Treatment Outcome with Carfilzomib, Lenalidomide and Dexamethasone for Newly Diagnosed and Relapsed/Refractory Multiple Myeloma
CME INFORMATION

OVERVIEW OF ACTIVITY
Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. Unlike ASCO, EHA does not offer access to any of the poster or plenary presentations from the annual meeting via the Internet. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents in multiple myeloma from the latest ASCO and EHA meetings, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

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

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: September 2013
Expiration date: September 2014
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.

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.

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Treatment Outcome with Carfilzomib, Lenalidomide and Dexamethasone for Newly Diagnosed and Relapsed/Refractory Multiple Myeloma

Presentations discussed in this issue


Slides from presentations at ASCO 2013/EHA 2013 and transcribed comments from recent interviews with Antonio Palumbo, MD (8/20/13) and Andrzej J Jakubowiak, MD, PhD (8/28/13)
Treatment Outcome with the Combination of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) for Newly Diagnosed Multiple Myeloma (NDMM) After Extended Follow-Up

Jakubowiak AJ et al.
Proc ASCO 2013;Abstract 8543.

Background

- Carfilzomib (CFZ) is a novel proteasome inhibitor with proven activity as a single agent and a manageable toxicity profile.
- It can be administered for an extended duration without significant treatment-related peripheral neuropathy (Blood 2012;120:2817).
- Earlier data from this Phase I/II trial of CFZ in combination with lenalidomide and low-dose dexamethasone (CRd) showed promising activity and depth of response in patients with NDMM (Blood 2012;120:1801).
  - Overall response rate: 98% after a median of 12 cycles
- **Study objective**: To report updated results from the Phase I/II trial for patients with NDMM after an extended treatment duration with CRd.

Phase I/II Trial Design

Eligibility (n = 53)

- Newly diagnosed Stages I-III multiple myeloma
- Transplant eligible and ineligible
- Symptomatic disease
- No Grade 3/4 peripheral neuropathy

CRd Induction

CRd Cycles 1-4

CRd Cycles 5-8

CRd Cycles 9-24

LEN Cycles 25+

CRd Maintenance

Transplant-eligible

≥PR

ASCT

Until disease progression or unacceptable toxicity

Stem cell collection

- Primary endpoints: Safety and maximum tolerated dose (Phase I); complete response (CR), near CR (nCR) and stringent CR (sCR) (Phase II)


Best Response (n = 53*)

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Median: 12 cycles</th>
<th>Median: 22 cycles †</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥Partial response (PR)</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>≥Very good PR</td>
<td>81%</td>
<td>87%</td>
</tr>
<tr>
<td>≥nCR</td>
<td>62%</td>
<td>74%</td>
</tr>
<tr>
<td>CR</td>
<td>47%</td>
<td>62%</td>
</tr>
<tr>
<td>sCR</td>
<td>42%</td>
<td>55%</td>
</tr>
<tr>
<td>Immunophenotypic CR (iCR)</td>
<td>40%</td>
<td>50% ‡</td>
</tr>
</tbody>
</table>

* Intention-to-treat population, including patients who stopped treatment early
† After an additional follow-up of 12 months
‡ Estimate of MRD-negative disease based on percentage of patients in sCR at 12 months (18/19) and at 22 months (22/24)

Time to Response

![Graph showing time to response](image)

Median time to response, mo
- ≥PR: 0.9
- ≥VGPR: 3.7
- ≥nCR: 6.7
- CR: 11.0
- sCR: 13.1

With permission from Jakubowiak AJ et al. Proc ASCO 2013;Abstract 8543.

Response After Extended Treatment

![Bar chart showing response percentages](image)

- nCR: 74%
- sCR*: 82%

* Of patients who achieved sCR, 25% had high-risk cytogenetics

With permission from Jakubowiak AJ et al. Proc ASCO 2013;Abstract 8543.
**Best Response in a Subset of Patients Who Did Not Proceed to Receive ASCT**

<table>
<thead>
<tr>
<th>Response rate</th>
<th>All patients (n = 53)</th>
<th>No transplant* (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥PR</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>≥Very good PR</td>
<td>87%</td>
<td>91%</td>
</tr>
<tr>
<td>≥nCR</td>
<td>74%</td>
<td>78%</td>
</tr>
<tr>
<td>sCR</td>
<td>55%</td>
<td>61%</td>
</tr>
</tbody>
</table>

ASCT = autologous stem cell transplantation

* Includes transplant-ineligible patients and/or those who deferred transplantation for various reasons


**Survival Outcomes**

**Progression-free survival (PFS)**

- Median follow-up: 25 months (range 5-37)
- 24-month rate 94%*

**Overall survival (OS)**

- Median follow-up: 25 months (range 5-37)
- 24-month rate 98%†

* For patients in sCR, the estimated 24-month PFS was 97%
† For patients in sCR, the estimated 24-month OS was 100%

With permission from Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.
Adverse Events* (n = 44)

* After a median of 16 months of CRd maintenance
- Peripheral neuropathy was limited to Grade 1 (32%) and Grade 2 (9%)

With permission from Jakubowiak AJ et al. Proc ASCO 2013;Abstract 8543.

