# 5 Minute JournalClub

**POST-ASH** Issue 5, 2013

# Phase II Study of Carfilzomib, Lenalidomide and Dexamethasone for Newly Diagnosed Multiple Myeloma

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can 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

- Consider the benefits and risks of the investigational agent MLN9708 for patients with previously untreated multiple myeloma.
- Evaluate the efficacy and safety of carfilzomib with or without immunomodulatory drugs for newly diagnosed or relapsed/refractory multiple myeloma.
- Assess emerging clinical trial data on the novel combination of bendamustine, bortezomib and dexamethasone in relapsed/refractory multiple myeloma.
- Determine the maximum tolerated dose of pomalidomide in combination with bortezomib and low-dose dexamethasone for relapsed or relapsed/refractory multiple myeloma.
- Compare and contrast the effects of bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide to those of bortezomib/melphalan/prednisone on the overall survival of patients with relapsed/refractory multiple myeloma.

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Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Onyx Pharmaceuticals Inc, Sanofi; Other Remunerated Activities: Acetylon Pharmaceuticals Inc.

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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

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POST-ASH Issue 5, 2013

# New proteasome inhibitor-based combination regimens in multiple myeloma

To go directly to slides and commentary for this issue, **click here**.

Dr Ken Anderson's memorable Karnofsky Award presentation at ASCO 2011 provided an intriguing overview of how profoundly the clinical face of multiple myeloma (MM) has changed in the postchemotherapy era, and the recent approval of 2 new agents is additional evidence of how quickly things are moving forward. In a previous issue of this series we focused on immunomodulatory drugs, including the recently (February 8) FDA-approved pomalidomide (Pom) for relapsed/refractory disease, and in this issue we look at the other key class of agents that has revolutionized the treatment of MM, proteasome inhibitors, which were the focus of Dr Anderson's lecture and much of his clinical and laboratory research at Dana-Farber.

In retrospect, it seems intuitive to block the mechanism by which proteins are processed and excreted in cells that are noteworthy for protein overproduction — specifically immunoglobulins — but while the translational science behind these molecules is fascinating, perhaps more important is the bottom line in terms of patient impact. In a recent ***JCO* editorial** Drs Sagar Lonial and Jonathan Kaufman make a compelling argument that in stark contrast to, for example, metastatic breast cancer, where sequential single agents are used, in MM combination regimens, although not usually curative, seem to yield better long-term outcomes. As bortezomib (BTZ) is a standard part of 2 of the most commonly used pretransplant induction regimens — RVD and CyBorD — and carfilzomib is now available for general use, it is easy to see how crucial these agents have become. Even more, at ASH we saw many interesting papers looking at various new proteasome inhibitor-based combinations that may one day soon be a part of the next generation of MM care.

## 1. Carfilzomib (CFZ)

This first-in-class irreversible proteasome inhibitor was approved last July for relapsed/refractory disease, but even before then there was considerable interest in testing it up front. At ASH 2011 Dr Andrzej Jakubowiak presented impressive Phase I findings with "CRd" in which the proteasome inhibitor was CFZ rather than BTZ, and this year an

NCI team added to the database by reporting **a Phase II trial of 15 patients**. Once again this combo was found to have a profound antimyeloma effect (14 responses) with acceptable tolerability and no reported Grade ≥3 peripheral neuropathy (PN).

Similarly, Dr Antonio Palumbo presented results from **a Phase II trial evaluating another CFZ combination** (CFZ/cyclophosphamide/low-dose dexamethasone [dex], or CCd) as up-front therapy in 58 patients over age 65 or ineligible for transplant. Study participants received 9 cycles of CCd followed by CFZ maintenance until progression. Of note, responses were seen in all patients, including those with adverse cytogenetics, and the progression-free survival at 1 year was 88%. Again, no Grade ≥3 PN was reported.

Finally, in the relapsed/refractory setting, **yet another CFZ triplet — CFZ/Pom/low-dose dex — showed encouraging activity**, with 15 of 30 patients responding, including many who had received extensive prior treatment and/or had adverse cytogenetics.

