

The logo features a white stopwatch icon with the number '5' inside the circular face. To the right of the icon, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

5 Minute Journal Club

SPECIAL EDITION

Issue 2, 2011

Benefits of Early ASCT for Newly Diagnosed Multiple Myeloma (MM) and the Incidence of Second Primary Cancer with Lenalidomide Maintenance in the Treatment of MM

For more visit ResearchToPractice.com/5MJCASCOHEME2011

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Counsel patients with myeloma who will receive maintenance or longer-term lenalidomide about the demonstrated clinical benefits of this treatment and the risk of developing a second primary cancer.
- Counsel patients with myeloma about the benefits of early ASCT in the era of novel agents.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Last review date: September 2011
Expiration date: September 2012

To go directly to the slides and investigator commentary for the featured abstracts, [click here](#).

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib ([ab 6500](#), [ab LBA6501](#)) in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study ([ab 6502](#)) comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial ([ab 6502](#)) demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd [\[ab 6511\]](#) and DASISION [\[ab 6510\]](#)) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)

This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings [\(ab 6507\)](#) in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma

For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports [\(ab 8007, ab 8008, ab 8009\)](#) have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study [\(ab 8020\)](#) that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL

Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study [\(ab 6508\)](#), response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma

The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP [\(ab 8000\)](#) and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction [\(ab 8001\)](#).

7. AML

AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first [\(ab 6503\)](#) showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The

second [\(ab 6504\)](#) demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study [\(ab 6505\)](#) was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial [\(ab 6506\)](#), the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

Neil Love, MD

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Benefits of Early ASCT for Newly Diagnosed Multiple Myeloma (MM) and the Incidence of Second Primary Cancer with Lenalidomide Maintenance in the Treatment of MM

Presentation discussed in this issue

Dimopoulos MA et al. **Lenalidomide and dexamethasone (LEN plus DEX) treatment in relapsed/refractory multiple myeloma (RRMM) patients (pts) and risk of second primary malignancies (SPM): Analysis of MM-009/010.** *Proc ASCO 2011*; **Abstract 8009.**

Slides from a presentation at ASCO 2011 and comments from Sergio Giralt, MD

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

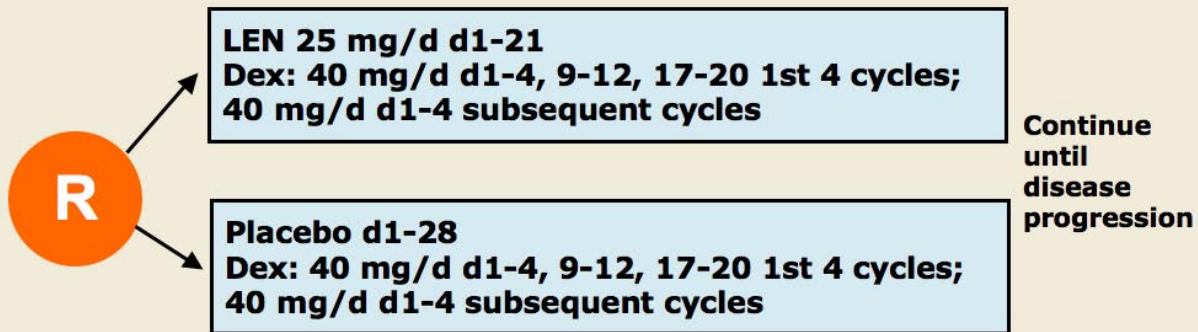
Dimopoulos MA et al.

Proc ASCO 2011; Abstract 8009.

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MM-009/010 Study Designs

- Analysis of pooled data from patients with relapsed/refractory multiple myeloma (RRMM) treated in 2 Phase III studies (MM-009) and (MM-010): N = 704



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

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Incidence Rates for SPM During Active Treatment Phase (Safety Population)

