5 Minute JournalClub

POST-ASH Issue 5, 2013

Phase I MM-005 Dose-Escalation Trial of Pomalidomide, Bortezomib and Dexamethasone for Relapsed/ Refractory 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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Harvard Medical School
Director, Jerome Lipper Multiple Myeloma Center
Director, LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
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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

Last review date: April 2013
Expiration date: April 2014

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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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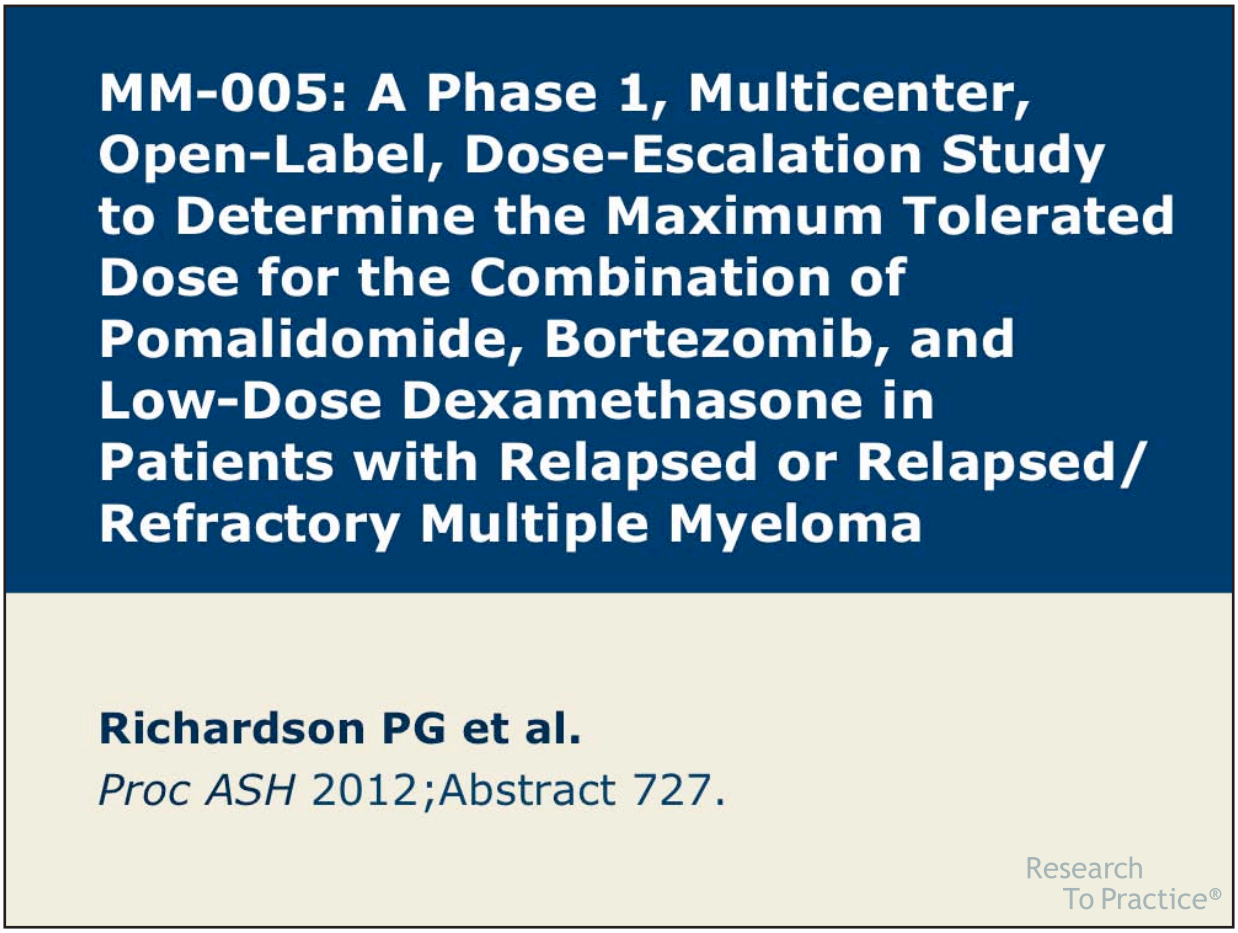
Phase I MM-005 Dose-Escalation Trial of Pomalidomide, Bortezomib and Dexamethasone for Relapsed/Refractory Multiple Myeloma

Presentation discussed in this issue

Richardson PG et al. **MM-005: A Phase 1, multicenter, open-label, dose-escalation study to determine the maximum tolerated dose for the combination of pomalidomide, bortezomib, and low-dose dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.** *Proc ASH* 2012;**Abstract 727**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Kenneth C Anderson, MD (3/29/13)



