5 Minute JournalClub

POST-ASH Issue 5, 2014

Pomalidomide and Low-Dose Dexamethasone for Relapsed/ Refractory MM

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel therapeutic options in the treatment of multiple myeloma (MM) and Waldenström's macroglobulinemia (WM) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with MM.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including anti-CD38 antibodies and AKT, BTK, KSP and novel proteasome inhibitors — under evaluation for newly diagnosed and relapsed/refractory MM and WM and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appraise recent clinical research findings on the efficacy and safety of novel proteasome inhibitor- and/or BTK inhibitor-based therapeutic strategies for WM, and consider this information for the treatment of patients.

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Rafael Fonseca, MD
Getz Family Professor of Cancer
Chair, Department of Internal Medicine
Mayo Clinic Arizona
Scottsdale, Arizona

Consulting Agreements: Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc; Contracted Research: Amgen Inc, Celgene Corporation.

Sagar Lonial, MD
Professor
Vice Chair of Clinical Affairs
Director of Translational Research, B-Cell Malignancy Program
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Advisory Committee and Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Sanofi.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: March 2014
Expiration date: March 2015

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POST-ASH Issue 5, 2014

To go directly to slides and commentary for this issue, **click here**.

Rafael Fonseca, MD

One might view current clinical research in multiple myeloma (MM) as being in a consolidation phase after the introduction of proteasome inhibitors, immunomodulatory drugs and bisphosphonates brought forth a huge wave of progress. This idea is reflected in many of the new MM reports presented in New Orleans, where we were treated to intriguing data attempting not only to help optimize the impact of our current tools but also to uncover novel agents that will launch a new era with even better outcomes. For this second MM issue of our ASH review series, Dr Rafael Fonseca comments on a handful of papers that help take the next step in what will hopefully be another quantum leap forward in this fascinating corner of oncology.

- **More on up-front carfilzomib/lenalidomide/dexamethasone (dex) (CRd)**

MM is only one of a number of tumor types in oncology today for which there is considerable interest in moving newly approved agents up earlier in the course of the disease. In this regard, we have already seen preliminary data from Andrzej Jakubowiak, and at ASH **the NCI presented** another major single-arm study evaluating induction CRd followed by maintenance therapy — in this case lenalidomide. As in the work presented by Dr Jakubowiak, in this study patients received long-term maintenance and transplant was optional, and with the extraordinary risk-benefit value of this regimen (near complete response [CR] or better in 73% of the 43 patients, 100% minimal residual disease negativity assessed by flow cytometry among 27 patients with near CR or stringent CR and no Grade 3 or 4 neuropathy), Dr Fonseca can foresee a time when treatment will be individualized based on depth of response, with transplant avoided in some patients and survival extended significantly. However, in terms of current practice, like most MM investigators Dr Fonseca believes that while preliminary data on this and similar regimens are very encouraging, carfilzomib should not be used up front outside of a trial setting and recommends that patients interested in this approach be referred to the major Intergroup study comparing CRd to RVD.

• Carfilzomib/cyclophosphamide/dex (CCd) up front in elderly patients

In the same vein as the previous study, another ASH data set reported on recent efforts to incorporate carfilzomib into popular and currently employed bortezomib-based up-front regimens. **This Phase II trial** looked at CCd (similar to CyBorD) induction in 55 evaluable patients aged 65 and over with newly diagnosed MM. The bottom line is that despite significant activity (47% near CR or better) and relatively good tolerability (14% of patients discontinued treatment because of toxicity, which is considerably fewer than in prior studies for elderly patients), Dr Fonseca — a major proponent of CyBorD — urges us all to hold off on CCd outside a clinical trial.

• Pomalidomide (POM)/carfilzomib/dex in relapsed/refractory (RR) disease

Combining the 2 new kids on the block, POM and carfilzomib, always seemed like a natural next step, and at ASH we saw encouraging data with this appealing regimen. **A multicenter Phase I/II effort** for patients with heavily pretreated lenalidomide-refractory MM (a median of 5 prior treatments) resulted in a 70% overall response rate among 79 evaluable patients and a manageable toxicity profile. Even more, this report demonstrates that the regimen is not only a viable option in very advanced disease but also an approach that is of great interest in up-front trials.

