



POST-ASH Issue 2, 2015

Clinical Profile of Oprozomib and Ixazomib in Relapsed or 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 up-front and salvage therapeutic options and modalities for the evaluation of treatment response in the management of newly diagnosed and relapsed or refractory multiple myeloma (MM) 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

- Analyze recent efficacy and safety results from the Phase III ASPIRE trial evaluating carfilzomib in combination with lenalidomide and low-dose dexamethasone in the treatment of relapsed or progressive, symptomatic MM.
- Evaluate the safety and efficacy of weekly carfilzomib combined with cyclophosphamide and dexamethasone for elderly patients with newly diagnosed MM.
- Compare and contrast the benefits and risks of pomalidomide and dexamethasone with cyclophosphamide or bortezomib for patients with lenalidomide-refractory MM.
- Assess the efficacy and safety of the investigational oral proteasome inhibitors ixazomib and oprozomib as maintenance therapy and single-agent treatment, respectively, for relapsed MM.
- Examine the role of age on the efficacy of lenalidomide and low-dose dexamethasone in patients with newly diagnosed MM enrolled in the FIRST trial.
- Appraise minimal residual disease testing modalities in patients with newly diagnosed MM who received carfilzomib in combination with lenalidomide and dexamethasone.

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Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary.

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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 2015

Expiration date: March 2016

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

Last fall when I first met clinical investigator Dr Ola Landgren, aside from wanting to greet him with a very Miami-esque “Hola Ola!” I was curious to learn what prompted Memorial Sloan Kettering to lure this prominent researcher away from the cozy confines of the National Cancer Institute (NCI) to be the chief of their multiple myeloma (MM) service.

It didn’t take long to see that Dr Landgren is a passionate clinician who, like many others in the field, believes that this disease, which traditionally has been treated in a palliative mode, now seems on the verge of prolonged control for many patients. Since that first encounter, our group has worked with Dr Landgren on a number of occasions, and each time, his astute perspectives and thoughtful commentary have helped bring greater clarity to the rapidly evolving but often opaque clinical research database in this disease. For that reason, we decided to sit down with him again to get his take on the key MM presentations from the recent American Society of Hematology (ASH) meeting in San Francisco. In the first of 2 issues focused on this disease, we review research efforts attempting to maximize the treatment benefit of 2 classes of agents that have revolutionized the field, proteasome inhibitors and immunomodulatory agents (IMiDs), and in short what we learned is that the marked benefit already observed to this point may increase substantially in the future as a result of a variety of permutations of approved and emerging agents. Here’s the summary:



Ola Landgren, MD, PhD

- **Triplet therapy for relapsed/refractory (R/R) disease:**

[The ASPIRE trial](#)

Many general oncologists question the concept of “using all your big guns up front,” learning long ago in another more common noncurable situation, metastatic breast cancer, that sequential single-agent chemotherapy yielded comparable long-term efficacy outcomes with better tolerability than combination approaches. In MM, although triple regimens like lenalidomide/bortezomib/dexamethasone (RVD) have been widely embraced in the induction setting, most clinicians have used a sequential “breast cancer-like” approach for R/R disease.

In San Francisco — in what Dr Landgren describes as “the number 1 myeloma message from ASH” — and soon after in the *New England Journal*, we saw perhaps the most convincing data available at this time suggesting a different approach. The ASPIRE trial aspired to compare carfilzomib/lenalidomide/low-dose dexamethasone (CRd) to Rd in patients who had previously received 1 to 3 systemic therapies. The study met its primary endpoint of progression-free survival (PFS), demonstrating a bump in efficacy from 17.6 to 26.3 months, and of particular interest, the complete response or better rate tripled (31.8% versus 9.3%). However, the overall survival (OS) analysis results did not cross the prespecified stopping boundary, but a trend for improvement was seen although few of the patients randomly assigned to Rd subsequently received carfilzomib. Other ongoing and future trials will hopefully further test this concept, but for now — particularly armed with these latest supportive data — many investigators (very much including Dr Landgren) are thinking about 3-drug combinations early in the R/R setting.

Almost as important, this large Phase III study presented an ideal opportunity to again evaluate the critical issue of carfilzomib and the heart, a topic tied into the not infrequent occurrence of early-onset dyspnea. In ASPIRE there was what Dr Landgren views as a minimal increase in the risk of cardiovascular events (Grade 3 or greater heart failure 1.8% versus 3.8%). An unrelated poster also presented in San Francisco specifically evaluated this issue prospectively in 62 patients who received carfilzomib and found 5 instances of cardiac events, 3 of which were considered attributable to the drug, and only 1 of 30 patients with available echocardiogram data pre- and postcarfilzomib treatment experienced an unexplained decrease in ejection fraction. The authors noted a frequent and dramatic rise in N-terminal pro-B-type natriuretic protein, which Dr Landgren believes could have been the result of aggressive hydration, but the study did not examine this possibility. As a result of these and other findings, at this point for most patients Dr Landgren generally recommends only clinical observation and careful hydration, without the need for specific cardiac monitoring.