Author Conclusions

- For patients with NDMM, CRd demonstrated rapid responses, with the depth of response improving over the duration of treatment.
- After an additional 12 months of CRd treatment and follow-up, the best response rates improved:
  - VGPR from 81% to 87%
  - ≥nCR from 62% to 74%
  - sCR from 42% to 55%
- Treatment with CRd resulted in a high rate of MRD-negative disease in 22 of 24 patients (92%) with sCR.
- The median PFS and OS were not reached after a median follow-up of 25 months.
  - 2-year PFS: 94%
  - 2-year OS: 98%

Author Conclusions (Continued)

- The CRd regimen was well tolerated after an extended treatment period.
  - Generally, toxicities were of mild to moderate severity.
  - The most common hematologic adverse event was thrombocytopenia, and infection was the most common nonhematologic adverse event.
- The response rates achieved in this study compare favorably to those seen in previous studies (Lancet Oncol 2010;11:29).
- Other Phase II studies for patients with NDMM are ongoing (Proc ASH 2012;Abstract 732).
- The Phase III ASPIRE trial for patients with relapsed multiple myeloma has been initiated (NCT01080391).


ASPIRE Phase III Trial Design

Estimated Enrollment: 780 (Closed)

Eligibility
Symptomatic, relapsed disease after 1 to 3 prior therapies
No prior CFZ or intolerance to lenalidomide or dexamethasone

Lenalidomide/dexamethasone arm

Cycles 1-12 (28 days each)
- Carfilzomib
days 1, 2, 8, 9, 15, 16
- Dexamethasone
days 1, 8, 15, 22
- Lenalidomide
days 1-21

Cycles 13-18 (28 days each)
- Carfilzomib
days 1, 2, 15, 16
- Dexamethasone
days 1, 8, 15, 22
- Lenalidomide
days 1-21

Cycles 19 and higher (28 days each)
- Dexamethasone
days 1, 8, 15, 22
- Lenalidomide
days 1-21

For more visit ResearchToPractice.com/5MJCHEM2013
Investigator Commentary: Updated Results of the Phase I/II Trial of CRd for Patients with NDMM After Extended Follow-Up

The CRd regimen in this population of younger patients yielded a stringent complete response rate of 42% after 12 cycles and 55% after 22 cycles. This is certainly an improvement over cyclophosphamide-containing regimens or even the RVD regimen. The time-to-response results are interesting. I would stress that more time was required to achieve complete response and stringent complete response. One might consider that around 30% of patients will achieve stringent complete responses after 1 year of therapy.

The time-to-response curves demonstrate that stopping therapy after 4 to 6 months will result in about a 70% decrease in the complete response rate. This is a relevant message for a physician because it indicates that short-term treatment is not a good idea. With increased toxicity, treatment should be stopped or the dose reduced, but short flashes of treatment certainly reduce the opportunity to achieve good response rates that translate into long-term duration of remission.

*Interview with Antonio Palumbo, MD, August 12, 2013*

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Final Results from the Phase Ib/II Study (PX-171-006) of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Patients with Relapsed or Progressive Multiple Myeloma

Wang M et al.
*Proc ASCO 2013;Abstract 8529.*

Niesvizky R et al.
*Proc EHA 2013;Abstract S577.*
# Background

- Carfilzomib (CFZ) is a selective proteasome inhibitor that is FDA approved as a single agent in the treatment of patients with relapsed or refractory multiple myeloma (MM).

- Previously, data from the Phase Ib portion of the PX-171-006 trial of CFZ in combination with lenalidomide and low-dose dexamethasone (CRd) for relapsed or progressive MM were reported (Clin Cancer Res 2013;19:2248).
  - The maximum tolerated dose (MTD) was not reached.
  - The maximum planned dose (MPD) showed promising safety and efficacy and was recommended for the Phase II study.

- **Study objective:** To report the final efficacy and safety results from the Phase Ib/II PX-171-006 trial with particular attention to the MPD cohort.