In a related manner, ASH also featured **2 data sets** providing updates from trials evaluating POM with low-dose dex in RR disease. Dr Fonseca's take-away from these presentations is that while patients with extensive prior treatment and adverse cytogenetic profiles often benefit from this therapy, myelosuppression in these individuals must be managed carefully with dose adjustments and growth factors.

• An all-oral "RVD"

For the past several years we have profiled the early development of the oral proteasome inhibitors ixazomib and oprozomib, and at ASH **Paul Richardson presented more data** from his Phase I/II study looking at ixazomib/lenalidomide/dex in previously untreated MM. This study, which evaluated twice-weekly ixazomib, revealed activity (94% response rate among 62 patients) similar to what is typically seen with RVD but slightly more peripheral neuropathy (PN) (Grade 3 in 5% of 64 patients) than has been observed in trials using weekly administration of this fascinating agent. Not surprisingly, Dr Fonseca is eagerly and optimistically awaiting the results of ongoing Phase III trials.

• Cool new compounds

For the immediate future most myeloma investigators like Dr Fonseca believe monoclonal antibodies represent the most likely path to dramatically catapult survival in this disease, and there is great hope that a rituximab-like agent may be identified. The 2 compounds we have heard the most about up to now are the anti-CD38 antibody daratumumab, which has garnered FDA breakthrough therapy status, and elotuzumab,

which is directed against human CS1 (a cell surface antigen glycoprotein that is highly expressed on MM cells) and appears to result in an R-squared-like synergy with lenalidomide.

However, for a disease diagnosed in "only" about 20,000 individuals a year in the United States, a stunning amount of active drug development is under way in MM, and at ASH we were provided with a preview of some of the agents and strategies we may be hearing a lot more about in the next few years:

– SAR650984

Similar to daratumumab, **this anti-CD38 antibody** was shown to have significant single-agent efficacy in patients with relapsed MM (31% response rate among 13 patients receiving the 10-mg/kg dose every 2 weeks) and minimal toxicity other than manageable infusion reactions. Dr Fonseca stated that "this is probably one of most important molecules for future MM therapy."

– Filanesib

A report from a **Phase II trial** of this selective inhibitor of kinesin spindle protein alone or in combination with dex demonstrated a 15% response rate among 55 evaluable patients receiving the combination and manageable toxicity. What seems most exciting about this data set is that activity was absent in patients with high serum levels of α-1 acid glycoprotein (which binds the drug, making it unavailable), potentially opening the door for a predictive biomarker.

– Afuresertib

AKT is a critical signaling node in MM, and this **single-arm Phase IB trial** evaluated the potent AKT inhibitor afuresertib in combination with dex and bortezomib in 81 patients with relapsed or refractory disease. The overall response rate was 65% and the clinical benefit rate was 73% among 37 patients in the safety expansion cohort. The results are favorable enough to justify further study, but of particular interest was the demonstration of consistent increases in the levels of the phosphorylated form of the drug target in MM cells.

• Bonus feature: Two compelling data sets in Waldenström's macroglobulinemia (WM)

WM is unusual in oncology in that investigators focused on both lymphomas and plasma cell disorders are involved in clinical research and patient care. Most importantly, borrowing from progress in both of these fields, the outlook for the 1,500 US patients diagnosed annually continues to improve as reflected in the following data sets:

– Carfilzomib

The lack of PN with carfilzomib, even in indirect comparison to weekly subcutaneous bortezomib, is particularly appealing in WM, in which PN is part of the disease biology. As such, this agent was **evaluated in a Phase II study** combining it with rituximab and dex for 31 patients with symptomatic WM. As reported at ASH, this combination resulted in a best overall response rate of 81% and significant IgM declines along with improved marrow profiles and hemoglobin levels. Even more important, PN of Grade 2 or higher was not reported, leading the authors to conclude that the regimen represents a "neuropathy-sparing approach" for the treatment of WM. In relation to these findings, Dr Fonseca verbalized his concern that the rarity of this disease has led to a dearth of FDA-approved therapies, making it a considerable challenge to obtain reimbursement for novel agents with proven patient benefit.