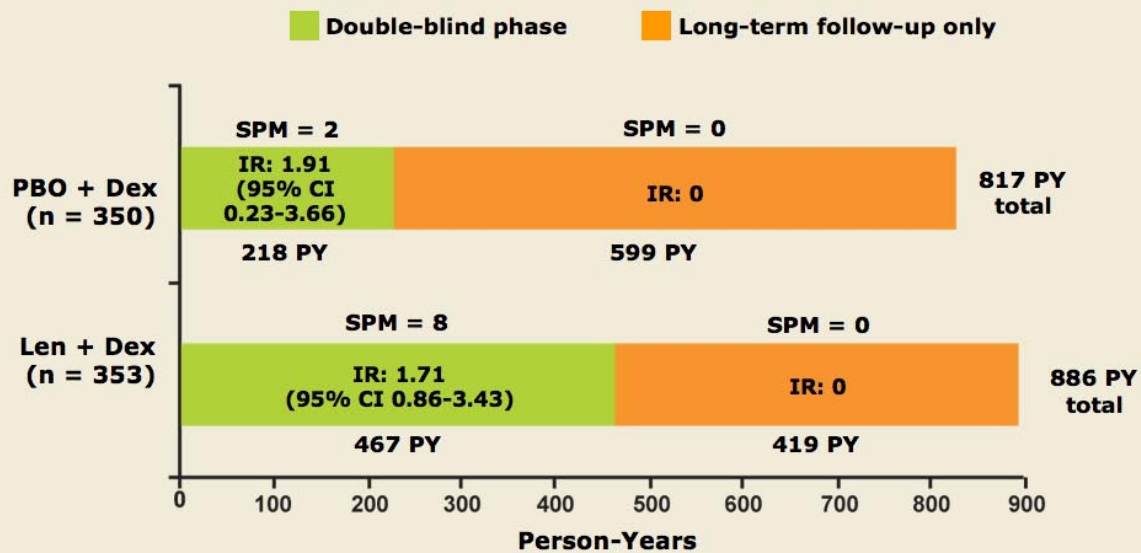
SPM	LEN + DEX (N = 353)		PBO + DEX (N = 350)	
	n (%)	Incidence (per 100 PY)	n (%)	Incidence (per 100 PY)
Invasive SPM	8 (2.3%)	1.71	2 (0.6%)	0.91
Hematologic	2 (0.6%)	0.42	0 (0%)	0.00
AML/MDS	2 (0.6%)	0.42	0 (0%)	0.00
B-cell malignancies	0 (0%)	0.00	0 (0%)	0.00
Solid tumors	6 (1.7%)	1.28	2 (0.6%)	0.91
Noninvasive SPM	11 (3.1%)	2.40	2 (0.6%)	0.91
Nonmelanoma skin cancer	11 (3.1%)		2 (0.6%)	
TOTAL SPM	18 (5.1%)*	3.98	3 (0.9%)*	1.38

* Pts with >1 SPM counted once in the total

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

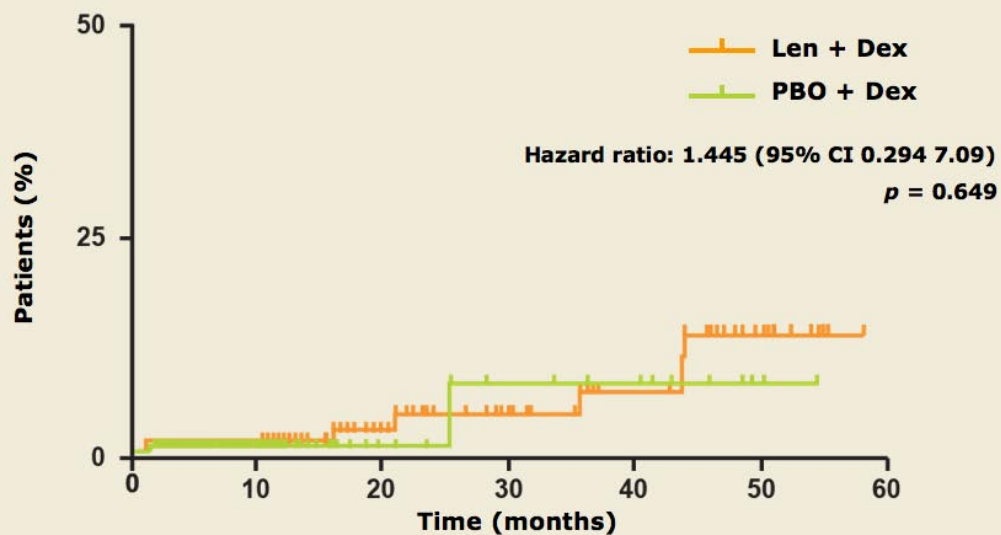
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Incidence Rates of Invasive SPM* During Treatment and Follow-Up



* Includes MDS and breast carcinoma in situ; excludes nonmelanoma skin cancers
 With permission from Dimopoulos MA et al. *Proc ASCO 2011*; Abstract 8009.

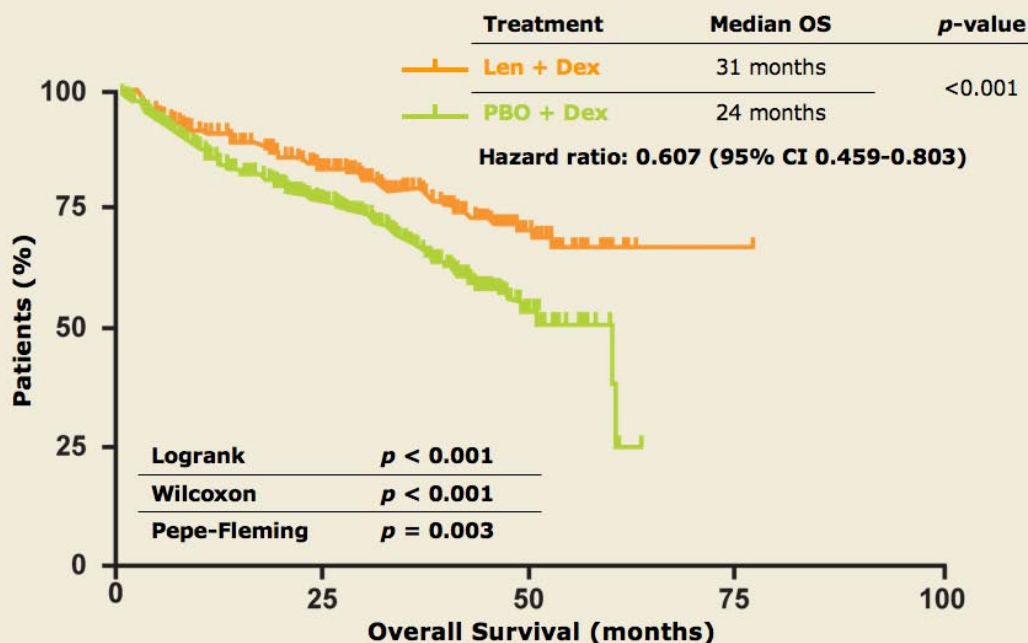
SPM in RRMM: MM-009/010 Time to Invasive SPM (Treatment Period)