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# Phase Ib/II Trial Design

**Eligibility (n = 84)**

- Relapsed or progressive MM
- Symptomatic disease
- 1-3 prior regimens including bortezomib, lenalidomide and/or thalidomide
- \( \geq 1 \) minimal response to prior therapy

**CRd (n = 84)**

- CFZ: 15-27 mg/m\(^2\) (IV), biweekly
- Len: 10-25 mg (PO), days 1-21
- Dex: 40 mg (PO), weekly

- **28-day cycle x \( \leq 12 \)**

- CFZ dosing was modified during cycles 13-18 (maintenance)

Len = lenalidomide; Dex = dexamethasone

- **Primary endpoints:** (Phase Ib) safety and determination of MTD or MPD

- **Secondary endpoints:** (Phase Ib/II) overall response rate (ORR), duration of response (DoR), progression-free survival (PFS)

- Response was assessed on day 15 of cycle 1 and on day 1 of subsequent cycles

### Study Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CFZ</th>
<th>Len</th>
<th>Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 6)</td>
<td>15 mg/m²</td>
<td>10 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>2 (n = 6)</td>
<td>15 mg/m²</td>
<td>15 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>3 (n = 8)</td>
<td>15 mg/m²</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>4 (n = 6)</td>
<td>20 mg/m²</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>5 (n = 6)</td>
<td>20 mg/m²</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>6/7 (MPD, n = 52)</td>
<td>20/27 mg/m²*</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

*CFZ: 20 mg/m², d1-2 during cycle 1; 27 mg/m² thereafter


### Best Response

<table>
<thead>
<tr>
<th>Response</th>
<th>MPD cohort (n = 52)</th>
<th>Overall (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>76.9%</td>
<td>69.0%</td>
</tr>
<tr>
<td>Stringent CR</td>
<td>3.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Very good PR</td>
<td>36.5%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>34.6%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Minimal response</td>
<td>0%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

Median duration of response: 22.1 mo (MPD cohort), 18.8 mo (overall)
Median time to response ≥PR: 1.0 mo for both groups

PFS Outcomes

MPD Cohort (N=52)
Median 15.4 months (95% CI 7.9-27.0)

Overall (N=84)
Median 11.8 months (95% CI 7.6-20.7)


Efficacy Results by Patient Subgroup

<table>
<thead>
<tr>
<th>Len naïve</th>
<th>ORR</th>
<th>Median DoR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD cohort (n = 14)</td>
<td>85.7%</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Overall (n = 25)</td>
<td>80%</td>
<td>21.4 mo</td>
<td>28.7 mo</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Len refractory</th>
<th>ORR</th>
<th>Median DoR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD cohort (n = 22)</td>
<td>68.2%</td>
<td>23.5 mo</td>
<td>9.9 mo</td>
</tr>
<tr>
<td>Overall (n = 29)</td>
<td>58.6%</td>
<td>13.8 mo</td>
<td>9.9 mo</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Bortezomib refractory</th>
<th>ORR</th>
<th>Median DoR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD cohort (n = 14)</td>
<td>71.4%</td>
<td>18.5 mo</td>
<td>12.9 mo</td>
</tr>
<tr>
<td>Overall (n = 17)</td>
<td>58.8%</td>
<td>18.5 mo</td>
<td>9.9 mo</td>
</tr>
</tbody>
</table>

Select Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>MPD cohort (n = 52)</th>
<th>Overall (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69.2%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>40.4%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>38.5%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36.5%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>32.7%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30.8%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>26.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>23.1%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17.3%</td>
<td>11.5%</td>
</tr>
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</table>


Author Conclusions

- The CRd regimen provided robust, rapid and durable responses in patients with relapsed or progressive MM.
  - This included 35% of patients in the overall population with lenalidomide–refractory MM.
  - Median PFS in the 30% of patients in the overall population with lenalidomide-naïve MM was 28.7 months.
  - Response rates and safety data in the MPD cohort compared favorably to the overall study population.
- CRd had an acceptable safety and tolerability profile with infrequent CFZ dose reductions (data not shown) and Grade 3 neuropathy and moderate discontinuation rates due to adverse events.
- Ongoing studies evaluating the CRd regimen include several Phase II trials in NDMM and the Phase III ASPIRE trial for patients with relapsed MM (NCT01080391).

Investigator Commentary: Final Results of the Phase Ib/II PX-171-006 Trial of CRd in Relapsed or Progressive MM

This important Phase Ib/II trial with 84 patients with relapsed/refractory MM has been presented before, and in fact it was the initial unpublished data from this study that gave us confidence to evaluate CRd in our up-front trial. However, the maximum planned dose of carfilzomib in this trial was 27 mg/m² and it was not escalated further, whereas in our trial our maximum planned dose was 36 mg/m² and we never reached MTD. This is important because the activity of carfilzomib is dose dependent. It is also clear that carfilzomib is more active in patients with less prior treatment. Currently I almost exclusively use carfilzomib in combination with other agents, both approved and as part of trials such as those combining it with HDAC inhibitors.

*Interview with Andrzej J Jakubowiak, MD, PhD, August 28, 2013*