– Ibrutinib

Now approved for mantle-cell lymphoma and chronic lymphocytic leukemia, perhaps it should not be that big of a surprise that ibrutinib is effective in WM, especially since a somatic mutation (MYD88 L265P) that appears to support malignant growth through Bruton tyrosine kinase is present in more than 90% of these patients. Indeed, in this **exciting Phase II study** 51 of 63 patients (81%) had best overall responses — which were usually rapid, often with rising hematocrit and reductions in serum IgM — strongly suggesting that this agent is destined to have a critical role in the care of these patients.

Next up, we focus on papers in Hodgkin lymphoma and the rapidly emerging role of the antibody-drug conjugate brentuximab vedotin.

Neil Love, MD
Research To Practice
Miami, Florida

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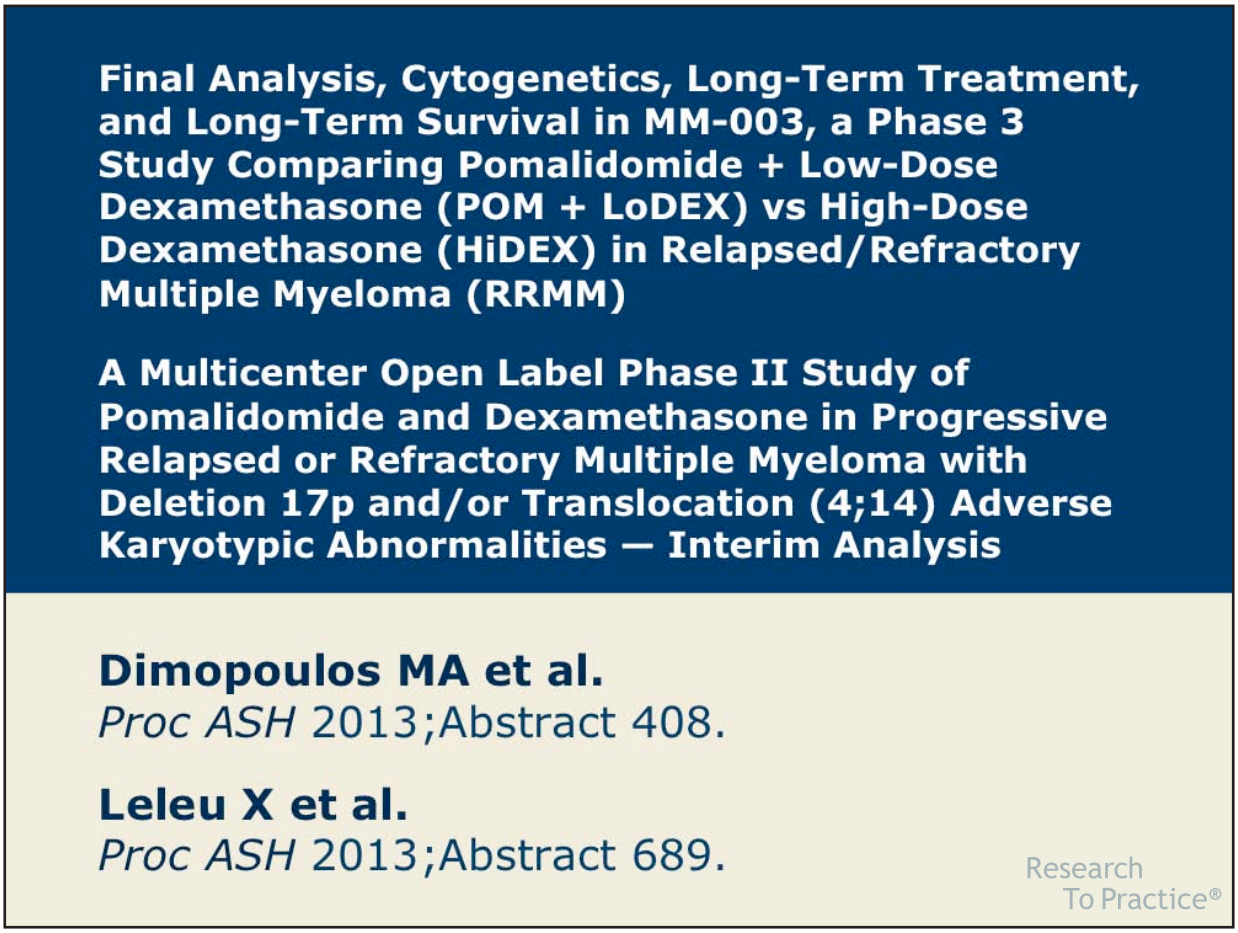
Pomalidomide and Low-Dose Dexamethasone for Relapsed/Refractory MM