**2. Ixazomib**

Formerly MLN9708, this boron acid-based proteasome inhibitor in clinical trial development is similar to BTZ but not only seems to cause less PN but is also orally administered, opening up the enticing possibility of an all-oral RVD-like induction regimen. At ASH we saw **updated data from a Phase I/II study** of ixazomib/lenalidomide/low-dose dex in 64 patients with previously untreated MM. Importantly, 92% responded and only 2 developed Grade 3 PN (3%), helping to significantly increase enthusiasm for ongoing Phase III efforts evaluating this combination versus lenalidomide/low-dose dex in previously untreated patients.

**3. More on bortezomib**

Bendamustine has a similar structure to alkylating agents and is thought to perhaps have synergistic activity with BTZ. For that reason, **a Phase II study looked at a CyBorD-like** regimen in which bendamustine was substituted for cyclophosphamide. Although significant activity was observed, including responses in 48 of 71 patients (68%), it is unclear whether this regimen will be used in US practice until further data emerge.

As usual Dr Paul Richardson was quite busy at ASH, and among his oral presentations was a **Phase I study evaluating BTZ/Pom/low-dose dex** in patients with relapsed/refractory MM. While data from only 15 patients were reported, the results suggest that BTZ in combination with POM is well tolerated and highly active, further justifying the ongoing Phase III clinical trial examining this strategy.

While we are all familiar with triplet regimens, many have wondered whether 4-drug combos might provide even greater benefit, and to that end, at ASH Dr Palumbo provided **updated results from his Phase III study** of BTZ/melphalan/prednisone/thalidomide (VMPT) with VT maintenance versus VMP alone in patients who were not transplant candidates. Previous reports showed that the quartet plus maintenance provided significantly longer disease control, and in Atlanta we came to learn that it also resulted in an overall survival advantage (HR 0.7). Of interest, patients (particularly those older than 75 years of age) in the VMPT-VT arm more commonly had to discontinue therapy or reduce the BTZ dose, suggesting that less intense therapy might be preferable, but Dr Anderson believes that subcutaneous weekly BTZ may allow more patients to be treated with this approach.

Next on this series… You've heard of "R squared" (lenalidomide/rituximab). How about "R squared/CHOP"? Check out our coverage of 2 major papers on this regimen in diffuse large B-cell lymphoma and other related ASH lymphoma papers.

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# Phase II Study of Carfilzomib, Lenalidomide and Dexamethasone for Newly Diagnosed Multiple Myeloma

## Presentation discussed in this issue

Korde N et al. **Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed multiple myeloma (MM) patients.** *Proc ASH* 2012;**Abstract 732**.

## Slides from a presentation at ASH 2012 and transcribed comments from recent interviews with A Keith Stewart, MBChB (1/9/13) and Kenneth C Anderson, MD (1/22/13)

# Background

- Carfilzomib (CFZ) is an irreversible proteasome inhibitor with potent antimyeloma effects and a significantly decreased incidence of peripheral neuropathy compared to bortezomib (*Onco Targets Ther* 2012;5:237).
- A Phase I/II study of CFZ in combination with lenalidomide (LEN) and low-dose dexamethasone (CRd) as front-line treatment for MM showed that the regimen was well tolerated with exceptional response rates (*Blood* 2012;120:1801).
- Therefore, this single-stage Phase II trial of front-line CRd followed by 1 year of LEN maintenance for transplant-eligible patients with MM defaulting to "delayed" ASCT was initiated.
- **Study objective:** Evaluate the efficacy and safety of the CRd regimen in patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2012;Abstract 732.

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# Phase II Study Eligibility and Endpoints (Abstract Only)

- **Eligibility:**
  - Newly diagnosed, untreated MM
  - Transplant-eligible and ineligible patients
- **Primary endpoint:** Incidence of Grade ≥3 neuropathy
- **Secondary objectives:**
  - Response rate
  - Profiling CFZ activity to biological endpoints
  - Impact of minimal residual disease (MRD) studies on clinical outcomes

Korde N et al. *Proc ASH* 2012;Abstract 732.

