Phase II Trials of Pomalidomide and Dexamethasone in Combination with Either Cyclophosphamide or Bortezomib in Relapsed or Refractory MM
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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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Ola Landgren, MD, PhD
Chief, Myeloma Service
Memorial Sloan Kettering Cancer Center
New York, New York

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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
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:

• **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 incurable 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
Phase II Trials of Pomalidomide and Dexamethasone in Combination with Either Cyclophosphamide or Bortezomib in Relapsed or Refractory MM

Presentations discussed in this issue

Baz R et al. Pomalidomide, cyclophosphamide, and dexamethasone is superior to pomalidomide and dexamethasone in relapsed and refractory myeloma: Results of a multicenter randomized phase II study. *Proc ASH* 2014;Abstract 303.

Lacy MQ et al. Pomalidomide, bortezomib and dexamethasone (PVD) for patients with relapsed lenalidomide refractory multiple myeloma (MM). *Proc ASH* 2014;Abstract 304.

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

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**Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study**

1 **Baz R et al.**

*Proc ASH* 2014;Abstract 303.

2 **Lacy MQ et al.**

*Proc ASH* 2014;Abstract 304.
Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study

Baz R et al.  
*Proc ASH 2014;Abstract 303.*

### Background

- The combination of pomalidomide and dexamethasone results in an overall response rate of 33%, median progression-free survival (PFS) of 4.2 months and median overall survival of 16.5 months for patients with multiple myeloma (MM) who received prior lenalidomide and bortezomib (*Blood* 2014;123(12):1826).
- Alkylating agents (melphalan, cyclophosphamide) represent a standard therapy for patients with MM, the latter being associated with less myelosuppression.
- The previously reported recommended Phase II dose of cyclophosphamide with standard-dose pomalidomide and dexamethasone was 400 mg orally on days 1, 8 and 15 of a 28-day cycle (Arm A, *Proc ASH 2012;Abstract 4062*).
- **Study objective:** To compare pomalidomide and dexamethasone to pomalidomide, dexamethasone and cyclophosphamide for patients with lenalidomide-refractory MM.

Baz R et al.  *Proc ASH 2014;Abstract 303.*
Phase II Trial Design

Eligibility (n = 70)
Lenalidomide-refractory MM
At least 2 prior therapies
ECOG PS ≤ 2

Arm B (28-day cycle)
Pomalidomide 4 mg PO d1-21
Dexamethasone 40 mg* PO d1, 8, 15, 22

Arm C (28-day cycle)
Pomalidomide 4 mg PO d1-21
Cyclophosphamide 400 mg PO d1, 8, 15
Dexamethasone 40 mg* PO d1, 8, 15, 22

Arm D: Cross over for progressive disease at discretion of patient and treating physician

* Dexamethasone 20 mg was administered if the patient was older than 75 years or unable to tolerate 40 mg of dexamethasone.

- Aspirin 81-325 mg daily was administered as prophylactic antithrombotic treatment unless contraindicated. If aspirin was contraindicated, patients received low-molecular-weight heparin or therapeutic anticoagulation with warfarin.


IMWG Response Rate

IMWG = International Myeloma Working Group; ORR = overall response rate; PR = partial response; CBR = clinical benefit rate; MR = minimal response; VGPR = very good partial response

With permission from Baz R et al. Proc ASH 2014;Abstract 303.
**PFS**

![Progression-free survival (months)](image)

- **Median PFS**
  - Arm B: 4.4 mo
  - Arm C: 9.5 mo

*p = 0.1078*

With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.

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**Overall Survival (OS)**

![Overall survival (months)](image)

- **Median OS**
  - Arm B+D: 16.8 mo
  - Arm C: Not reached

*p = 0.1308*

With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.
Select Grade 3/4 Adverse Events

* Includes 1 patient with grade 5 pneumonia.
With permission from Baz R et al. Proc ASH 2014;Abstract 303.

Author Conclusions

- In comparison to pomalidomide and dexamethasone the combination of pomalidomide, cyclophosphamide and dexamethasone resulted in:
  - Superior response rate (ORR: 65% versus 39%)
  - Improvements in PFS and OS of borderline significance
- The combination of pomalidomide, cyclophosphamide and dexamethasone was well tolerated, with a possible increase in hematologic adverse events, which were manageable.
- This regimen compares favorably with other pomalidomide-based regimens in terms of efficacy, toxicities and cost.
- The addition of cyclophosphamide for patients experiencing disease progression on pomalidomide and dexamethasone results in minimal clinical benefits (data not shown).