Presentations discussed in this issue

Dimopoulos MA et al. **Final analysis, cytogenetics, long-term treatment, and long-term survival in MM-003, a Phase 3 study comparing pomalidomide + low-dose dexamethasone (POM + LoDEX) vs high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).** *Proc ASH* 2013;**Abstract 408**.

Leleu X et al. **Pomalidomide plus low-dose dexamethasone in relapsed or refractory multiple myeloma (RRMM) with deletion (del)17p and/or translocation t(4;14).** *Proc ASH* 2013;**Abstract 689**.

Slides from presentations at ASH 2013 and transcribed comments from a recent interview with Rafael Fonseca, MD (2/14/14)



Final Analysis, Cytogenetics, Long-Term Treatment, and Long-Term Survival in MM-003, a Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEX) vs High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM)

Dimopoulos MA et al.

Proc ASH 2013;Abstract 408.

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Background

- Patients with advanced RRMM have limited effective options.
- The presence of high-risk cytogenetics is predictive of a short overall survival benefit (*Blood* 2007;109:3489).
- Pomalidomide (POM) is an oral immunomodulatory agent with direct antimyeloma and stromal cell-support inhibitory effects.
- POM recently received FDA approval for the treatment of MM after ≥2 prior therapies, including lenalidomide (Len) and bortezomib (Btz), and after disease progression ≤60 days from completion of last therapy.
- Earlier results of the MM-003 Phase III trial demonstrated clinical efficacy and tolerability with POM + LoDex in patients with RRMM (*Proc EHA* 2013;Abstract S1151).
- **Study objective:** To determine the long-term efficacy of POM and LoDex versus HiDex for patients with RRMM in the MM-003 trial.

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

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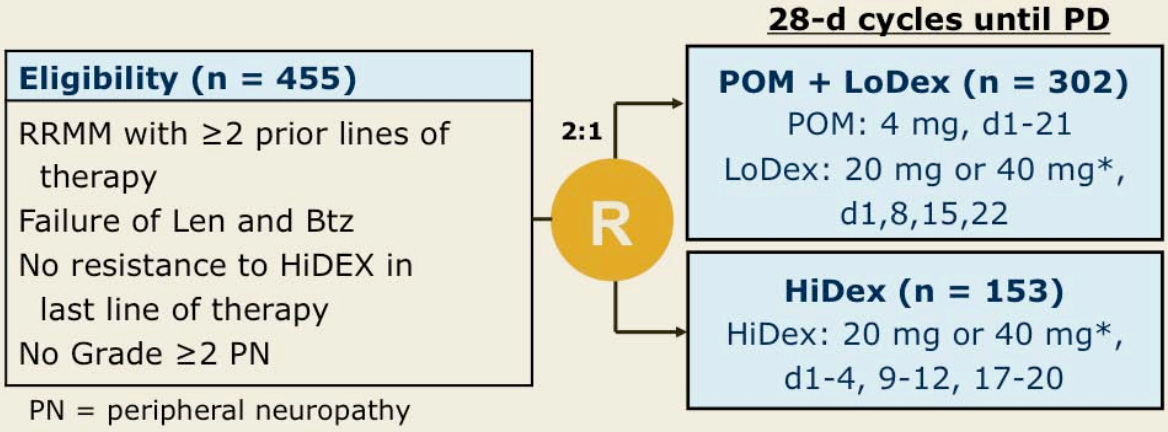
Phase III MM-003 Trial Design