Pomalidomide (P) triplets in R/R disease

In keeping with the theme of combination versus sequential single agents, a number of studies were also unveiled at ASH examining P in concert with other agents. A randomized Phase II study evaluating Pd with or without cyclophosphamide in 70 patients demonstrated the superiority of the triplet in terms of response rate (65% versus 39%) and also revealed borderline significant improvements in PFS and OS. Similarly, a single-arm Phase II study (n = 47) evaluating the P version of RVD (PVd) demonstrated an 85% overall response rate with an impressive waterfall plot. Both of these regimens are seen by Dr Landgren as additional evidence — albeit with many fewer patients — that the “ASPIRE” principle of using triplets in the R/R setting is quite sound.

• Up-front induction regimens

More on CRd

At ASH, Dr Landgren and his former NCI colleagues updated their important Phase II trial evaluating up-front CRd. Although this specific presentation focused on the optimal assessment of minimal residual disease and showed that next-generation sequencing was more sensitive than flow cytometry, in discussing the study Dr Landgren noted that the median age of patients

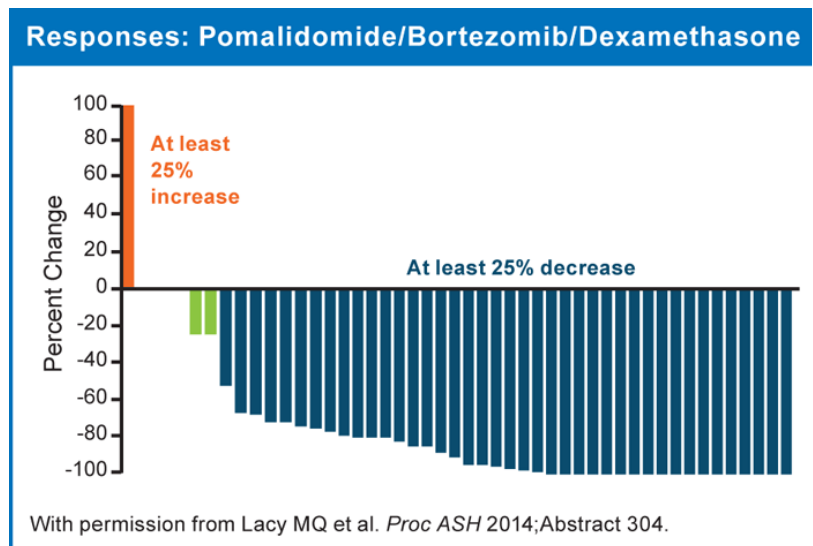
on the trial was 65 and that no difference was observed in benefit between younger and older individuals. In fact, the oldest trial participant was an 88-year-old man. As such, he sees no reason not to use the most effective induction regimen available, even in older patients.

Phase I-II study of the weekly carfilzomib version of "CyBorD" (weekly CCd) in patients age 65 and over

Dr Antonio Palumbo played a key role in pioneering the initial research on weekly bortezomib, and it should therefore come as no surprise that at ASH he presented findings from a study using a similar approach with carfilzomib. What he showed was that the efficacy and tolerability associated with a once-weekly carfilzomib strategy appear comparable to that of twice-weekly administration. Interestingly, as part of the study, after 9 cycles, patients were maintained on carfilzomib alone and it was noted that with time, responses became deeper. Dr Landgren believes that these results indicate that although effective, the weekly CCd regimen is slightly inferior to other combinations like CRd that include an IMiD, but he does conclude that in countries where lenalidomide is not approved as an up-front therapy, it is a reasonable consideration. Furthermore, he believes that if weekly carfilzomib becomes a reality in general, it would be an important advance for patients.

Additional data from the FIRST trial in older versus younger patients

At the ASH 2013 meeting, the landmark Phase III FIRST study grabbed headlines by revealing a marked improvement in PFS and OS in favor of indefinite Rd compared to 18 months of either Rd or melphalan/prednisone/thalidomide (MPT). One important aspect of the study is that most of the 1,623 participants were older, and although the news wasn't as big at this year's conference, we saw data evaluating outcomes in patients over age 75. Significantly, essentially no difference was observed in efficacy or tolerability compared to younger patients, and although Dr Landgren recognizes that patients who enter trials are generally more fit and have fewer comorbidities, he



sees these results fitting his model of providing the most effective induction antitumor regimen (currently RVD or CRd) to all fit patients regardless of age and myeloma risk status.

- **Oral proteasome inhibitors: The future of maintenance therapy?**

In San Francisco we also saw more data on a critical trend that ties directly into the concept of continuous treatment. Although it could be that oral agents will provide greater efficacy either because of intrinsic antitumor activity or that patients are able to receive more consistent dosing, there can be no denying that even if equivalent, there would be a powerful impact on patient quality of life, particularly in the long-term maintenance setting.