Background

- Pomalidomide (POM) is a distinct immunomodulatory agent with a mechanism of action involving antimyeloma activity, stromal cell-support inhibition and immune modulation.
- POM combined with low-dose dexamethasone (LoDex), demonstrated activity in relapsed/refractory (RR) multiple myeloma (MM) in patients who had previously received lenalidomide (Len) and/or bortezomib (BTZ) (*Proc ASCO* 2012;Abstract 8016).
- The combination of Len with BTZ (a proteasome inhibitor) and Dex demonstrated preclinical synergy with promising efficacy in the front-line and salvage settings in MM.
- **Study objective:** To determine the maximum tolerated dose (MTD) of POM in combination with BTZ and LoDEX for patients with relapsed or RR MM.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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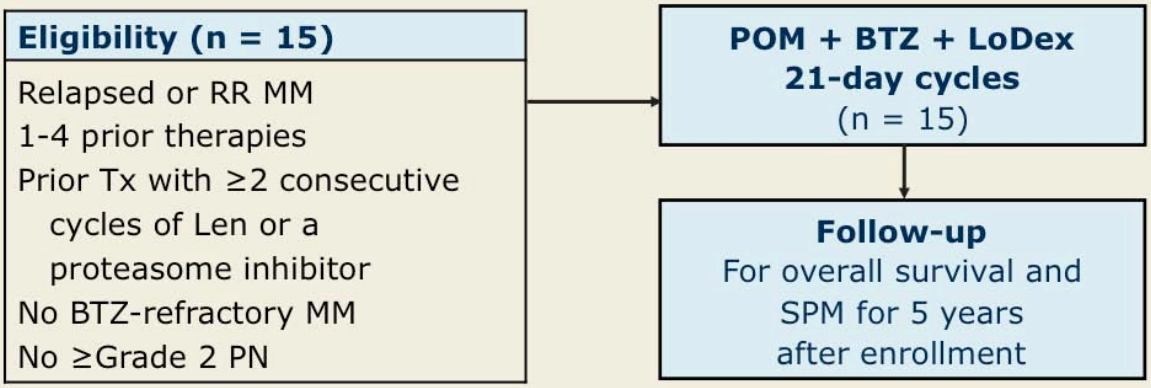
MM-005: Phase I Trial Design



PN = peripheral neuropathy; SPM = second primary malignancy

- **Primary endpoint:** MTD
- **Secondary endpoints included:** Response (IMWG criteria), overall survival and safety
- Patients were evaluated every 21 ± 3 days; supportive care provided as needed.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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3 + 3 Design

Cohort	POM	BTZ	LoDex*
1 (n = 3)	1 mg/d	1 mg/m^2	20 mg
2 (n = 3)	2 mg/d	1 mg/m^2	20 mg
3 (n = 3)	3 mg/d	1 mg/m^2	20 mg
4 (n = 3)	4 mg/d	1 mg/m^2	20 mg
5 (n = 3)	4 mg/d	1.3 mg/m^2	20 mg
Expansion (n = 6)	MTD/maximum planned dose (MPD)		

* 10 mg for patients >75 years

- **POM:** d1-14
- **BTZ:** d1, 4, 8, 11 for cycles 1-8, then d1, 8 from cycle 9 onward
- **LoDex:** d1-2, 4-5, 8-9, 11-12 for cycles 1-8, then d1-2, 8-9 from cycle 9 onward
- **Required concomitant medications:** Aspirin or low-molecular-weight heparin for thromboprophylaxis and an antiviral prophylaxis agent

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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Summary of Best Response

Cohort	VGPR (n)	PR (n)	SD (n)
1 (n = 3)	1	1	1
2 (n = 3)	0	1	2
3 (n = 3)	2	1	0
4 (n = 3)	1	2	0
5 (n = 3)	0	2	1
All patients	**ORR (≥PR)**	**VGPR**	**SD**
Cohorts 1-5 (n = 15)	73%	27%	27%

PR = partial response; VGPR = very good PR; SD = stable disease; ORR = overall response rate

- Median time to response: 1 cycle (range 1-2)
- Most responses are currently ongoing

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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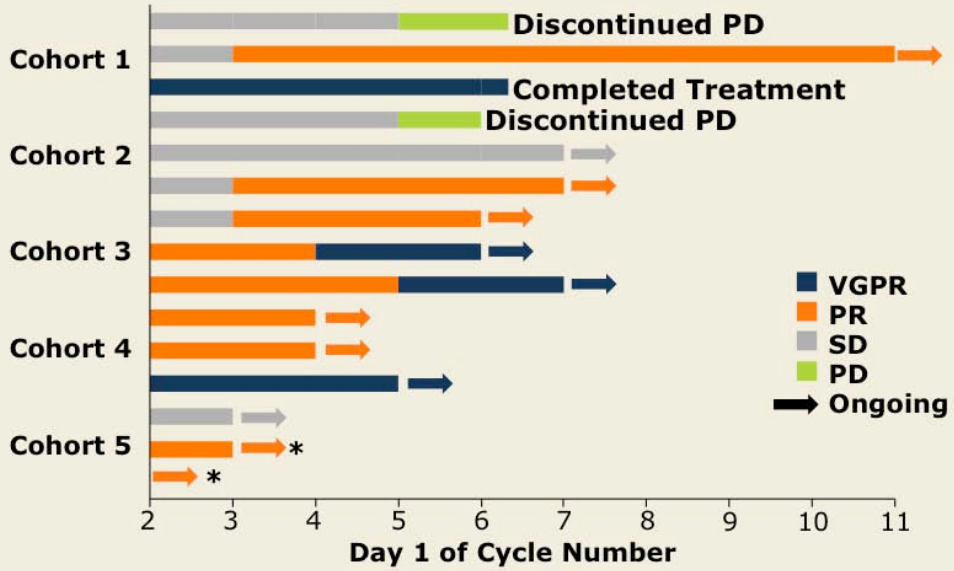
Duration of Response