PN = peripheral neuropathy

* LoDex or HiDex: 20 mg (>75 years) or 40 mg (≤75 years)

- Thromboprophylaxis was required for all patients receiving POM and those at high risk of thromboembolic events
- **Primary endpoint:** Progression-free survival (PFS)

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

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PFS and OS for Intention-to-Treat (ITT) Population

Outcome	POM + LoDEX (n = 302)	HiDEX (n = 153)	HR	*p*-value
Median PFS	4.0 months	1.9 months	0.50	<0.001
Median OS	13.1 months	8.1 months	0.72	0.009

HR = hazard ratio; OS = overall survival

- Median follow-up: 15.4 months
- 85 patients (56%) on the HiDEX arm received subsequent POM

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

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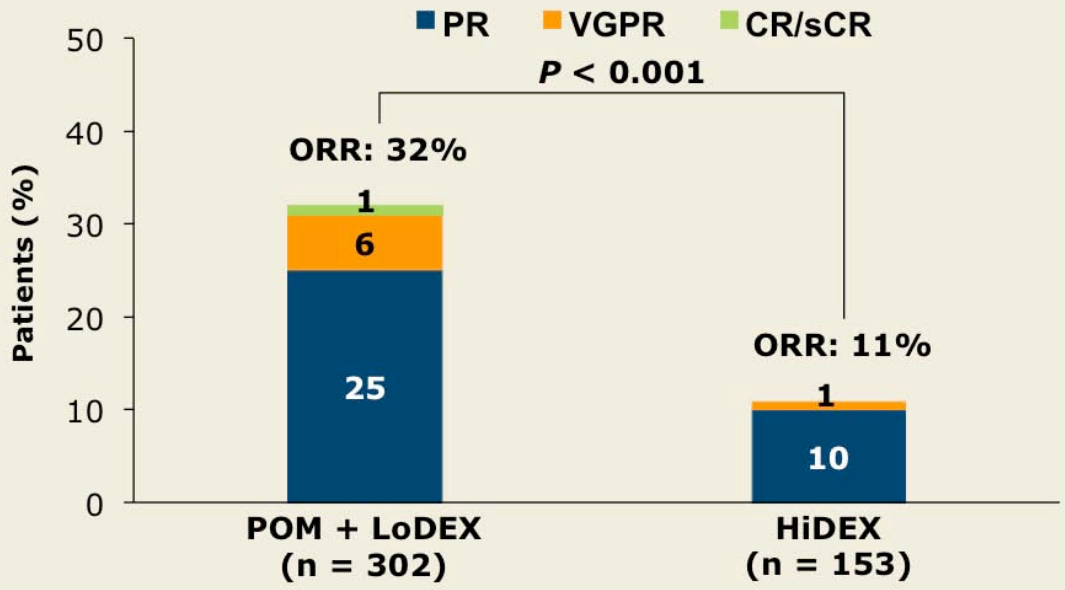
PFS and OS by Cytogenetic Profiling

Del17p/t(4;14)	POM + LoDEX (n = 77)	HiDEX (n = 35)	HR	*p*-value
Median PFS	3.8 months	1.1 months	0.44	<0.001
Median OS	9.9 months	4.9 months	0.67	0.092
Standard risk	**n = 148**	**n = 72**	**HR**	***p*-value**
Median PFS	4.2 months	2.3 months	0.55	<0.001
Median OS	14.0 months	9.0 months	0.85	0.380

- POM + LoDEX significantly improved PFS regardless of the presence of adverse cytogenetics
- 46% of patients with del17p/t(4;14) on the HiDEX arm received POM
- 64% of patients with standard-risk disease on the HiDEX arm received POM

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Response Rates in the ITT Population