The oral MM agent that is farthest along in development is ixazomib, which is similar to bortezomib, and at ASH we saw more encouraging data from a Phase II up-front study evaluating the agent combined with Rd in the induction setting followed by ixazomib alone as maintenance therapy.

Perhaps even more importantly, however, since ASH we have learned via press release that the pivotal Phase III TOURMALINE-MM1 trial evaluating ixazomib with Rd versus Rd in patients with R/R MM at first interim analysis achieved its primary endpoint of improving PFS. Hopefully these data will be unveiled at the upcoming ASCO meeting, but either way it seems quite plausible that this will help pave the way for widespread availability of this agent in the near future and hopefully will serve as another important step forward in terms of patient quality of life.

Of course, ixazomib is not alone, as oprozomib, an oral agent similar to carfilzomib, is also being developed. Unlike its close cousin, however, this drug has been plagued a bit by tolerability issues, particularly gastrointestinal toxicities, and at ASH we saw more data from a Phase Ib/II study of 2 dosing schedules that demonstrated good efficacy but again challenges with side effects.

- **Special bonus: Serum versus urine measurement of free light chains (FLC) in light chain MM**

The inconvenience and inaccuracy of 24-hour urine measurement of FLC led to the use of serum evaluation (Freelite® kit), but little is known about how these 2 approaches directly compare. For that reason, as part of the IFM/DFCI 2009 study of RVD induction with immediate versus delayed autologous bone marrow transplant, investigators conducted both these methods of response assessment in the 16.4% of patients (n = 115) enrolled on the trial who secreted only light chains. Based on these results, it appears that serum FLC evaluation was much more accurate, and the authors (and Dr Landgren) conclude that serum FLC should replace urine measurement in these patients.

On the second MM issue of this series, we will review other recent data on new agents in this disease, including the recently approved histone deacetylase inhibitor panobinostat and several exciting monoclonal antibodies, including elotuzumab and

daratumumab, but before then we will jump into chronic lymphocytic leukemia with lots of new information relevant to clinical practice today and, very likely, tomorrow.

Neil Love, MD

Research To Practice

Miami, Florida

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Clinical Profile of Oprozomib and Ixazomib in Relapsed or Refractory MM

Presentations discussed in this issue

Kumar S et al. **Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients (pts) with previously untreated multiple myeloma (MM): Phase 2 study results.** *Proc ASH 2014*; **Abstract 82.**

Vij R et al. **Clinical profile of single-agent oprozomib in patients (Pts) with multiple myeloma (MM): Updated results from a multicenter, open-label, dose escalation Phase 1b/2 study.** *Proc ASH 2014*; **Abstract 34.**

Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Ola Landgren, MD, PhD (2/9/15)

Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients with Previously Untreated Multiple Myeloma (MM): Phase 2 Study Results¹

Clinical Profile of Single-Agent Oprozomib in Patients with Multiple Myeloma: Updated Results from a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study²

¹ Kumar SK et al.
Proc ASH 2014; Abstract 82.

² Vij R et al.
Proc ASH 2014; Abstract 34.

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Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients with Previously Untreated Multiple Myeloma (MM): Phase 2 Study Results

Kumar SK et al.

Proc ASH 2014;Abstract 82.

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Background

- Triplet regimens combining a proteasome inhibitor, an immunomodulatory agent and a steroid have been shown to be active and well tolerated in patients with previously untreated MM.
- Ixazomib is an investigational proteasome inhibitor that has shown single-agent activity in relapsed/refractory MM, with a manageable safety profile, including limited peripheral neuropathy (PN) (*Blood* 2014;124:1047).
- Results of weekly ixazomib with lenalidomide (len) and dexamethasone (dex) in a Phase I/II trial for untreated MM were previously reported (*Lancet Oncol* 2014;15:1503):
 - Treatment comprised the triplet induction regimen followed by single-agent ixazomib maintenance therapy.
- **Study objective:** To report the long-term safety and efficacy of ixazomib maintenance therapy in patients who received triplet induction therapy in the Phase I/II trial.

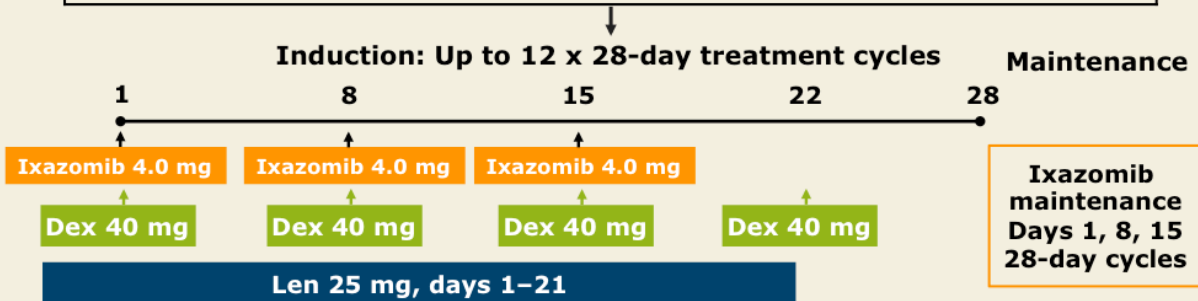
Kumar SK et al. *Proc ASH 2014;Abstract 82.*

