



Hematologic Oncology
Issue 1, 2013

**MM-003: Phase III Study of Pomalidomide
and Low-Dose Dexamethasone versus
High-Dose Dexamethasone in Relapsed/
Refractory Multiple Myeloma**

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 Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings, 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 are aware of crucial practice-altering findings. Unlike ASCO, EHA does not offer access to any of the poster or plenary presentations from the annual meeting via the Internet. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, 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 agents in multiple myeloma from the latest ASCO and EHA meetings, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in multiple myeloma, and consider this information in clinical practice.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors, immunomodulatory agents and novel antibodies alone or in combination with approved systemic treatments for patients with relapsed/refractory multiple myeloma.
- Assess the benefits and risks of carfilzomib in combination with an alkylating or immunomodulatory agent for patients with newly diagnosed multiple myeloma.
- Determine the effectiveness and tolerability of pomalidomide in combination with low-dose dexamethasone for patients with relapsed or refractory multiple myeloma and adverse cytogenetics or renal impairment.

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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: September 2013

Expiration date: September 2014

To go directly to slides and commentary for this issue, [click here](#).

The revolution in treatment of multiple myeloma (MM) that occurred over the better part of the last decade is evident in the waiting room of every medical oncologist. Thanks to regimens that include immunomodulatory agents (IMiDs) — particularly lenalidomide (len) — and proteasome inhibitors, specifically bortezomib (bz), along with the widespread utilization of bisphosphonates, it is no longer uncommon to see patients on active treatment for 10 years or more. Of course much is still to be done with this challenging disease, and I met with a leader in the field, Dr Antonio Palumbo, for his take on where we are today and where we might be heading.



Antonio Palumbo, MD

For some time Dr Palumbo has been a vocal proponent, along with many other MM investigators, of using the most effective therapies as early as possible in the disease course — often for prolonged durations. Based on his research and that of many others, for younger patients his standard is triple-agent induction followed by high-dose chemotherapy and autologous stem cell transplant and then long-term maintenance treatment. On the flip side, Dr Palumbo has taken a leadership role in the use of preemptive dose reductions for the elderly, allowing for longer-term therapy as opposed to what he calls “short flashes of treatment.”

From this clinical framework, Dr Palumbo commented on several new data sets from the ASCO and the European Hematology Association (EHA) annual meetings, attempting to better define the role of the 2 most recently approved agents for MM — carfilzomib

(cz) and pomalidomide (pom) — and several other promising candidates in the later stages of development.

1. Cz triplets

At ASCO this year we saw more on CRd (cz/len/low-dose dexamethasone [lddex]), a cousin of RVD (len/bz/dex), currently one of the most commonly used IMiD/proteasome inhibitor induction regimens.

The final report from the Phase Ib/II trial in relapsed/refractory disease led by Dr Michael Wang that started it all in 2008 demonstrated excellent tolerability with CRd — particularly a lack of significant peripheral neuropathy — and impressive efficacy in patients with extensive prior treatment.

These findings inspired Dr Andrzej Jakubowiak and colleagues to launch an up-front trial that was again reported at ASCO. The antitumor activity in this study is interesting because the depth of response increased with more treatment, and by a median of 22 cycles 87% of patients had achieved a VGPR or better. In keeping with his approach of maximizing the depth of response as early in the disease course as possible, Dr Palumbo is hopeful that accumulating data on CRd and other cz-based up-front regimens will result in an important step forward in induction treatment.

In that context, Dr Palumbo presented at EHA the initial results from a **Phase II up-front trial** evaluating the CCd regimen (cz/cyclophosphamide [cy]/lddex), which resembles another major induction triplet in current practice, CyBorD (cy, bz and dex). CCd was not only well tolerated, but the efficacy seemed equivalent if not superior to that of the bz-based approach.

