



POST-ASH Issue 2, 2015

**Phase I/II Study of Weekly
Carfilzomib, Cyclophosphamide
and Dexamethasone in Patients
with Newly Diagnosed 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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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:

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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

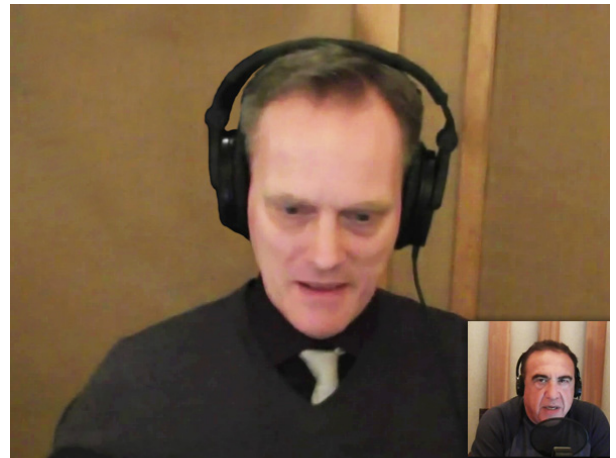
Last review date: March 2015

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

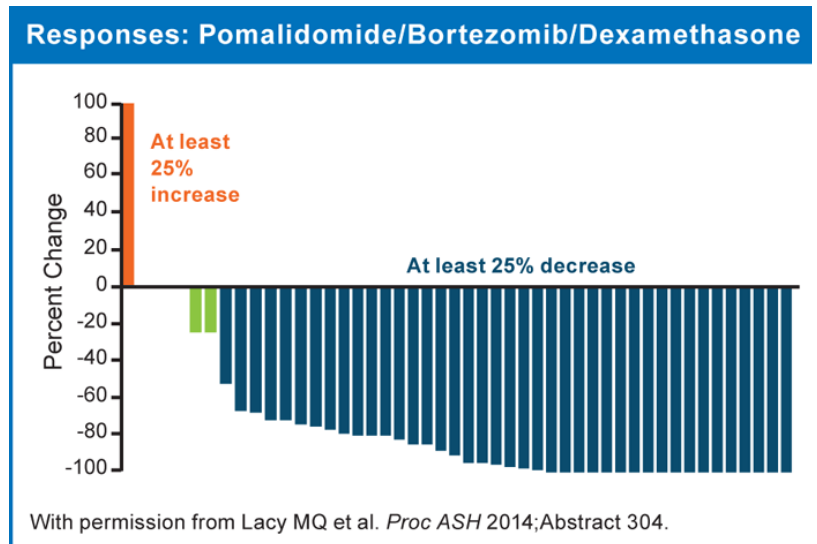
on the trial was 65 and that no difference was observed in benefit between younger and older individuals. In fact, the oldest trial participant was an 88-year-old man. As such, he sees no reason not to use the most effective induction regimen available, even in older patients.

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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Phase I/II Study of Weekly Carfilzomib, Cyclophosphamide and Dexamethasone in Patients with Newly Diagnosed MM

Presentation discussed in this issue

Palumbo A et al. **Weekly carfilzomib, cyclophosphamide and dexamethasone (wCCd) in newly diagnosed multiple myeloma patients: A phase I-II study.** *Proc ASH 2014*; **Abstract 175**.

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

Weekly Carfilzomib, Cyclophosphamide and Dexamethasone (wCCd) in Newly Diagnosed Multiple Myeloma Patients: A Phase I-II Study

Palumbo A et al.

Proc ASH 2014; Abstract 175.

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Background

- Carfilzomib is a second-generation proteasome inhibitor with significant activity and a favorable toxicity profile, including limited neurotoxicity and neutropenia in patients with multiple myeloma (MM).
- The agent is administered as a twice-weekly infusion. However, administration could become more feasible and patient friendly if a weekly infusion schedule were adopted.
- **Study objective:** To determine the maximum tolerated dose (MTD) of once-weekly carfilzomib combined with cyclophosphamide and dexamethasone (wCCd) and to assess the efficacy and safety of this combination in elderly patients with newly diagnosed MM.

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Rationale for Investigating a Once-Weekly Schedule of Carfilzomib

	Bortezomib twice weekly	Bortezomib once weekly	p-value
Complete response	35%	30%	0.27
3-year progression-free survival	47%	50%	1.00
3-year overall survival	89%	88%	0.54
Hematologic adverse events (AEs)	45%	44%	0.83
Nonhematologic AEs	51%	35%	0.003
Peripheral neuropathy	28%	8%	<0.001
Gastrointestinal AEs	11%	6%	0.08
Median dose intensity	59%	84%	<0.001
Dose reduction	41%	17%	<0.001
Discontinuation	15%	5%	<0.001

Palumbo A et al. *Proc ASH* 2014;Abstract 175; Brinchen S et al. *Blood* 2010;116(23):4745-53.