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Phase I/II Trial Design (NCT01217957)

Eligibility (n = 65): Phase I (n = 15), Phase II (n = 50)

Patients with previously untreated MM
ECOG PS 0-2
No DVT/PE; No Grade ≥ 2 PN



DVT = deep vein thrombosis; PE = pulmonary embolism

- Mandatory thromboembolism prophylaxis with aspirin 81-325 mg/d or low-molecular-weight heparin while receiving len/dex
- **Primary endpoint:** Complete response (CR) + very good partial response (VGPR)

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

Best Response: All Patients

All patients (n = 49)*	Induction	Overall
CR + VGPR + partial response (PR)	44 (90%)	44 (90%)
CR	11 (22%)	17 (35%)
Stringent CR (sCR)	5 (10%)	8 (16%)
VGPR	18 (37%)	12 (24%)
Near CR (nCR)	2 (4%)	4 (8%)
PR	15 (31%)	15 (31%)
Minimal response (MR)	3 (6%)	3 (6%)
Stable disease (SD)	2 (4%)	2 (4%)

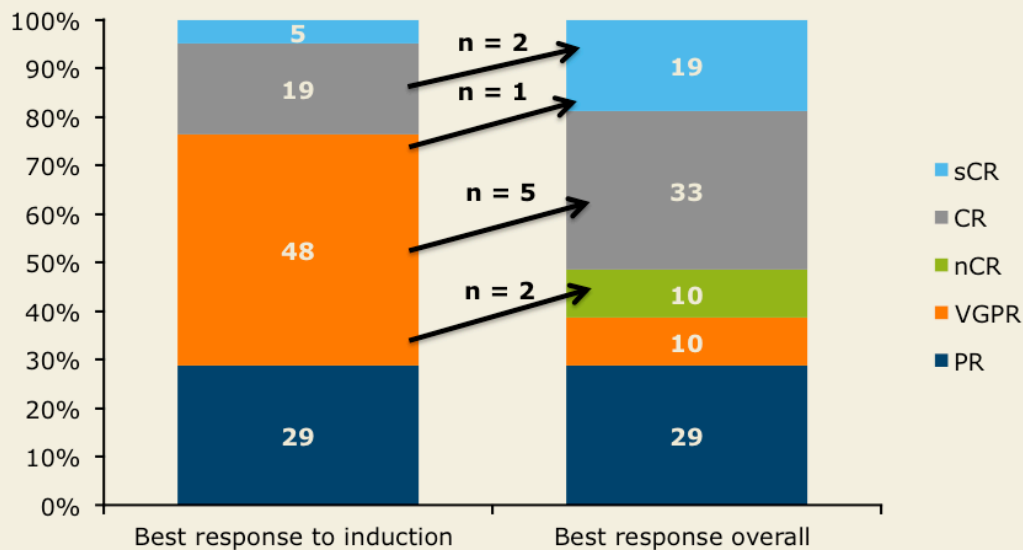
* 14 patients discontinued induction therapy to undergo ASCT. Best response to induction therapy included

- sCR = 4 (29%)
- VGPR = 4 (29%)
- PR = 6 (43%)

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

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Best Response: Patients in the Phase II Portion Receiving Maintenance Therapy (N = 21)