Similarly, at ASCO and then again at EHA we were treated to **data on CMP** (cz/melphalan/prednisone) as up-front therapy for elderly patients. Again there was significant activity and good tolerability, and while Dr Palumbo believes that both alkylating agent combinations with cz are effective, in his view cyclophosphamide-based regimens are the way forward because of better tolerability.

With the rapid emergence of impressive up-front data with cz regimens, it will be interesting to see whether regulatory agencies, investigators and payers will require direct head-to-head trials against bz-based treatments to see a change in practice. In this regard, the NCCN now lists **CRd as a category 2A up-front option**.

2. Pom/lddex

In December 2012 at ASH Dr Meletios Dimopoulos presented initial findings from the Phase III MM-003 trial documenting an overall survival benefit with the use of pom/

Iddex for patients with relapsed/refractory MM. At ASCO and EHA **the results were updated**, and **subset data from this seminal effort** provided evidence of safety and efficacy in patients with moderate renal impairment and modest activity in patients with adverse cytogenetic profiles. In commenting on these studies, Dr Palumbo stated his belief that this regimen provides useful clinical responses in 30% to 50% of patients with disease progressing on len. He also predicted greater long-term benefit if pom/Iddex were used earlier in the disease course, ideally soon after progression on another IMiD.

3. Monoclonal antibodies (mAbs)

The recent emergence of 2 distinct compounds with preliminary activity in MM may soon make this disease fertile ground for the regular use of mAbs. The first agent is elotuzumab, which targets the CS1 antigen, and at ASCO and then again at EHA we got more information from Dr Sagar Lonial's **Phase II trial** combining this drug with len and Iddex. While this mAb has no single-agent activity, the combination resulted in an eye-popping median PFS of 25.8 months, and one wonders whether we are looking at the myeloma version of "R squared" in lymphoma (len/rituximab). However, Dr Palumbo cautions us to take a conservative view and hold our excitement until Phase III data are available.

Daratumumab, another FDA breakthrough designation recipient, is an anti-CD38 antibody that has shown significant single-agent activity, including an encouraging 31% clinical response rate in a single-arm **Phase I/II dose-escalation study** presented at ASCO and updated at EHA. In Dr Palumbo's eyes CD38 may be as important in MM as CD20 is in lymphoma, and while he won't speculate as to whether the efficacy of this agent will even come close to what we have seen with rituximab in lymphoma, he is enthusiastic about this potential and recently began entering patients on trials of this agent in his own clinic.

4. Oral proteasome inhibitors

The promise of all-oral combination regimens has many excited about MLN9708 (ixazomib), which has a similar structure to bz but lacks the inconvenience of subcutaneous or IV administration. At ASCO Dr Shaji Kumar presented more from an **expanded Phase I study** of ixazomib demonstrating similar efficacy to what has been observed with bz but with improved tolerability. In that regard, Dr Palumbo is particularly interested in seeing this and other oral agents studied in elderly patients for whom the ease of drug delivery might allow more prolonged treatment and greater disease control.

Over the next few years, we shall see if the next generation of new agents and strategies typified by these EHA and ASCO papers bump ahead outcomes similarly to the initial introduction of IMiDs and proteasome inhibitors, but MM investigators including Dr Palumbo seem determined to push the disease at the least into CML-like control and maybe even cure. Next on this series we consider a number of summer papers on CLL, and one data set in particular that may signal a major shift in choice of anti-CD20 antibody in this disease.

Neil Love, MD

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MM-003: Phase III Study of Pomalidomide and Low-Dose Dexamethasone versus High-Dose Dexamethasone in Relapsed/Refractory Multiple Myeloma

Presentation discussed in this issue

San Miguel JF et al. **MM-003: A Phase III, multicenter, randomized, open-label study of pomalidomide (POM) plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).** *Proc ASCO 2013*; **Abstract 8510**.