No. at Risk	Time (months)						
	0	10	20	30	40	50	60
Len + Dex	353	176	108	66	48	19	0
PBO + Dex	350	66	28	17	15	2	0

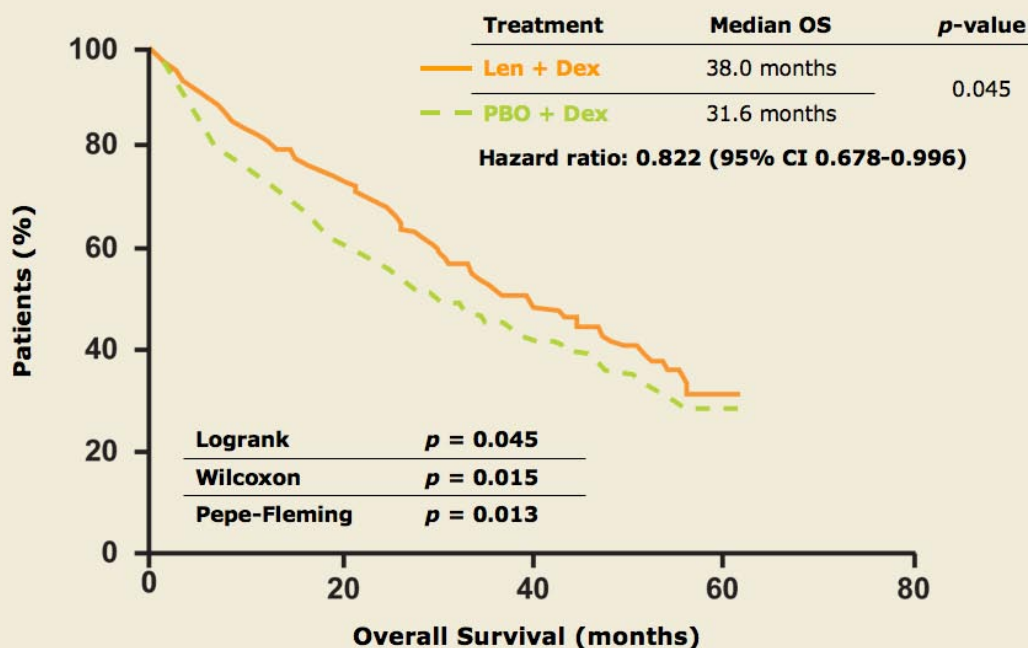
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LEN + DEX in RRMM: Overall Survival (Up to Unblinding)



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LEN + DEX Overall Survival Including Data After Crossover



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Conclusions

- No difference in incidence rates of invasive SPMs in LEN + DEX arm versus PBO + DEX in MM-009/010
- SPM incidence rates were low and similar to the background incidence among persons similarly aged in the general population
- OS 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.

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Investigator Commentary: The Incidence of SPMs After Long-Term Follow-Up of MM-009/010 in RRMM

Dr Niesvizky presented long-term follow-up of MM-009/010, which were the pivotal studies for approval of lenalidomide in relapsed/refractory multiple myeloma. The incidence of observed versus expected cancer was relatively similar, and many of these patients had already received high-dose melphalan and other treatments. So in this population there did not seem to be an increased risk of SPMs.

Lenalidomide has stem cell activity, and it is plausible that it can affect stem cells to a point that there may be development of SPMs, but it doesn't seem to be a common phenomenon. When SPMs develop after lenalidomide, it happens after prolonged alkylator therapy or after high-dose alkylating agent exposure, such as in the transplant setting.

I initiate lenalidomide maintenance therapy for any patient who has not achieved a complete remission or in patients who have a high risk for relapse, even if they have achieved a CR. I delay lenalidomide maintenance for 5 to 6 months after transplant because I believe the "perfect storm" is to administer a drug that may be stem cell toxic at a time when the stem cells are beginning to proliferate and find their essential microenvironments.

Sergio Giralt, MD