Pomalidomide, Bortezomib and Dexamethasone (PVD) for Patients with Relapsed Lenalidomide Refractory Multiple Myeloma (MM)

Lacy MQ et al. *Proc ASH 2014;Abstract 304.*

**Background**

- Pomalidomide and dexamethasone has been extensively studied in patients with lenalidomide-refractory MM.
- The combination of IMiDs and proteasome inhibitors has potential for deeper and more durable responses.
- The Phase I MM-005 study evaluating *twice weekly* bortezomib with pomalidomide and dexamethasone reported promising results (*Proc ASH 2013;Abstract 1969*):
  - ORR = 75% and VGPR or better = 30%
- **Study objective:** To evaluate the safety and efficacy of the maximum tolerated dose combination of pomalidomide, *once weekly* bortezomib and dexamethasone (PVD) for patients with relapsed, lenalidomide-refractory MM.

Lacy MQ et al. *Proc ASH 2014;Abstract 304.*
Phase II Trial Design

Pomalidomide 4 mg daily days 1-21

Bortezomib 1.3 mg/m² (IV or SC)
Dexamethasone 40 mg

days 1, 8, 15, 22

28-day cycle

After 8 cycles, dexamethasone and bortezomib were stopped and pomalidomide continued until disease progression.

Thromboprophylaxis was administered to all patients as either aspirin or full-dose anticoagulation.

Lacy MQ et al. Proc ASH 2014;Abstract 304.

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IMWG Response

At least 25 % increase

At least 25 % decrease

With permission from Lacy MQ et al. Proc ASH 2014;Abstract 304.
# Efficacy

<table>
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<tr>
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<th>N = 47</th>
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<tr>
<td>Overall response rate</td>
<td>85%</td>
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<tr>
<td>Stringent complete response (n)</td>
<td>3</td>
</tr>
<tr>
<td>Complete response (n)</td>
<td>6</td>
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<tr>
<td>VGP (n)</td>
<td>12</td>
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<tr>
<td>Partial response (n)</td>
<td>19</td>
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<tr>
<td>Median PFS</td>
<td>10.7 mo</td>
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<tr>
<td>Median duration of response</td>
<td>13.7 mo</td>
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<tr>
<td>Six-month event-free survival</td>
<td>100%</td>
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<td>Twelve-month event-free survival</td>
<td>94%</td>
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Lacy MQ et al. *Proc ASH 2014; Abstract 304.*

# Hematologic Adverse Events

- **Anemia**
  - Grade 3+: 2%
  - All grades: 70%

- **Thrombocytopenia**
  - Grade 3+: 2%
  - All grades: 81%

- **Neutropenia**
  - Grade 3+: 68%
  - All grades: 89%

With permission from Lacy MQ et al. *Proc ASH 2014; Abstract 304.*
Author Conclusions

- PVD is a highly effective combination in patients with MM refractory to lenalidomide:
  - Confirmed responses in 85% of patients
- Weekly administration of bortezomib and dexamethasone enhanced the tolerability and convenience of this regimen.
- Toxicities were manageable, mostly consisting of mild cytopenias.
- PVD is a highly attractive option for patients with relapsed and refractory MM.

Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Investigator Commentary: Triplet Pomalidomide-Based Therapies for Patients with Relapsed/Refractory MM

Carfilzomib-based 3-drug combinations, such as the one studied in the ASPIRE trial (*N Engl J Med* 2015;372:142), have set a high bar that will be hard to beat. Each of these current trials was a Phase II study evaluating a pomalidomide-based triplet regimen for patients with relapsed/refractory MM. As is typical for this type of study, the sample sizes were relatively small. The study by Baz and colleagues evaluated pomalidomide/dexamethasone versus pomalidomide/cyclophosphamide/dexamethasone. The authors concluded that the 3-drug combination translated into better response and PFS rates. Similar results were reported with the study of PVD.

So compared to a 2-drug combination, these 3-drug combinations of an IMiD/dexamethasone with either a proteasome inhibitor or cyclophosphamide produce deeper, longer-lasting responses. The depth of response was less with the combination containing cyclophosphamide, however. These combinations provide some more options for 3-drug therapy for patients who do not have access or have contraindications to carfilzomib.

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