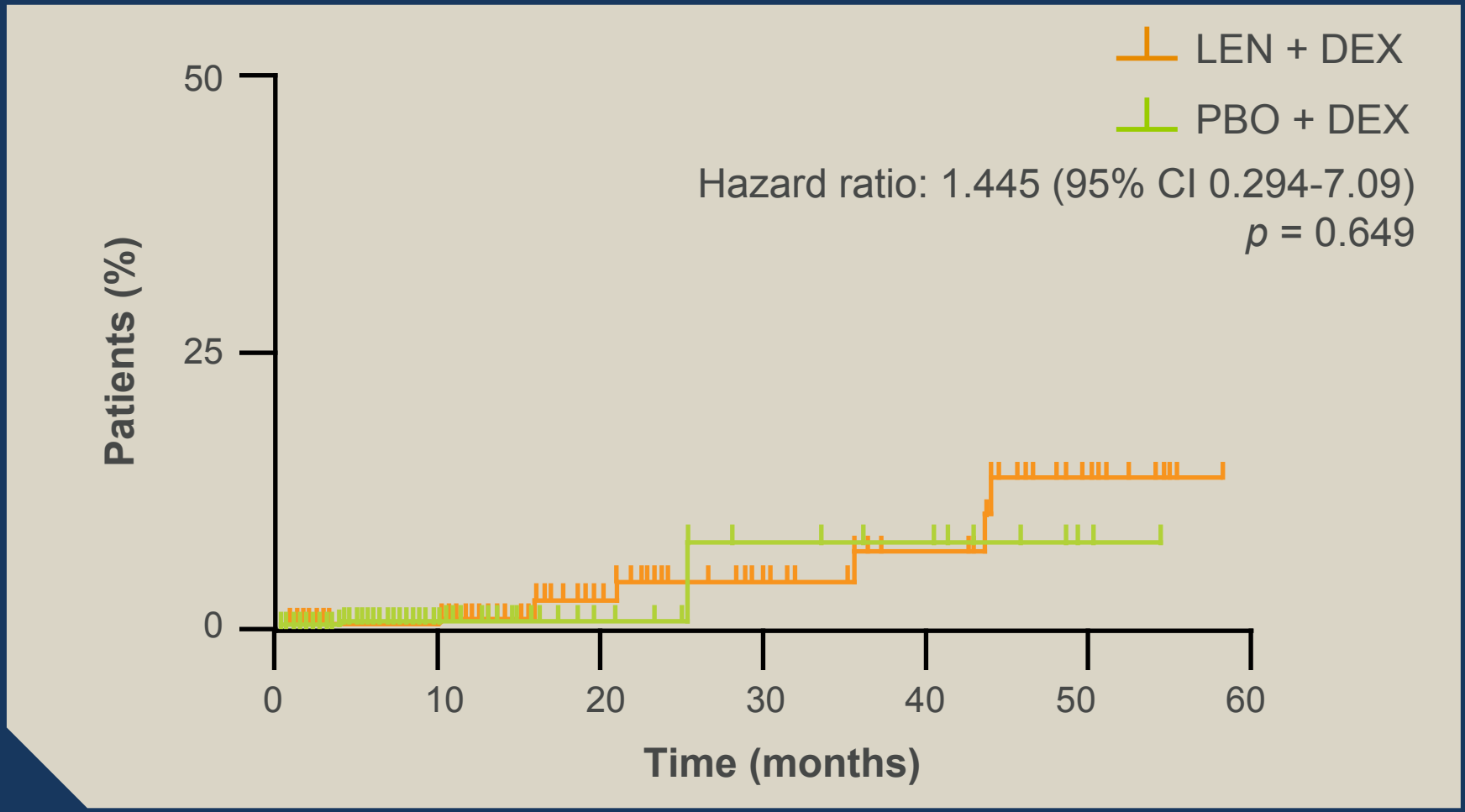
Time to Invasive SPM — Treatment Period



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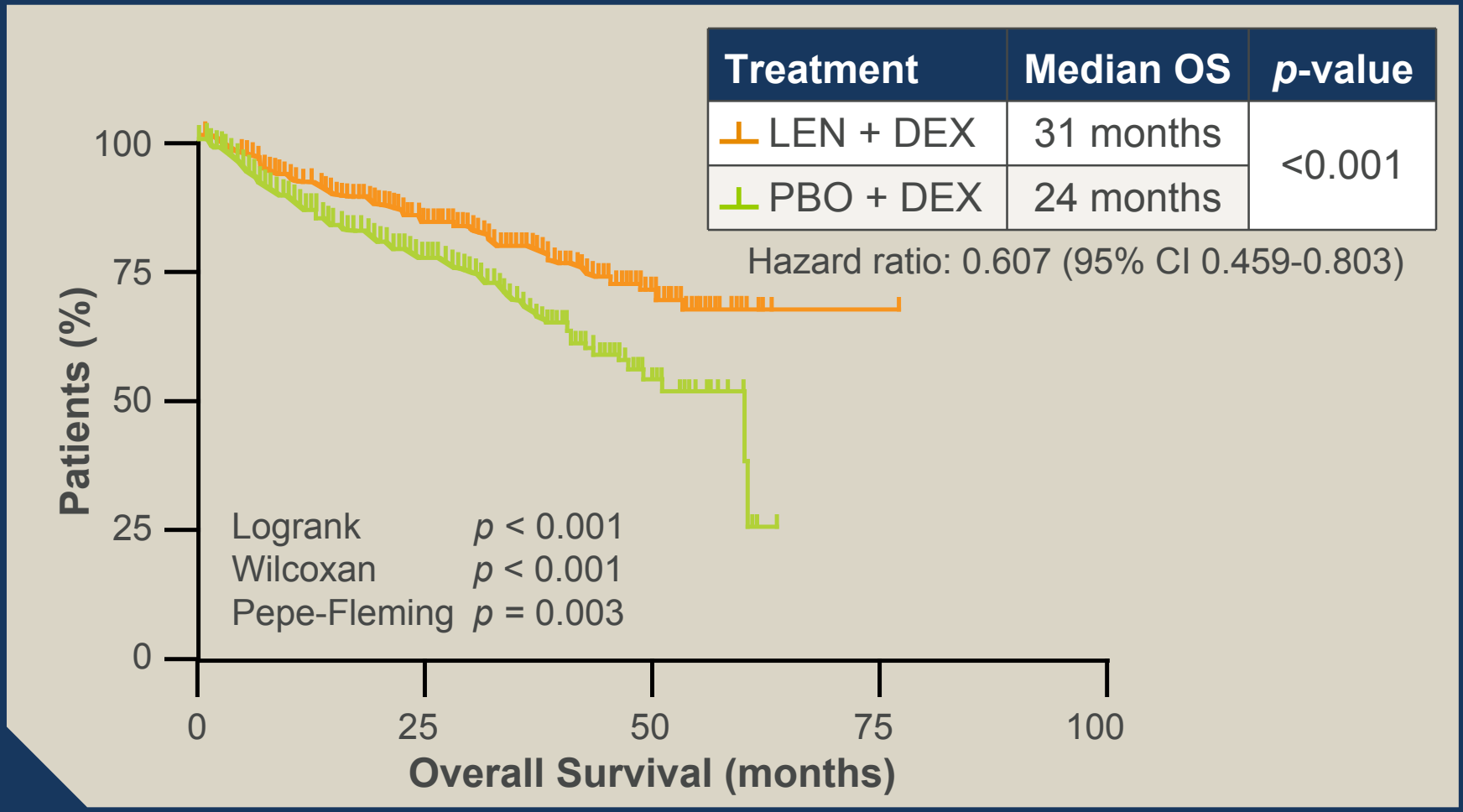
LEN + DEX Overall Survival (OS) (Up to Unblinding)



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Author Conclusions

- No difference in incidence rates of invasive SPMs in LEN + DEX arm versus PBO + DEX arm in MM-009/010
- SPM incidence rates were low and similar to the background incidence among persons similarly aged in the general population
- Overall survival was significantly longer for patients who received LEN + DEX
  - Confirmed with long-term follow-up despite ~50% of patients in the PBO + DEX arm crossing over to receive LEN-based therapy
- The overall benefit-risk profile of LEN in RRMM remains strongly positive