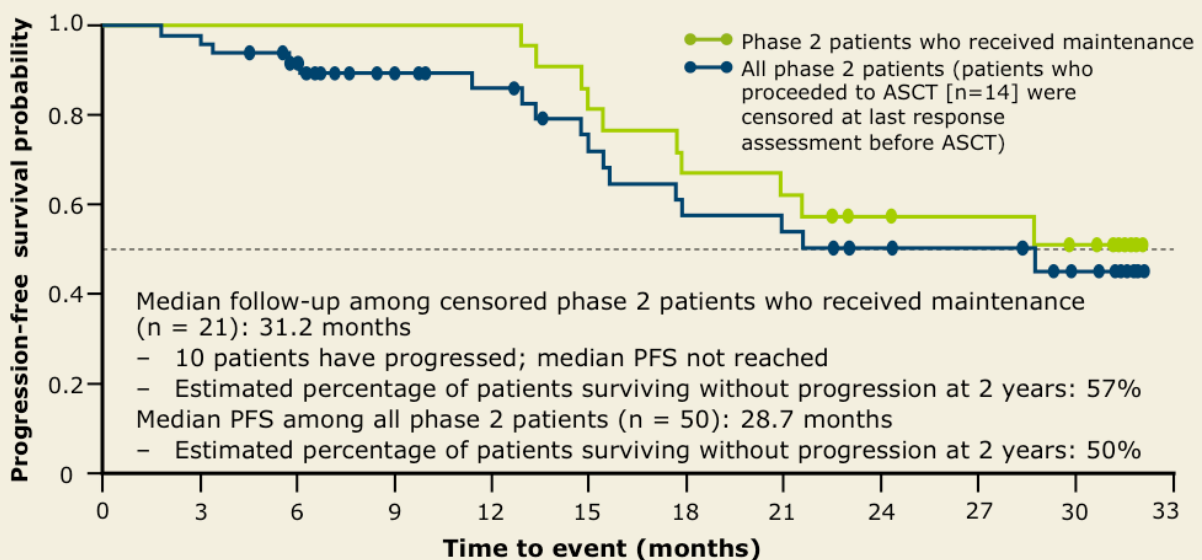


- Patients with improved response during maintenance: 10 (48%)
 - VGPR to nCR (n = 2); VGPR to CR (n = 5); VGPR to sCR (n = 1); CR to sCR (n = 2)

With permission from Kumar SK et al. *Proc ASH* 2014;Abstract 82.

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Progression-Free Survival (PFS)

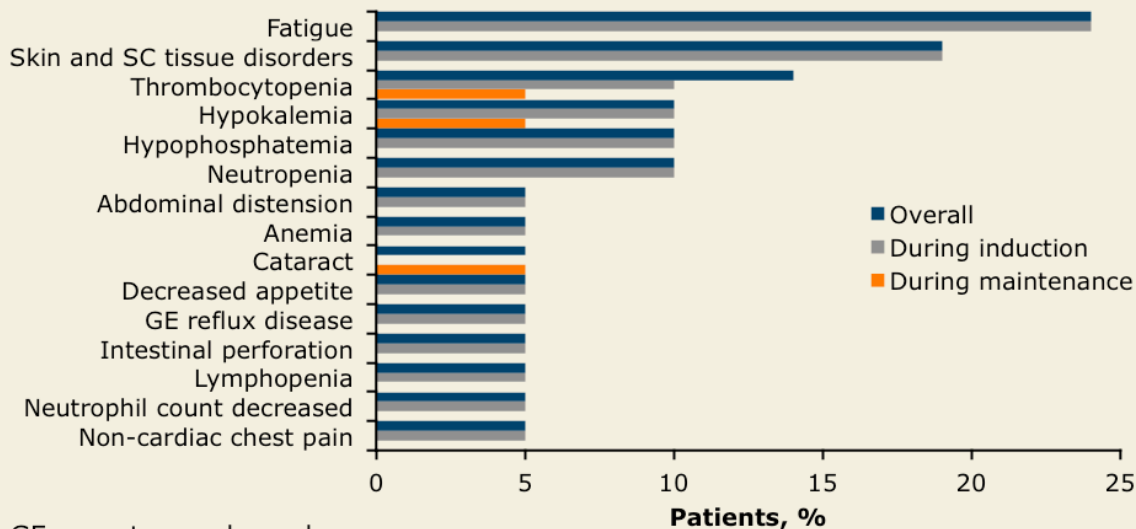


- All 21 patients who received ixazomib maintenance were alive after a follow-up of 25.1-33.9 months

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Grade 3 Ixazomib-Associated Adverse Events (AEs)



GE = gastroesophageal

- Grade 3 AEs were reported in 13 (62%) patients overall: Induction (52%), maintenance therapy (14%)
- No Grade 4 AEs among the 21 patients who received ixazomib maintenance

With permission from Kumar SK et al. *Proc ASH 2014*;Abstract 82.

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Author Conclusions

- The all-oral combination of ixazomib/len/dex is active as induction therapy, with a manageable safety profile at the recommended Phase II dose for patients with previously untreated MM:
 - \geq PR = 90% after up to 12 cycles of induction therapy
- Data on 21 patients indicate that single-agent ixazomib maintenance for up to 1.9 years was feasible, with a manageable profile for patients not undergoing ASCT:
 - Ixazomib maintenance improved responses
 - It contributed to durable responses
 - New onset of toxicity was limited during ixazomib maintenance
- A Phase III trial of ixazomib or placebo in combination with len/dex for patients with previously untreated MM is ongoing (TOURMALINE-MM2; NCT01850524).

Kumar SK et al. *Proc ASH 2014*;Abstract 82.

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Investigator Commentary: Long-Term Efficacy and Safety of Ixazomib Maintenance Therapy After Induction Therapy with Ixazomib/Len/Dex for Previously Untreated MM

This is a study of the long-term use of single-agent ixazomib maintenance therapy after induction therapy with ixazomib/len/dex. In the Phase II portion of the study, 50 patients were followed up for about 1.5 years. The study showed that the continuation of ixazomib maintenance is well tolerated and improves responses. Also, it contributes to durable responses. This is extremely important. Evidence suggests that it will provide us with another oral maintenance agent, a proteasome inhibitor, beyond the immunomodulatory drug len. However, we need larger studies with longer follow-up to confirm these results. Though promising, ixazomib is investigational and cannot be used outside of a protocol setting. A study of ixazomib or placebo with len/dex in the relapsed/refractory setting is ongoing (NCT01564537). If that study is successful, ixazomib may become available.