Median duration of response: 7.5 mo (POM + LoDEX) vs 5.1 mo (HiDEX); $p = 0.031$

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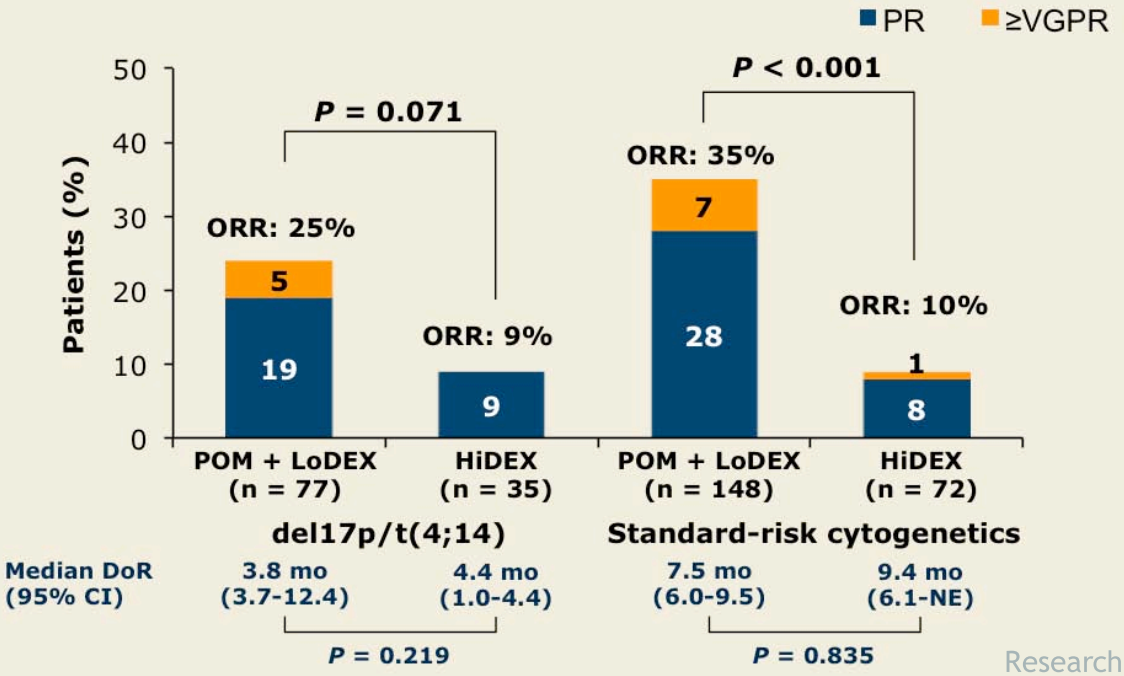
Response Rates by Cytogenetic Profiling



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Baseline Characteristics Predictive of Long-Term Treatment and Survival with POM + LoDEX

Characteristic	OS ≤3 mo (n = 54)	OS >12 mo (n = 148)	*p*-value
ECOG PS (0 vs 1-2)	19% vs 81%	46% vs 54%	<0.0001
Age (≤65 vs >65 y)	41% vs 59%	57% vs 43%	0.035
ISS stage	46% vs 50%	76% vs 20%	<0.0001
Presence of plasmacytoma	20%	4%	0.0002
Baseline LDH (>1.5 x ULN)	20%	2%	<0.0001
Baseline hemoglobin*	9.4 g/dL	10.3 g/dL	<0.0001
Baseline platelet counts*	98 x 10^9/L	150 x 10^9/L	0.020

* Median value

- The same variables were significant for duration of treatment of ≤3 vs >12 mo

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Author Conclusions

- Significant OS and PFS benefits for POM + LoDEX versus HiDEX were confirmed with additional follow-up.
- POM + LoDEX is active in patients with high-risk cytogenetics, especially in those with del17p.
- For all patients, normal levels of LDH and albumin and treatment with POM + LoDEX were predictive of longer survival.
- For patients who received POM + LoDEX, better ECOG PS, absence of plasmacytoma, lower ISS stage and normal LDH levels, hemoglobin and platelet counts were predictive of longer duration of treatment and OS.
- POM + LoDEX is a standard treatment for patients with RRMM, including those with adverse cytogenetic features.