Slides from presentations at ASCO 2013/EHA 2013 and transcribed comments from a recent interview with Antonio Palumbo, MD (8/20/13)

Efficacy, Safety, and QoL in MM-003, a Phase 3, Multicenter, Randomized, Open-Label Study of Pomalidomide (POM) + Low-Dose Dexamethasone (LoDEX) vs High-Dose Dexamethasone (HiDEX) in RRMM¹

MM-003: A Phase III, Multicenter, Randomized, Open-Label Study of Pomalidomide (POM) plus Low-Dose Dexamethasone (LoDEX) versus High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM)²

San Miguel JF et al.

¹ *Proc EHA 2013*; Abstract S1151.

² *Proc ASCO 2013*; Abstract 8510.

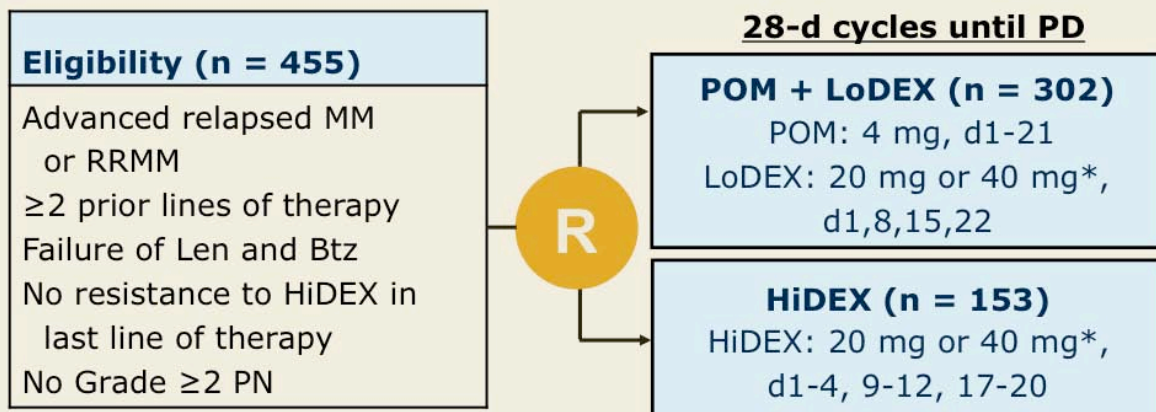
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Background

- Patients with RRMM with disease progression after treatment with bortezomib (Btz) and lenalidomide (Len) or thalidomide have a poor prognosis with a short overall survival (OS) and reduced quality of life.
- HiDEX is an established treatment for RRMM.
- POM demonstrated efficacy in patients with RRMM after Len and/or Btz therapy (*Blood* 2013;121:1968).
- Recently, pomalidomide (POM) was FDA approved for the treatment of MM in patients who have received ≥ 2 prior therapies, including Len and Btz, and have experienced disease progression within 60 days of their last therapy.
- **Study objective:** To determine the efficacy and safety of POM + LoDEX versus HiDEX in advanced RRMM.

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151; *Proc ASCO* 2013;Abstract 8510.

