



5 Minute Journal Club

Hematologic Oncology
Issue 1, 2013

MM-003: Pomalidomide and LoDex versus HiDex in Patients with Relapsed/ Refractory Multiple Myeloma and Renal Impairment or Adverse Cytogenetics

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: Pomalidomide and LoDex versus HiDex in Patients with Relapsed/Refractory Multiple Myeloma and Renal Impairment or Adverse Cytogenetics

Presentations discussed in this issue

Weisel KC et al. **Pomalidomide + low-dose dexamethasone (POM + LoDex) vs high-dose dexamethasone (HiDex) in relapsed/refractory multiple myeloma (RRMM): MM-003 analysis of patients (pts) with moderate renal impairment (RI).** *Proc ASCO 2013*; **Abstract 8527.**

Goldschmidt H et al. **Pomalidomide + low-dose dexamethasone (POM + LoDex) vs high-dose dexamethasone (HiDex) in relapsed/refractory multiple myeloma (RRMM): Impact of cytogenetics in MM-003.** *Proc ASCO 2013*; **Abstract 8528.**

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

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): MM-003 Analysis of Patients (pts) with Moderate Renal Impairment (RI)¹

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): Impact of Cytogenetics in MM-003²

¹ Weisel KC et al.

Proc ASCO 2013; Abstract 8527.

² Goldschmidt H et al.

Proc ASCO 2013; Abstract 8528.

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Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): MM-003 Analysis of Patients (pts) with Moderate Renal Impairment (RI)

Weisel KC et al.

Proc ASCO 2013;Abstract 8527.

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Background

- Patients with multiple myeloma (MM) that is refractory to lenalidomide (Len) and bortezomib (Btz) have a poor prognosis.
- In addition, renal impairment (RI), which is experienced by 20% of patients with MM at diagnosis, is associated with poor outcomes (*JCO 2005;23:9219*).
- Pomalidomide (POM) in combination with LoDex is effective against RRMM previously treated with Btz and Len, including in patients with RI (*Proc ASH 2012;Abstract 4072*).
- Recently, POM was FDA approved for the treatment of MM after ≥ 2 prior therapies, including Len and Btz.
- **Study objective:** To determine the efficacy and safety of POM + LoDex versus HiDex for patients with advanced RRMM with or without moderate RI.

Weisel KC et al. *Proc ASCO 2013;Abstract 8527.*

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Phase III MM-003 Trial Design

Eligibility (n = 455)

Advanced relapsed or RRMM
 Failure of Len and Btz
 No resistance to HiDex in last line of Tx
 CrCl \geq 45 mL/min
 No Grade \geq 2 PN

CrCl = creatinine clearance;
 PN = peripheral neuropathy

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

- The study arms were evaluated with regard to patients with or without moderate RI (baseline CrCl <60 mL/min versus \geq 60 mL/min)
- Primary endpoint:** Progression-free survival (PFS)

28-d cycles until PD

POM + LoDex (n = 302)

POM: 4 mg, d1-21
 LoDex: 20 mg or 40 mg*,
 d1,8,15,22

HiDex (n = 153)

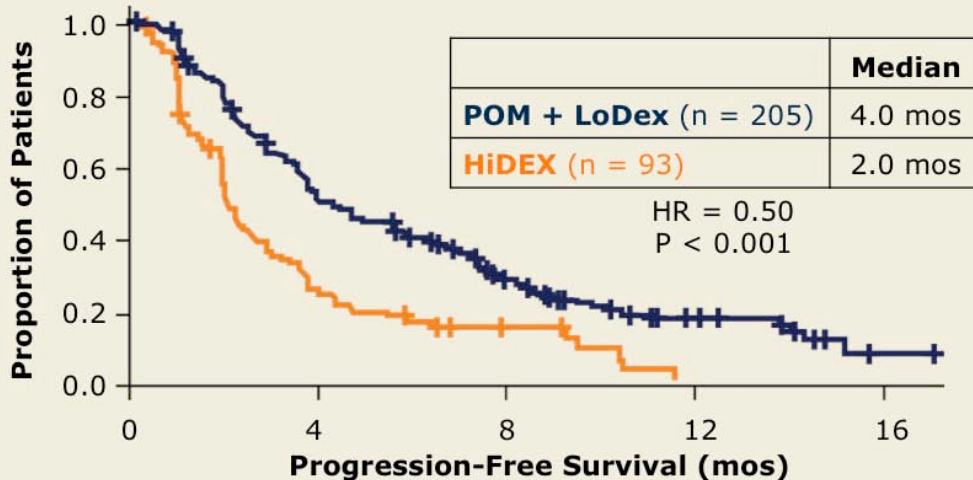
HiDex: 20 mg or 40 mg*,
 d1-4, 9-12, 17-20



Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

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PFS for Patients without RI (CrCl \geq 60 mL/min)

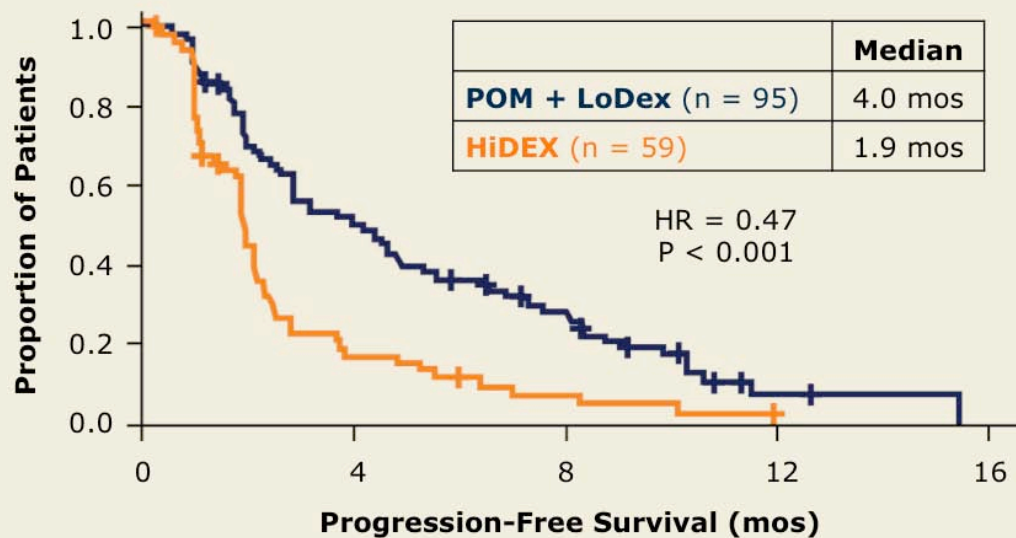


- Patients with baseline CrCl \geq 60 mL/min were more likely to be younger, male and with better performance status than those with baseline CrCl <60 mL/min.
- 55% of patients on the HiDex arm subsequently received POM.

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PFS for Patients with Moderate RI (CrCl <60 mL/min)



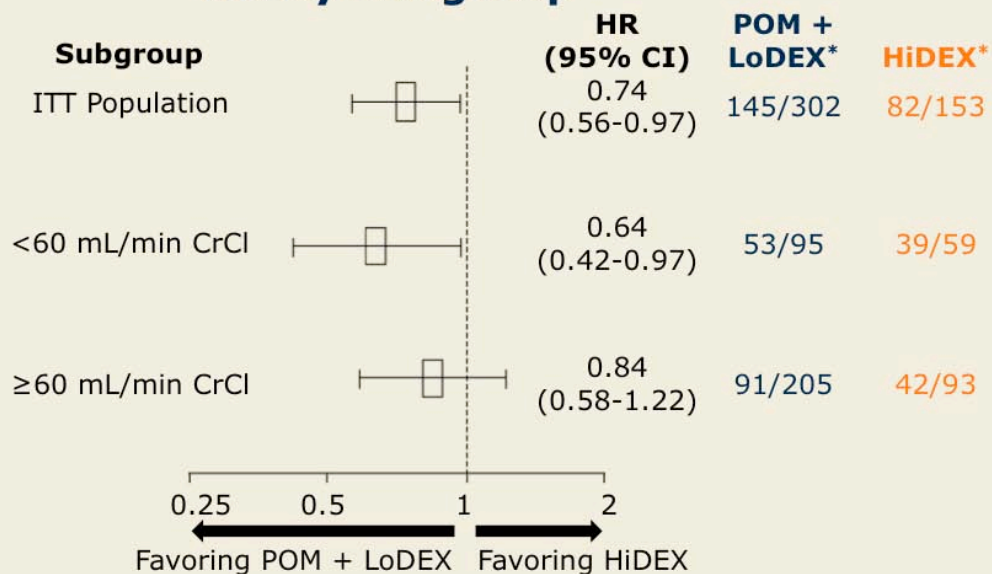
- 42% of patients on the HiDex arm subsequently received POM.