* Unconfirmed PR as of data cutoff
Total number of completed cycles: 59

With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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Summary of Trial Outcomes

- Total planned enrollment (n = 21)
  - Currently evaluable patients (n = 15)
- 12/15 patients on dose-escalation study remain on treatment
- No dose-limiting toxicities (DLTs) were observed at any dosage
- Confirmation of MTD is ongoing
- With appropriate dose adjustments, no patient discontinued all treatments
  - One patient discontinued BTZ due to persistent Grade 2 PN but continued to receive POM or LoDex, per protocol
- 5 patients have been added to the MTD/MPD expansion cohort, and none experienced DLTs at cycle 1
  - These patients were treated at the dosage administered to Cohort 5

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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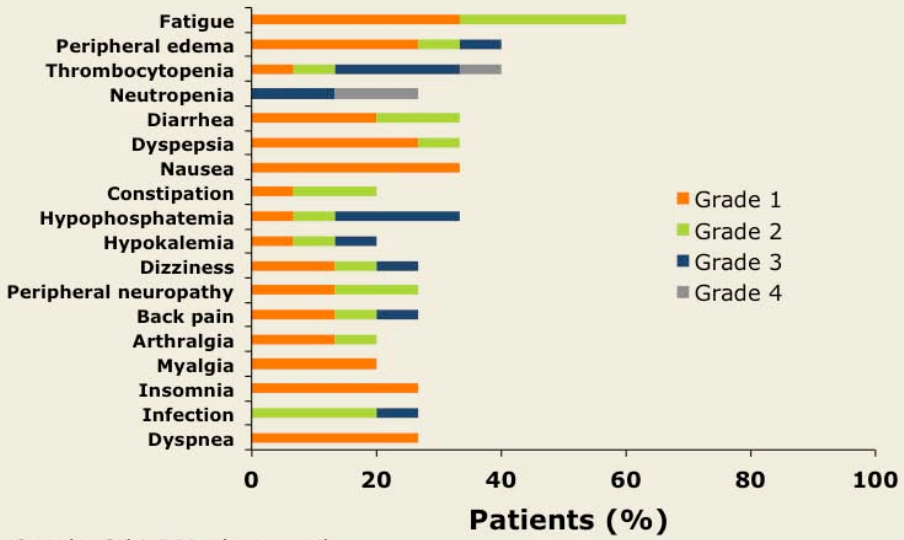
Select Adverse Events (≥20% of Patients)



- No Grade 3/4 PN observed
  - Grades 1 and 2 PN reported for 4 and 2 patients, respectively
- No DVT observed; no treatment discontinuation due to adverse events

With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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Author Conclusions

- The combination of POM with BTZ/LoDex was well tolerated in patients with RR MM.
- POM/BTZ/Dex was active and produced responses in RR MM across all cohorts.
- The efficacy of POM/BTZ/Dex is encouraging with a favorable tolerability profile in the studied population, including those with RR MM harboring adverse cytogenetics (data not shown).
- The MPD identified in this trial will serve as the recommended dose for the recently activated Phase III MM-007 trial comparing POM/BTZ/Dex to BTZ/Dex.
- The observed activity of POM/BTZ/Dex provides a strong rationale for POM use in different therapeutic combinations.
- Phase I/II trials evaluating POM/steroids with other agents are ongoing in RR MM.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

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Investigator Commentary: Phase I MM-005 Dose-Escalation Study of Combination Therapy with POM/BTZ/Dex for RR MM

In this study, POM was escalated from 1 to 4 mg/d and BTZ from 1 to 1.3 mg/m^2. No dose-limiting toxicities were observed at any dose level, and the combination of POM (4 mg) with BTZ (1.3 mg/m^2) and Dex (20 mg) is the regimen for further clinical evaluation. No Grade 3 or 4 peripheral neuropathy or deep vein thrombosis was observed, and none of the patients discontinued therapy. The ORR was 73%, with 27% VGPR and 27% stable disease.

POM received accelerated FDA approval based on a Phase II trial demonstrating an ORR of 34% and an overall survival of approximately 14 months. Preclinical studies demonstrated that the combination of the immunomodulatory drugs thalidomide or lenalidomide with proteasome inhibitors mediates synergistic myeloma cytotoxicity, and clinical trials demonstrated high overall and extent of response. This study suggests that the addition of BTZ to the next-generation and more potent immunomodulatory drug POM markedly enhances response and is well tolerated. It has provided the framework for an ongoing Phase III clinical trial of BTZ/Dex versus POM/BTZ/Dex for patients with relapsed or refractory MM.

Interview with Kenneth C Anderson, MD, March 29, 2013