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# Phase II Study Methods (Abstract Only)

- Treatment consists of eight 28-d cycles of:
  - CFZ, 20/36 mg/m$^2$ IV (d1, 2, 8, 9, 15, 16)
  - LEN, 25 mg PO (d1-21)
  - Dexamethasone, 20/10 mg IV/oral (d1, 2, 8, 9, 15, 16, 22, 23)
- Transplant-eligible patients default to "delayed" ASCT per protocol by harvesting/cryopreserving stem cells after 4 cycles of CRd, followed by treatment continuation for cycles 5-8
- After 8 cycles of CRd, patients with ≥stable disease receive cycles 9-20 of LEN maintenance (10 mg; d1-21)
- Bone marrow samples collected at baseline, cycle 1/d2, CR/end of cycle 8 and CR/end of cycle 20
- Molecular responses are assessed by MRD studies using flow cytometry, PCR and FDG PET-CT on achievement of CR/end of cycle 8 (during cycles 1–8) and CR/end of cycle 20 (during cycles 9–20)

Korde N et al. *Proc ASH* 2012;Abstract 732.



# Best Response After a Median of 4 CRd Cycles (Abstract Only)

| Response | n = 15 |
|---|---|
| **ORR** | 93% |
| **VGPR** | 5 (33%) |
| **sCR + nCR** | 6 (40%) |
| **PR** | 3 (20%) |
| **SD** | 1 (6%) |

- Median time from initiation of CRd to sCR: 5 cycles
- 4 patients with sCR had no evidence of immunophenotypic abnormal plasma cells by flow cytometry during MRD assessment
- PET-CT results for 3 of 4 patients who achieved sCR showed a substantial decrease in maximum standardized uptake value (SUV) avid lytic lesion from baseline (average SUV decline: 76%)
- All patients maintained their best response and have no evidence of clinical disease progression

Korde N et al. *Proc ASH* 2012;Abstract 732.

# Select Grade ≥3 Adverse Events (Abstract Only)

| Grade ≥3 AE | (n = 15) |
|---|---|
| **Hematologic** | |
| **Lymphopenia** | 10 (66%) |
| **Thrombocytopenia** | 1 (6%) |
| **Nonhematologic** | |
| **Hypophosphatemia** | 3 (20%) |
| **ALT increase** | 2 (13%) |
| **Congestive heart failure** | 2 (13%) |
| **Fatigue** | 1 (6%) |
| **Rash** | 1 (6%) |

- No patients with Grade ≥3 neuropathy

Korde N et al. *Proc ASH* 2012;Abstract 732.

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# Author Conclusions

- Using an approach that merges functional imaging with molecular responses beyond traditional clinical biomarkers, this study showed that CRd followed by LEN maintenance and delayed ASCT is a highly potent and tolerable combination regimen for patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2012;Abstract 732.

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**Investigator Commentary: Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide and Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma**

This study evaluating CFZ in combination with lenalidomide and dexamethasone in the up-front setting reported a high response rate and an impressive complete remission rate. These results are probably the best reported in myeloma to date and were previously only achievable with stem cell transplantation. The fact that these results can be obtained without a transplant offers high hope for patients. One would hope to be able to use this regimen if CFZ receives approval for use in the front-line setting.

***Interview with A Keith Stewart, MBChB, January 9, 2013***

The results from this study demonstrated that the overall response rate to CFZ, lenalidomide and dexamethasone is nearly universal and the extent of the response is also high. The authors evaluated responses using the most stringent criteria that have been used in myeloma. The results highlight that when CFZ is combined with lenalidomide and dexamethasone, the frequency and the extent of the response are exceptional.

***Interview with Kenneth C Anderson, MD, January 22, 2013***