Interview with Ola Landgren, MD, PhD, February 9, 2015

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Clinical Profile of Single-Agent Oprozomib in Patients with Multiple Myeloma: Updated Results from a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study

Vij R et al.

Proc ASH 2014;Abstract 34.

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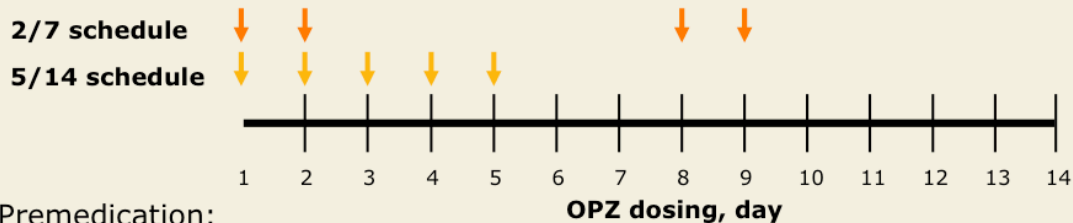
Background

- Oprozomib (OPZ) is an orally bioavailable epoxyketone proteasome inhibitor.
- It selectively and irreversibly binds to its target.
- Preliminary findings demonstrated promising antitumor activity of single-agent OPZ in patients with hematologic cancers, including multiple myeloma (MM) (*Proc ASH* 2013;Abstract 3184):
 - Clinical benefit rate (CBR) in MM, 23.1%
- **Study objective:** To determine the safety and efficacy of OPZ in the subset of patients with MM enrolled on a Phase Ib/II trial.

Vij R et al. *Proc ASH* 2014;Abstract 34.

Ongoing Phase Ib/II Trial Design (NCT01416428)

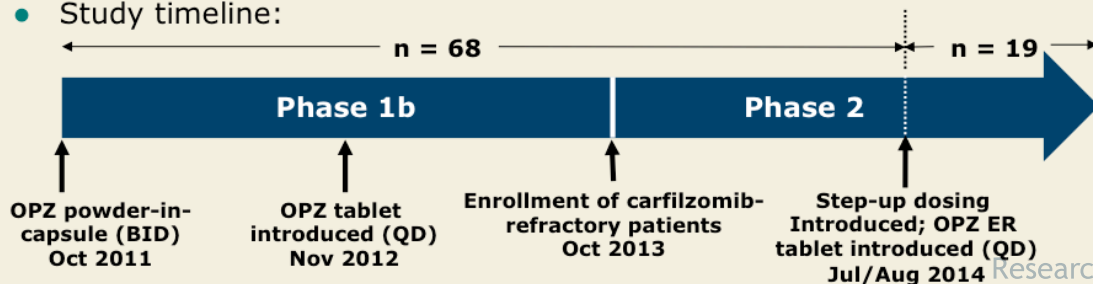
- Study dosing schema:



- Premedication:

- 5-HT₃ inhibitor (phase 1b and phase 2)
- Dexamethasone (4 mg PO or IV; phase 2 only)

- Study timeline:



With permission from Vij R et al. *Proc ASH* 2014;Abstract 34.

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Eligibility Criteria and Endpoints

- Target accrual (n = 349)
- Patients with hematologic cancer
 - Relapsed after ≥ 1 line of therapy (Phase Ib)
 - Relapsed and/or refractory after 1 to 3 lines of therapy (Phase II)
- No evidence of CNS lymphoma
- No New York Heart Association Class III/IV congestive heart failure
- No Grade ≥ 3 peripheral neuropathy (PN) or Grade 2 PN with pain
- **Primary endpoints**
 - Phase I: Determination of the maximum tolerated dose (MTD)
 - Phase II: Overall response rate (ORR)
- **Secondary endpoints** include safety/tolerability and CBR

Vij R et al. *Proc ASH* 2014;Abstract 34.

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Enrollment to Date

- As of November 3, 2014, patients with hematologic cancer receiving OPZ (n = 129)
 - Patients with MM (n = 87):
 - Phase Ib, 2/7 schedule (n = 21)
 - Phase Ib, 5/14 schedule (n = 20)
 - Phase II cohort:
 - 5/14 schedule, 240 mg/d (n = 27)
 - 2/7 step-up schedule, 240 then 300 mg/d (n = 10)
 - 5/14 step-up schedule, 150 then 180 mg/d (n = 9)

Vij R et al. *Proc ASH* 2014;Abstract 34.