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Faculty Comments

DR BENSINGER: A signal of increased second primary cancer has been seen with lenalidomide in some of the maintenance trials. This retrospective pooled analysis found that no statistically significant difference was observed in the numbers of second primary tumors in patients with relapsed/refractory myeloma who received lenalidomide/dexamethasone versus those who received dexamethasone and placebo. This adds assurance to the idea that lenalidomide by itself may not increase the incidence of second primary cancer. An issue I would have liked to have seen addressed is whether prior melphalan exposure has any effect on the incidence of second primary cancer. In discussions of maintenance therapy, prior melphalan exposure is brought up as having a possible interaction.

Guidelines for Risk Stratification in Multiple Myeloma: Report of the International Myeloma Workshop Consensus Panel 2

Munshi NC et al.

Blood 2011;117(18):4696-700.

Introduction

- Multiple myeloma is a heterogeneous disease with a variable disease course and survival ranging from <1 year with aggressive disease to >10 years with disease that is indolent at presentation.
- Evaluation of prognostic factors and risk stratification is important in defining treatment strategies, in the comparison of outcomes of therapeutic trials and in predicting survival.
- Risk stratification aspects evaluated by the consensus panel:
  - Purpose and timing, especially at diagnosis and relapse
  - Relationship to therapy and clinical and laboratory features, including genomic changes used to stratify patients and predict outcome

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification: Purpose

- Risk stratification:
  - Should only be used to determine prognosis and treatment stratification
  - Does not indicate therapy initiation
  - Does not indicate therapy selection

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification: Timing

- Timing
  - Diagnosis:
    - All current risk stratification is applicable to patients with newly diagnosed disease.
  - Relapse:
    - Change in risk factors at relapse has been documented, and the same genetic abnormalities characteristic of poor outcome at diagnosis may suggest poor outcome if detected at relapse.
    - Patients with good risk at diagnosis should be evaluated for high-risk features at relapse.

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification Factors

- Detection of any cytogenetic abnormality is considered to suggest higher-risk disease.
- Cytogenetics with specific abnormalities and FISH with specific markers need to be performed on bone marrow samples.
- Poor risk, cytogenetically detected:
  - Chromosomal 13 or 13q deletion
  - t(4;14)
  - del(17p)
- Poor risk, FISH detected:
  - t(4;14)
  - t(14;16)
  - del(17p)

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification Factors (continued)

- Predictors of high-risk disease:
  - High serum β2M level
  - ISS Stage II and III incorporating high β2M
  - Low albumin
- Additional individual risk factors (unknown applicability, with no indication for change in treatment approach):

LDH	IgA
Extramedullary disease	Renal failure
High serum free light chain	Plasmablastic disease
Plasma cell leukemia	Serum free κ/λ ratio

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Investigation for Risk Stratification

- Recommended investigation:
  - Serum albumin and β2M to determine ISS stage
  - Bone marrow examination for t(4;14), t(14;16) and del(17p) on identified plasma cells by FISH
  - LDH
  - Immunoglobulin type — IgA
  - Histology — plasmablastic disease
- Additional investigation:
  - Cytogenetics
  - Gene expression profiling
  - Labeling index
  - MRI/PET scan
  - DNA copy number alteration by CGH/SNP array

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Faculty Comments

DR BENSINGER: The panel confirmed what is known in the myeloma community — that certain features, such as serum albumin and the ISS staging that includes β2M, have been shown to be important for stratifying high versus low risk. Also, the cytogenetic abnormalities we have been aware of for several years have important prognostic value and convey high-risk features. It was also agreed that although certain features have been shown in some studies to be important for prognosis, the data were not enough to include in risk stratification at present. These include chromosome 1q abnormalities, gene expression and SNP arrays. The need is recognized for global standardization of gene expression and SNP arrays. These assays are not yet ready for widespread use for all patients with myeloma.