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Overall Survival (OS) by Baseline Renal Function

HR by Subgroup



* Number of events/number of patients

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Response Rates by Baseline Renal Function

Response	CrCl <60 mL/min		CrCl ≥60 mL/min	
	POM + LoDex (n = 95)	HiDex (n = 59)	POM + LoDex (n = 205)	HiDex (n = 93)
ORR (≥PR)	28%	8%	33%	11%
≥MR	36%	12%	41%	17%

ORR = overall response rate; PR = partial response; MR = minimal response

- Regardless of baseline renal function, ORR was significantly improved with POM + LoDex versus HiDex ($p < 0.001$)

Weisel KC et al. *Proc ASCO 2013*;Abstract 8527.

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Grade 3/4 Adverse Events in ≥10% of Patients

Event	CrCl <60 mL/min		CrCl ≥60 mL/min	
	POM + LoDex (n = 95)	HiDex (n = 59)	POM + LoDex (n = 203)	HiDex (n = 90)
Neutropenia	48%	19%	48%	14%
FN	5%	0%	11%	0%
Anemia	39%	42%	30%	32%
Thrombocytopenia	20%	36%	23%	20%
Infections	33%	25%	30%	23%
DVT/PE	0%	0%	2%	0%
PN	1%	2%	2%	1%
Discontinuations	12%	10%	7%	10%

FN = febrile neutropenia; DVT/PE = deep vein thrombosis/pulmonary embolism

Weisel KC et al. *Proc ASCO 2013*;Abstract 8527.

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Author Conclusions

- This study demonstrates that poor renal function (baseline CrCl <60 mL/min but ≥45 mL/min) does not affect the efficacy and safety of POM + LoDex in RRMM.
- Similar to the overall study population, POM + LoDex extended PFS compared to HiDex for patients with RRMM in both renal function subgroups.
- POM + LoDex improved OS in the ITT population and in patients with moderate RI.
 - ORR was similar between renal subgroups
- The tolerability of POM + LoDex was acceptable and comparable across subgroups, with few discontinuations due to adverse events.
- Prescribing information for POM will be updated with dose recommendations for patients with RI after the completion of the ongoing MM-008 trial.

Weisel KC et al. *Proc ASCO 2013*;Abstract 8527.

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Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): Impact of Cytogenetics in MM-003

Goldschmidt H et al.

Proc ASCO 2013;Abstract 8528.

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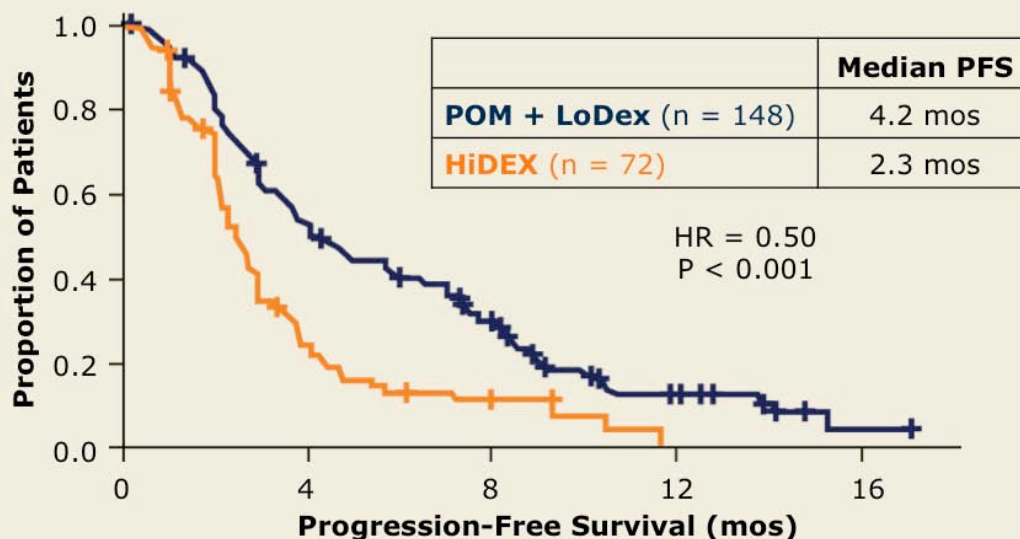
Background