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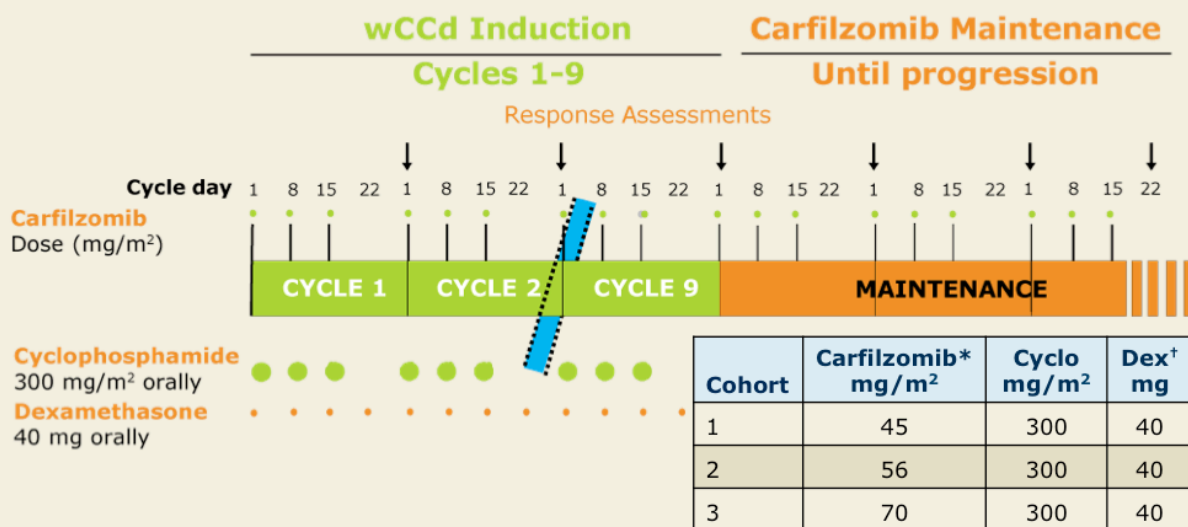
Patient Eligibility

- Symptomatic newly diagnosed MM
- ≥65 years of age or ineligible for autologous stem cell transplant
- Measurable disease (≥0.5 g/dL of M-protein or urine light-chain excretion of >200 mg/24 hours)
- ECOG PS 0-2
- Adequate hepatic function (ALT ≤3.5 times the upper limit of normal and serum direct bilirubin ≤2 mg/dL)
- Creatinine clearance ≥15 mL/min
- No prior systemic therapy for MM
- No relapsed or refractory disease
- No history of severe heart disease
- No uncontrolled hypertension or congestive heart failure

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Phase I/II Trial Design



* All patients received 20 mg/m² carfilzomib on D1 of cycle 1; subsequent doses were escalated to the indicated levels; † Or 20 mg of dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Preliminary Response Data

	Phase I (n = 12)	MTD - 70 mg/m ² (n = 19)	Total (n = 28)
Median cycles received, n (range)	9 (1-9)	4 (1-9)	8 (1-9)
Overall response rate (≥PR)	92%	79%	86%
≥VGPR	75%	58%	64%
sCR + CR + nCR	33%	21%	25%