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Duration of Treatment (DoT)

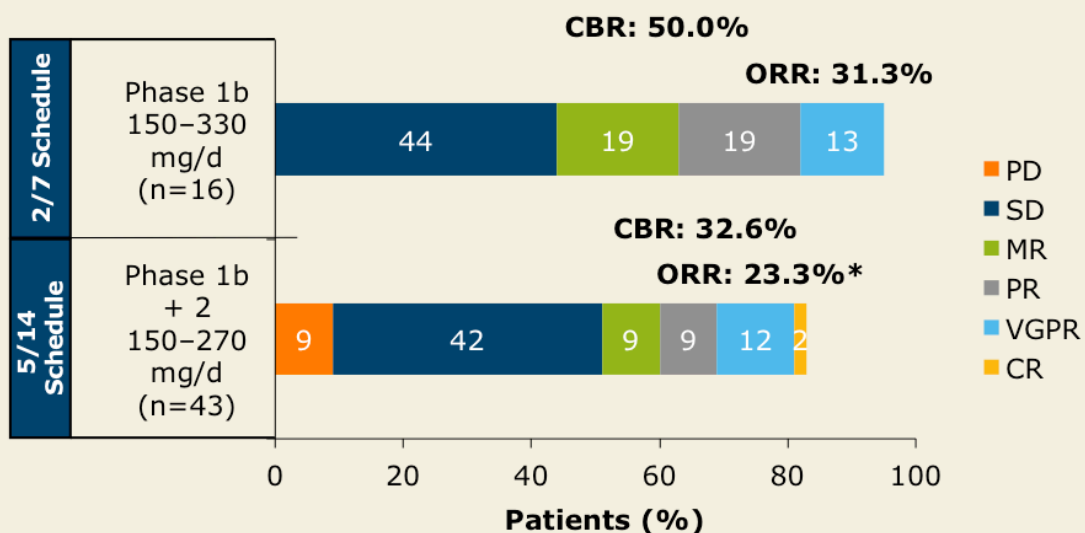
Phase Ib	2/7 Schedule	5/14 Schedule*
	150-330 mg/d (n = 21)	150-270 mg/d (n = 47)
Median DoT	23.4 weeks	6.7 weeks
Phase II	2/7 Step-up	5/14 Step-up
	240 then 300 mg/d (n = 10)	150 then 180 mg/d (n = 9)
Median DoT	5.6 weeks	6.7 weeks

* Phase Ib + II

- Treatment duration in the step-up cohorts (Phase II) was limited by the recent enrollment of patients.
- Phase Ib: 2/7 schedule, MTD = 300 mg/d
5/14 schedule, MTD = 240 mg/d

Vij R et al. *Proc ASH* 2014;Abstract 34.

Response (Phase Ib – 2/7 Schedule)



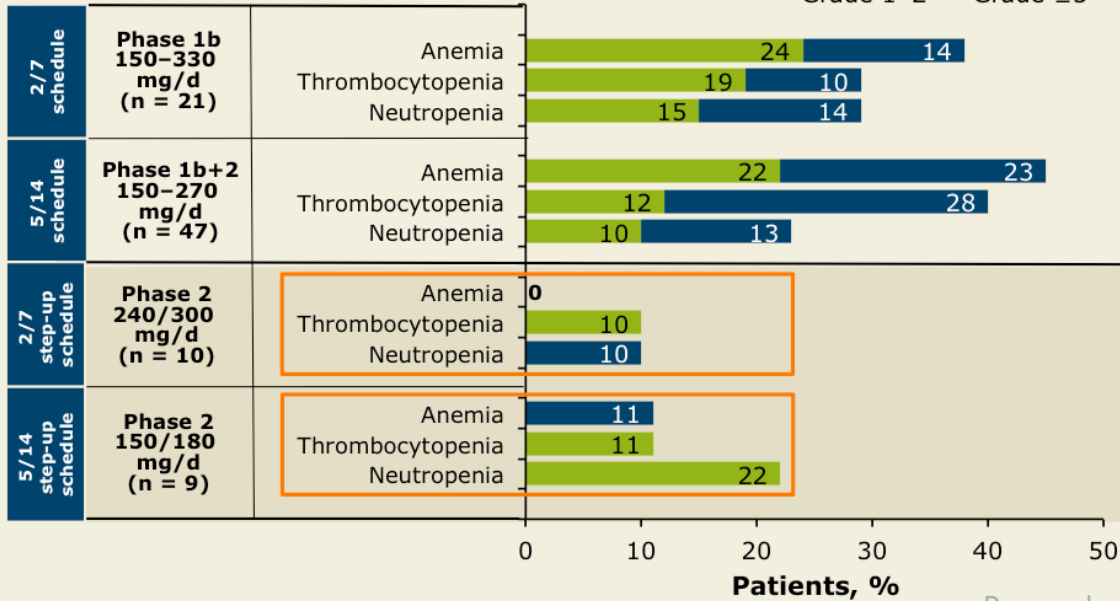
- ORR for 11 patients with carfilzomib-refractory MM (Phase II): 18.2%
- Response data not shown for step-up cohorts because of limited treatment exposure