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

A Multicenter Open Label Phase II Study of Pomalidomide and Dexamethasone in Progressive Relapsed or Refractory Multiple Myeloma with Deletion 17p and/or Translocation (4;14) Adverse Karyotypic Abnormalities — Interim Analysis

Leleu X et al.

Proc ASH 2013;Abstract 689.

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Background

- Patients who have multiple myeloma (MM) with del17p and/or t(4;14) have a poor survival rate related to early relapse and development of resistance to multiple agents.
- The IFM 2009-02 study demonstrated the efficacy of POM + LoDEX in patients with RRMM treated with Btz and/or Len (*Blood* 2013;121:1968).
- In that study, the median time to disease progression was much shorter for patients with del17p and/or t(4;14) who were previously exposed to a median of 5 to 6 lines of therapy.
- **Study objective**: To evaluate the efficacy and safety of POM in patients with RRMM with del17p and/or t(4;14).

Leleu X et al. *Proc ASH* 2013;Abstract 689.

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IFM 2010-02 Study Design

28-d cycles until PD

Eligibility (n = 50)
Relapsed or refractory MM Del17p and/or t(4;14) Exposed to Len

→ **POM + LoDEX**
POM: 4 mg, d1-21
LoDEX: 40 mg, d1, 8, 15, 22

- Aspirin/low-molecular-weight heparin administered once daily
- **Primary endpoint:** Time to progression (TTP)
- **Secondary endpoints:** included safety, response rate, duration of response, OS, PFS

Leleu X et al. *Proc ASH* 2013;Abstract 689.

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Patient Characteristics

	ITT (n = 50)
Median no. of prior lines of therapy	3
2 lines	32%
3 lines	38%
>3 lines	22%
Refractory/exposed to	
Len	84%/100%
Btz	54%/96%
Len + Btz	54%
Alkylator	36%/90%

- Patients with del17p: 40%; t(4;14): 60%. Those with del17p and t(4;14) included in both groups

Leleu X et al. *Proc ASH* 2013;Abstract 689.

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Response

Response	ITT (n = 50)	Del17p (n = 22)*	t(4;14) (n = 32)*
Overall response rate	22%	32%	16%
≥VGPR	6%	9%	3%
PR	16%	23%	12.5%
Progressive disease	14%	18%	16%
Clinical benefit rate (≥MR)	34%	32%	34%
Median duration of response (DoR)	6 mo	8.3 mo	2.4 mo
Patients with 8-mo DoR	44%	67%	25%

* Patients with both del17p and t(4;14) included in both groups

- Median follow-up: 8.2 mo

Leleu X et al. *Proc ASH* 2013;Abstract 689.

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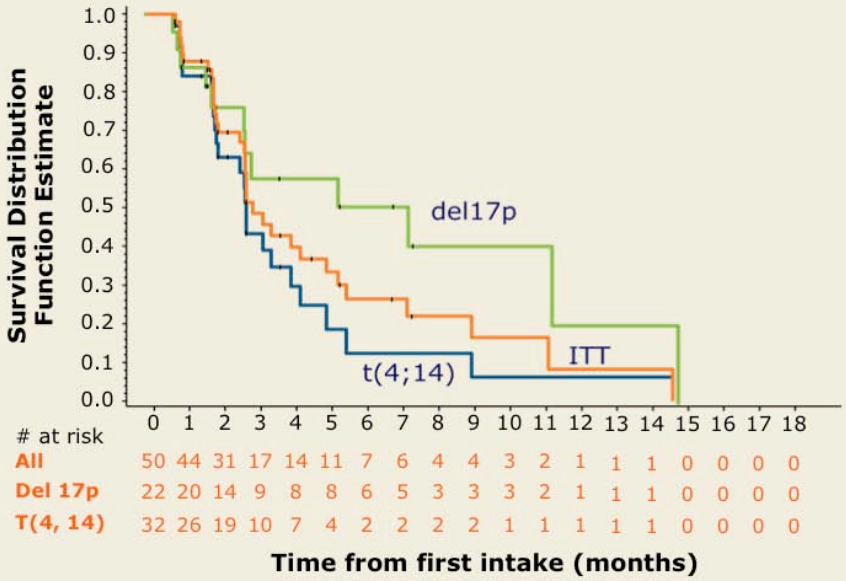
Time to Progression (TTP)