Phase III MM-003 Trial Design



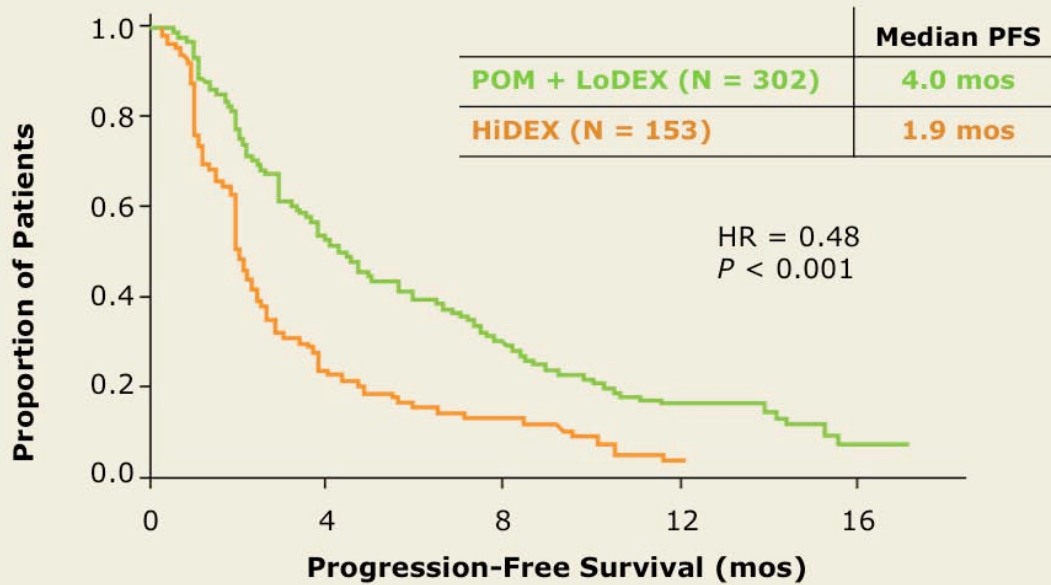
PN = peripheral neuropathy

* LoDEX or HiDEX: 20 mg (>75 years) or 40 mg (≤ 75 years)

- Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin or equivalent was required for all patients receiving POM and those at high risk of thromboembolic events
- **Primary endpoint:** Progression-free survival (PFS)

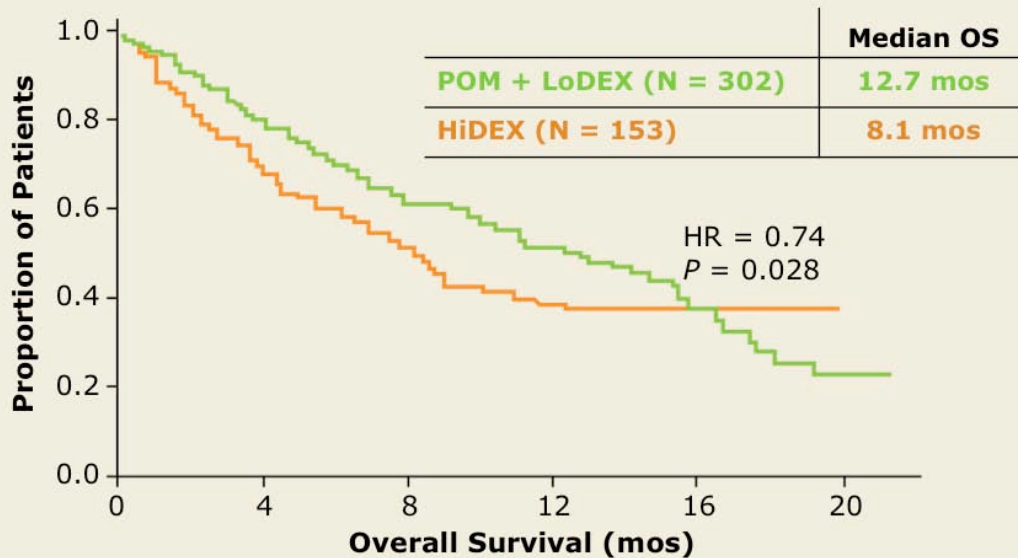
San Miguel JF et al. *Proc EHA* 2013;Abstract S1151; *Proc ASCO* 2013;Abstract 8510.

PFS — Intention-to-Treat (ITT) Population (Median Follow-Up: 10 Months)



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OS — ITT Population (Median Follow-Up: 10 Months)



- Nearly 50% of patients (n = 76) on the HiDEX arm received POM

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Subgroup Analyses of PFS and OS

Subgroup (POM + LoDEX vs HiDEX)	HR	
	PFS	OS
ITT population (n = 302, 153)	0.48	0.74
Len and Btz refractory (n = 225, 113)	0.52	0.77
Len as last prior Tx (n = 85, 49)	0.38	0.53
Btz as last prior Tx (n = 132, 66)	0.52	0.87

- HR <1.0 favors POM + LoDEX

San Miguel JF et al. *Proc EHA 2013*;Abstract S1151; *Proc ASCO 2013*;Abstract 8510.