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Hematologic Adverse Events

Hematologic Adverse Events, %

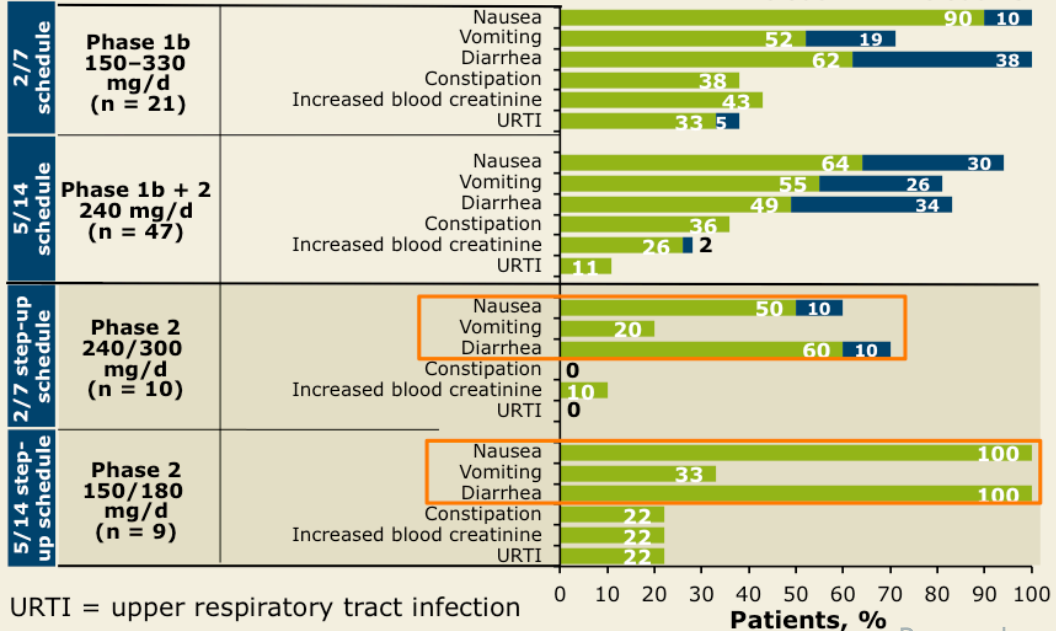


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Nonhematologic Adverse Events

Non-Hematologic Adverse Events, %



URTI = upper respiratory tract infection

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PN, Rash, Gastrointestinal (GI) Bleeding and Deaths

- Treatment-emergent or worsening PN occurred in 5 patients (6%).
 - Patients with Grade ≥ 3 PN: 1 (1%)
- Treatment-emergent rash occurred in 6 patients (7%).
 - No Grade ≥ 3 rash was observed
- Patients who developed serious adverse events: 28
- Patients who died: 3 (6%)
 - Patients who died of upper GI bleeding on the 5/14 schedule (Phase II, 240 mg/d): 2
 - Patient who died of disease progression on the 5/14 schedule (Phase II, 240 mg/d): 1

Vij R et al. *Proc ASH* 2014;Abstract 34.

Author Conclusions

- The most common Grade ≥ 3 nonhematologic adverse events with single-agent OPZ were diarrhea, nausea and vomiting.
- The rates of treatment-emergent PN and rash were low.
- The recommended Phase II dose and schedule are
 - 2/7 step-up schedule: 240 then 300 mg/d
 - 5/14 step-up schedule: 150 then 180 mg/d
- Preliminary data suggest that step-up dosing is associated with improved tolerability, with few Grade ≥ 3 GI AEs.
- Accrual on the 2/7 and 5/14 schedules (Phase II) is ongoing.
 - Target enrollment for Phase II: 94 patients with MM
 - All current and newly enrolled patients are receiving a new formulation of OPZ (extended-release tablets)
- Single-agent OPZ continues to show promising antitumor activity with responses in carfilzomib-refractory disease.

Vij R et al. *Proc ASH* 2014;Abstract 34.

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Investigator Commentary: Efficacy and Safety Results of a Phase Ib/II Trial of Single-Agent OPZ in Hematologic Cancer

OPZ is the fourth proteasome inhibitor that has been evaluated in patients with MM. The preceding proteasome inhibitors are bortezomib, carfilzomib and ixazomib. Both ixazomib and OPZ are orally bioavailable. This dose-escalation Phase Ib/II study is in its early stages. So far, it is fair to say that drug development focusing on OPZ has been hampered by toxicities that relate to GI symptoms — nausea, diarrhea and vomiting. It appears that OPZ is effective but associated with these toxicities. Hence, the dosing and schedule are being adjusted. Although OPZ is a promising agent, more data are needed to confirm its efficacy and tolerability.

Interview with Ola Landgren, MD, PhD, February 9, 2015

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