- Median TTP: ITT population 2.9 mo, del17p 7.3 mo, t(4;14) 2.8 mo

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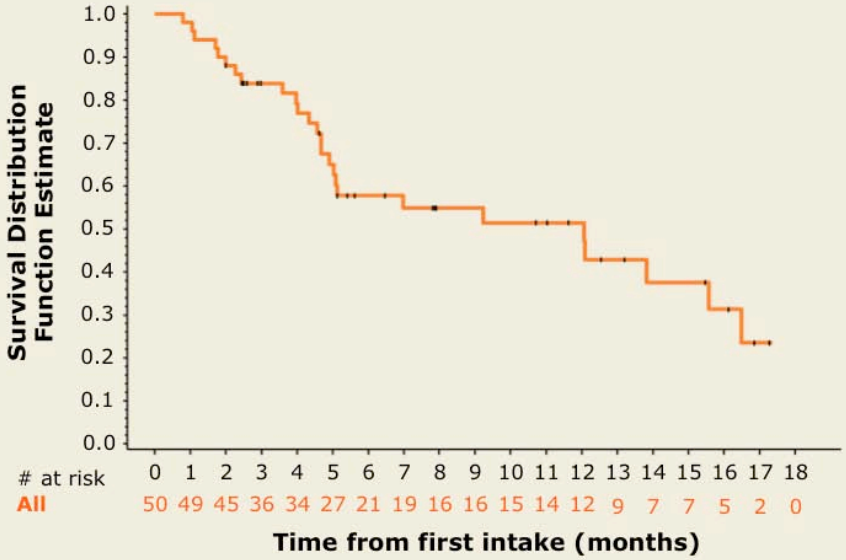
OS



- Median OS: ITT population 12 mo, del17p 12 mo, t(4;14) 9.2 mo
- 8-mo OS rate: ITT population 55%, del17p 58%, t(4;14) 50%

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Adverse Events (AEs)

Event (n = 50)	Any AE	Serious AE
Hematologic	72%	16%
Nonhematologic	16%	48%
Drug related	88%	36%

- Grade 3/4 AEs occurred in 90% of patients
- Treatment discontinuation: 72% (16% due to drug-related AEs, 24% due to serious AEs)

Leleu X et al. *Proc ASH* 2013;Abstract 689.

Author Conclusions

- The combination of POM and dexamethasone is manageable and provides responses in patients with adverse cytogenetics.
- Use of POM and dexamethasone earlier in the disease course appears to benefit patients with del17p.
- This benefit was not seen in patients with t(4;14).
- Triplet POM-based regimens should be considered for future studies in patients with adverse cytogenetics, particularly with t(4;14).

Leleu X et al. *Proc ASH* 2013;Abstract 689.

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Investigator Commentary: Pomalidomide (POM) and Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)

The studies by Dimopoulos and Leleu confirm that POM is effective for RRMM. Both of the studies evaluated the effects of high-risk cytogenetics in RRMM. The Phase III MM-003 study confirmed that POM with LoDEX is more effective than HiDEX for patients with RRMM. For patients with standard-risk cytogenetics the overall response rate was higher compared to those with high-risk cytogenetics.

Patients with high-risk genetic markers, who are able to receive a fifth or sixth line of therapy, have genetic subtypes that are not as bad because they have experienced responses to prior lines of therapy. Hence, I would be cautious about overinterpreting the results regarding the effects of adverse cytogenetics in RRMM. The validity of high-risk genetic markers is greater in the up-front setting. However, even in the RRMM setting, adverse cytogenetics affect clinical outcomes.

(Continued)

Most of the patients receiving POM have received multiple prior lines of therapy, so myelosuppression can be an issue. This can be managed with dose adjustments and occasionally with the use of growth factors. It is also important that patients receive thromboprophylaxis. Peripheral neuropathy is not a significant side effect with POM. Overall, it is a well-tolerated agent.

Interview with Rafael Fonseca, MD, February 14, 2014

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