Response Rates: ITT Population

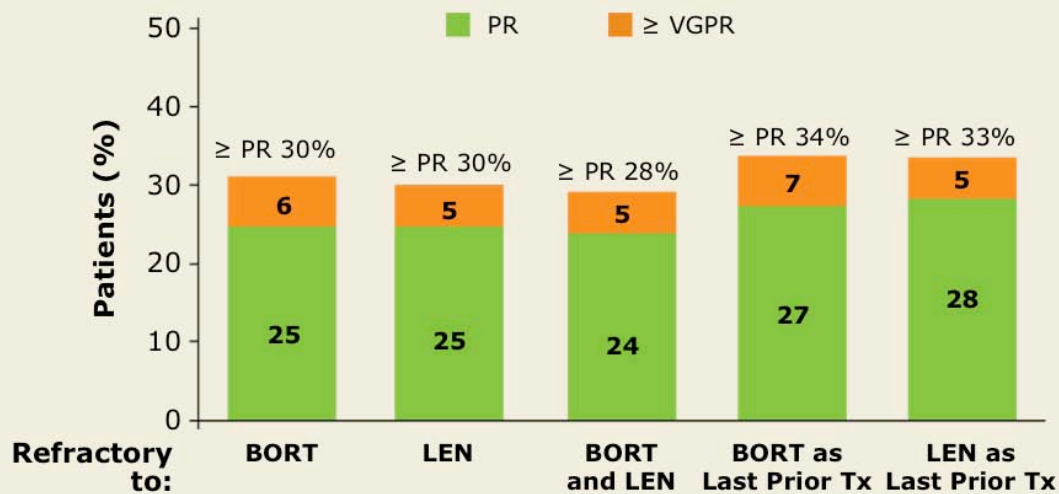
Response	POM + LoDEX (n = 302)	HiDEX (n = 153)	p-value
ORR	31%	10%	<0.001
≥VGPR	6%	1%	—
sCR/CR	1%	0%	—
≥MR	39%	16%	—
≥SD	82%	61%	—

ORR = overall response rate; VGPR = very good partial response; CR = complete response; sCR = stringent CR; MR = minimal response; SD = stable disease

- PFS of ≥MR with POM + LoDEX: 8 months

San Miguel JF et al. *Proc EHA 2013*;Abstract S1151; *Proc ASCO 2013*;Abstract 8510.

Response Rates by Last Prior Therapy for Patients in the POM + LoDEX Arm



- Response rate was consistent among all subgroups, including patients who received Len or Btz as last prior therapy.