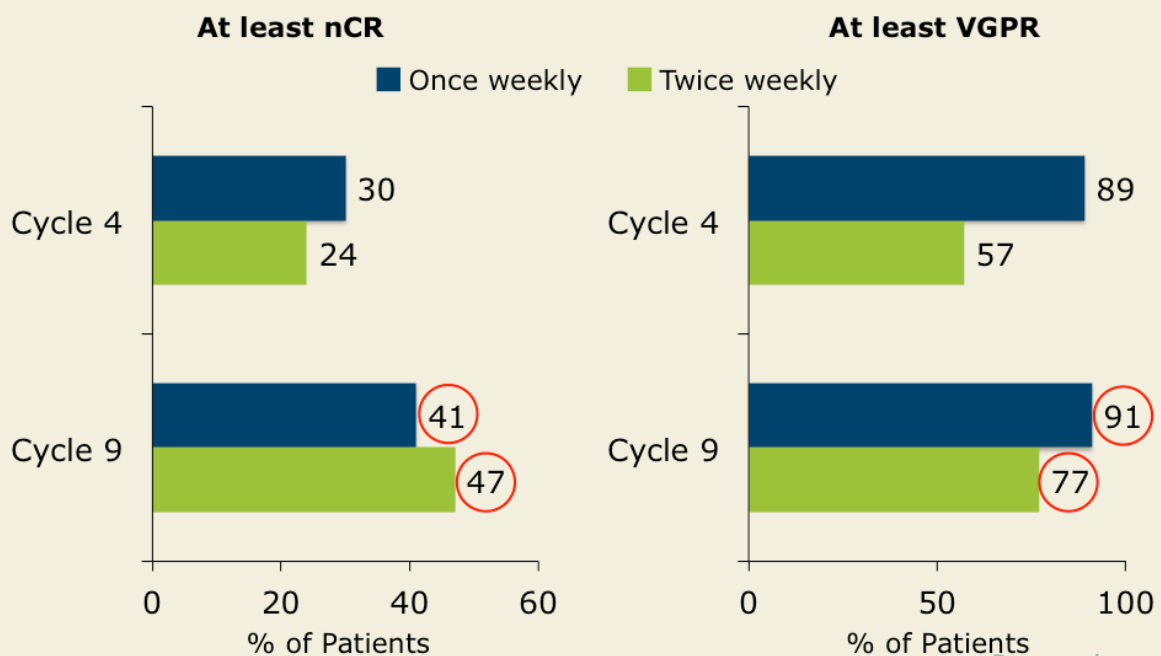
- 28 of 30 patients were evaluable for response (2 patients not evaluable for response due to early discontinuation [pulmonary edema] and first cycle ongoing)
- Median time to first response (≥PR) was 1 month
- Median duration of response not reached

PR = partial response; VGPR = very good partial response; sCR = stringent complete response; nCR = near complete response

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Response Rate by Treatment Duration



Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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AE Summary

	Phase I (n = 12)	MTD (n = 21)	Total (n = 30)
Any serious AE (SAE)	8%	19%	17%
Any treatment-related SAE	8%	19%	13%
Dose reduction due to AE	25%	0%	10%
On-study death	0%	5%	3%

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Key Objectives Summary

	CCd once weekly	CCd twice weekly
≥nCR*	41%	47%
PR*	99%	91%
Grade 3 or 4 hematologic AE	23%	27%
Grade 3 or 4 nonhematologic AE	30%	29%
Median delivered carfilzomib dose*	3,534 mg	2,904 mg
Dose reduction	10%	21%
Discontinuation	13%	14%

* After 9 cycles of CCd

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Author Conclusions

- This is the first prospective study evaluating once-weekly carfilzomib for patients with treatment-naïve MM.
- wCCd therapy appears to be safe and effective in patients with newly diagnosed MM.
- Responses became deeper with subsequent cycles, and toxicities were manageable.
- The response rate observed with weekly carfilzomib, compares favorably to that seen in similar studies of standard twice-weekly carfilzomib infusion.
- These are early results, and longer follow-up is required to confirm these observations.

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

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Investigator Commentary: A Phase I/II Study of wCCd in Newly Diagnosed MM

This relatively small Phase I/II study evaluated carfilzomib with cyclophosphamide and dexamethasone, which is a variant of CyBorD. CyBorD has been found among various groups to be a combination that works. People have started implementing it, but we do not have many data to back that combination up.

This study used the combination of bortezomib/cyclophosphamide and dexamethasone as the framework, but they replaced bortezomib with carfilzomib. The investigators used the once-a-week dosing for carfilzomib, which was day 1, 8 and 15 at a MTD of 70 mg/m². The results were clearly interesting and indicate that you can deliver carfilzomib therapy once a week.

This combination was not quite as efficacious as the combination of carfilzomib, lenalidomide and dexamethasone, but cyclophosphamide is a much cheaper drug and the use of lenalidomide as up-front treatment is not yet approved in certain parts of the world, such as Europe. So I do believe that this combination could be of major interest in many instances. It could also be used in situations in which lenalidomide is contraindicated.

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

continued

Investigator Commentary: A Phase I/II Study of wCCd in Newly Diagnosed MM (continued)

Another feature of this study that's a bit unique is that after they delivered the 9 cycles of wCCd, they administered carfilzomib as maintenance therapy. That has not really been done in many other studies. It's interesting to use this agent as a maintenance therapy.

At this point we are still using the twice-a-week dosing of carfilzomib because that's what is approved by the FDA and that's where all the strong data currently are. But I do think that, based on preliminary data that are coming out as we speak, it seems that the once-a-week schedule at a little higher dose could be equal to a lower dose twice a week. It's likely that we will soon switch over to once a week. This would be a major improvement for patients because coming into the clinic twice a week has an effect on their lifestyle.

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

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