- MM harboring cytogenetic abnormalities such as del17p and t(4;14) is associated with poor outcomes.
- Patients with MM who have exhausted treatment with bortezomib (Btz) and lenalidomide (Len) have a poor prognosis and limited effective treatment options.
 - Presence of high-risk cytogenetics also predicts shorter survival (*Leukemia* 2012;26:149)
- POM + LoDex demonstrated clinical efficacy in patients with RRMM and high-risk cytogenetics previously treated with Btz and/or Len (*Clin Lymphoma Myeloma Leuk* 2013;13:S44).
- **Study objective:** To prospectively examine the efficacy and safety of POM + LoDex versus HiDex for patients with RRMM in the MM-003 trial meeting the modified high-risk cytogenetic criteria, defined as presence of del17p and/or t(4;14).

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

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PFS for Patients with Standard-Risk Cytogenetics

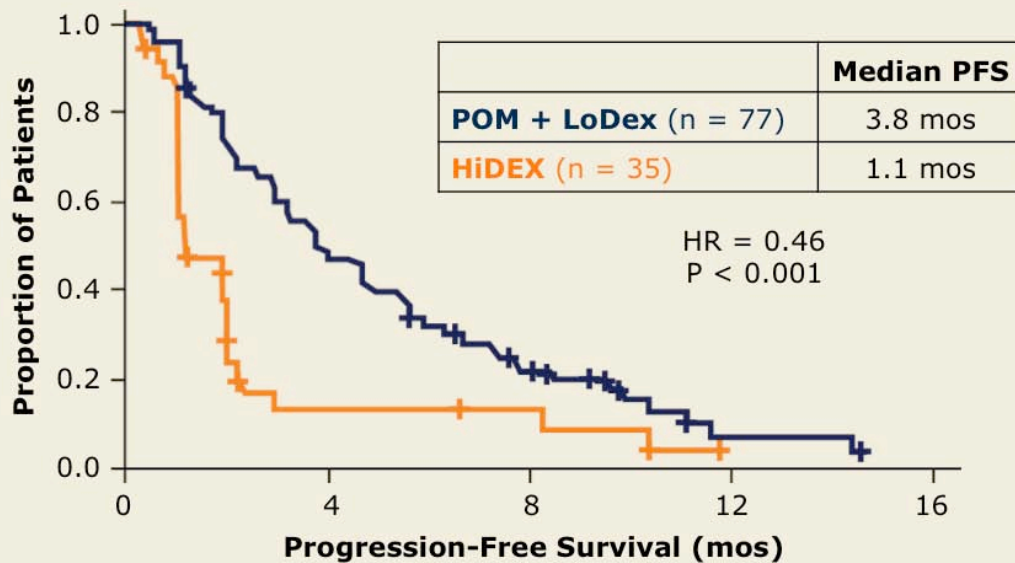


- 56% of patients on the HiDex arm subsequently received POM.

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PFS for Patients with Modified High-Risk Cytogenetics