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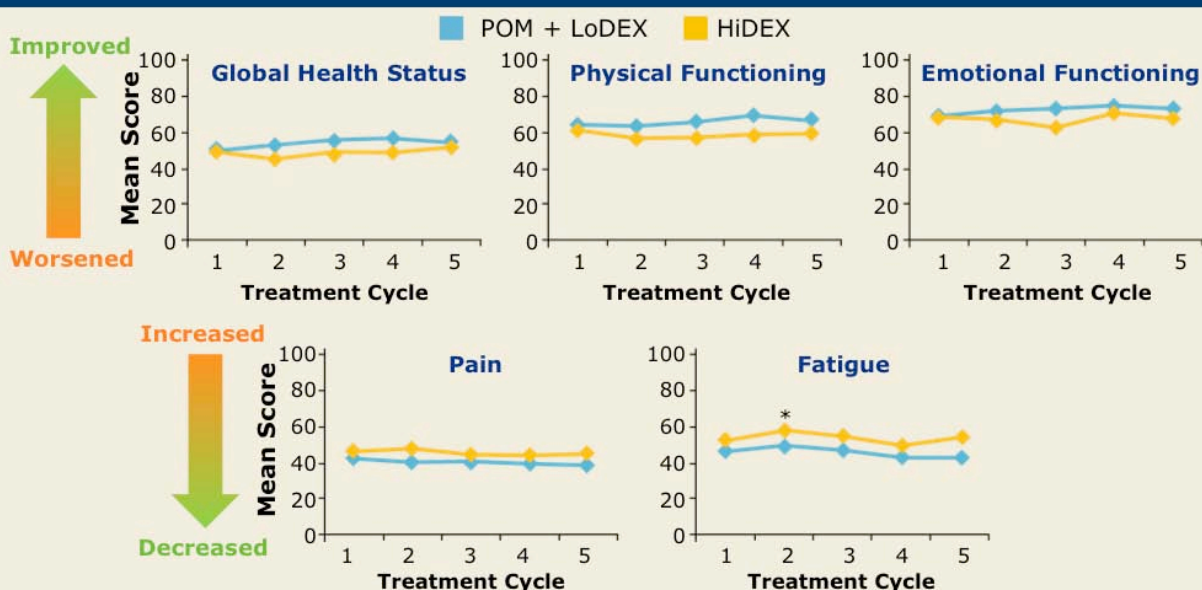
Grade 3 or 4 Adverse Events

Event	POM + LoDEX (n = 300)	HiDEX (n = 150)
Neutropenia	48%	16%
Febrile neutropenia	9%	0%
Anemia	33%	37%
Thrombocytopenia	22%	26%
Infections	30%	24%
Pneumonia	13%	8%
Bone pain	7%	5%
DVT/PE	1%	0%
Peripheral neuropathy	1%	1%

DVT/PE = deep vein thrombosis/pulmonary embolism

San Miguel JF et al. *Proc EHA 2013*;Abstract S1151; *Proc ASCO 2013*;Abstract 8510.

Health-Related Quality of Life (HRQoL): Changes Over Time



**POM + LoDEX consistently improved HRQoL measurements vs HiDEX
Improved in physical functioning and decreased pain and fatigue**

* $P < .05$

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Author Conclusions

- Updated analyses reconfirm the advantage of POM + LoDEX compared to HiDEX despite 50% of patients in the HiDEX arm receiving subsequent POM.
- POM + LoDEX significantly improved PFS and OS compared to HiDEX.
- The benefit of POM + LoDEX was maintained regardless of refractoriness to Btz and Len, even as last prior treatment.
- The safety profile of POM + LoDEX is predictable and manageable. POM + LoDEX is generally well tolerated in patients with heavily pretreated RRMM.
- POM + LoDEX consistently improved HRQoL versus HiDEX for patients with heavily pretreated RRMM who had fully benefited from Btz and Len.
- In light of the OS advantage, POM + LoDEX, an oral treatment option, should be considered a new standard approach for patients with RRMM.

San Miguel JF et al. *Proc EHA 2013*;Abstract S1151; *Proc ASCO 2013*;Abstract 8510.

Investigator Commentary: Phase III MM-003 Study of POM + LoDEX versus HiDEX for Patients with Advanced RRMM

POM is an excellent way to continue therapy with an immunomodulatory agent after Len. Therapy for patients who have developed Len-refractory disease should be switched to POM. This may represent an extension phase, maintaining disease remission for 30% to 50% of patients.

POM should not be administered at the end stage of myeloma treatment because it is less effective then. For end-stage MM, POM yielded a median PFS of 4 months versus 2 months with HiDEX in the Phase III MM-003 study. I am sure that if POM had been used immediately after Len, after first relapse, the median PFS might have been prolonged to 6 or 8 months. Additionally, the study resulted in a median OS of about 13 months with POM versus 8 months with HiDEX. The combination of POM with LoDEX improved the quality of life for patients with relapsed or refractory MM.

Interview with Antonio Palumbo, MD, August 12, 2013

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