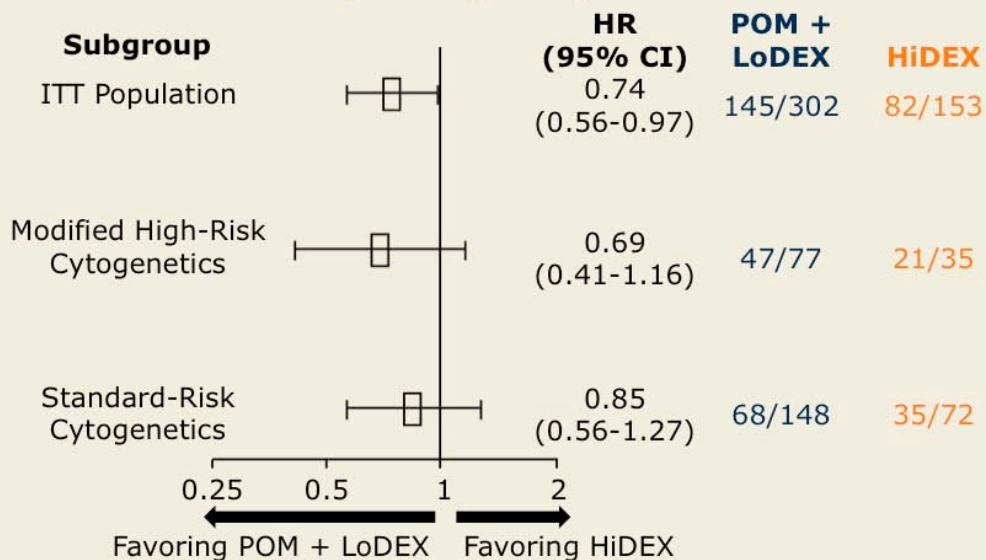
- 43% of patients on the HiDex arm subsequently received POM.

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Overall Survival (OS) by Cytogenetic Risk Category

HR by Subgroup



With permission from Goldschmidt H et al. *Proc ASCO 2013;Abstract 8528.*

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Response Rates by Cytogenetic Risk Category

Response	Modified high risk		Standard risk	
	POM + LoDex (n = 77)	HiDex (n = 35)	POM + LoDex (n = 148)	HiDex (n = 72)
ORR (≥PR)	23%	6%	34%	7%
≥MR	30%	11%	44%	15%

ORR = overall response rate; PR = partial response; MR = minimal response

- Regardless of cytogenetic risk category, ORR was significantly improved with POM + LoDex versus HiDex ($p < 0.001$)

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

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Grade 3/4 Adverse Events in ≥10% of Patients

Event	Modified high risk		Standard risk	
	POM + LoDex (n = 76)	HiDex (n = 35)	POM + LoDex (n = 147)	HiDex (n = 70)
Neutropenia	54%	31%	50%	14%
FN	9%	0%	12%	0%
Anemia	46%	46%	31%	33%
Thrombocytopenia	28%	43%	24%	19%
Infections	28%	26%	38%	20%
DVT/PE	0%	0%	2%	0%
PN	3%	0%	1%	3%
Discontinuations	7%	9%	10%	8%

FN = febrile neutropenia; DVT/PE = deep vein thrombosis/pulmonary embolism

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

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Author Conclusions

- Regardless of the cytogenetic risk category, treatment with POM + LoDex significantly prolonged PFS compared to HiDex.
- Treatment with POM + LoDex improved overall survival compared to HiDex, independent of cytogenetic status.
- The overall response rate was similar between cytogenetic groups.
- Consistent with previous reports, treatment with POM + LoDex was generally well tolerated, with manageable adverse events.
- POM + LoDex could be considered as a treatment option for patients with MM who have exhausted Btz and Len treatment options, regardless of cytogenetic status.

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

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Investigator Commentary:

Analysis of the MM-003 Trial of POM + LoDex versus HiDex in Advanced RRMM with or without Moderate Renal Impairment

The efficacy of POM and Len may be superimposable. The appropriate dosing is the issue for POM, so one should follow the dosing recommendations. I would administer POM to a patient with RRMM experiencing renal impairment. A creatinine-clearance cutoff of 60 mL/min does not significantly change clinical outcomes. We need to investigate dose reduction in patients with clearance of less than 30 mL/min. I would carefully check hematologic toxicities and would probably reduce the dose of POM if those were too high. However, data to support this approach are not presently available.

Analysis of the MM-003 Trial According to Cytogenetic Status

High-risk MM conveys worse prognosis. The observed benefit with POM for patients with advanced RRMM with high-risk cytogenetics is comparable to that with Btz. In fact, I don't believe a drug exists that is able to overcome high-risk disease. It is possible to rescue some patients with intermediate-risk disease with an intense regimen such as CyBorD or Btz.

Interview with Antonio Palumbo, MD, August 12, 2013

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