5 Minute JournalClub

POST-ASH Issue 5, 2013

Phase I/II Study of Carfilzomib, Pomalidomide 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
Boston, Massachusetts

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
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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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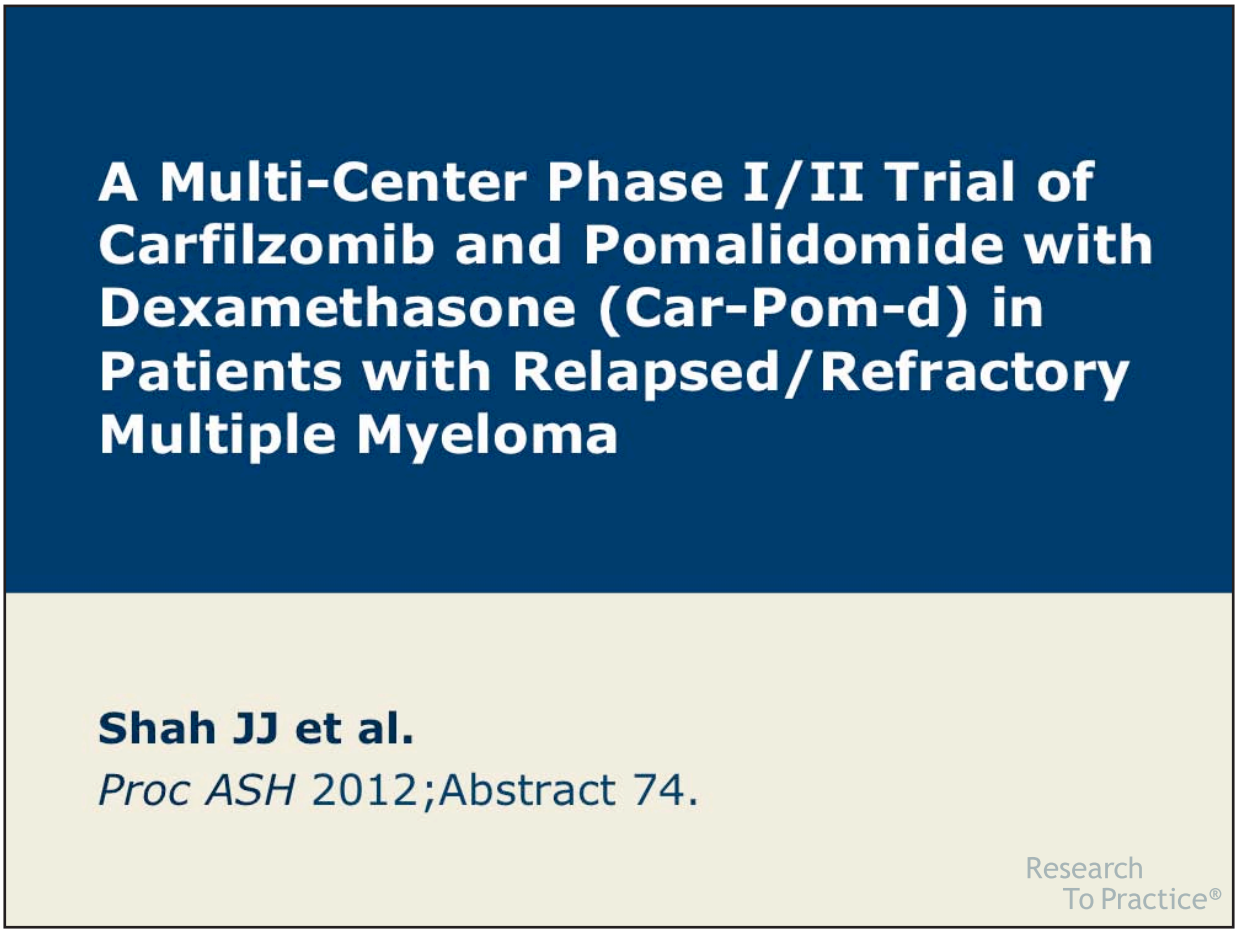
Phase I/II Study of Carfilzomib, Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma

Presentation discussed in this issue

Shah J et al. **A multi-center Phase I/II trial of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in patients with relapsed/refractory multiple myeloma.** *Proc ASH* 2012;**Abstract 74**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Kenneth C Anderson, MD (1/22/13)



Background

- Carfilzomib, an irreversible proteasome inhibitor (PI), and pomalidomide, an immunomodulatory drug (IMiD), are novel agents that have each demonstrated single-agent activity in relapsed/refractory multiple myeloma (MM).
- Preclinical evidence supports the combination of PIs with IMiDs to overcome drug resistance and improve response rates (*Blood* 2002;99:4525).
- In addition, early data with carfilzomib and lenalidomide (Len)/dexamethasone yielded encouraging high response rates in relapsed or refractory MM (*Proc ASH* 2009;Abstract 304).
- **Study objective:** To determine the maximum tolerated dose (MTD), efficacy and safety of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) for patients with relapsed or refractory MM.

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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3 + 3 Phase I Dose-Escalation Study

- All patients had Len-refractory MM that was relapsed/refractory to their most recent therapy
- Carfilzomib dose on d1, 2 of cycle 1 for all cohorts was 20 mg/m^2
- For all cohorts, dexamethasone dose was reduced to 20 mg after cycle 4

Cohort (n = 12)	Carfilzomib	Pomalidomide	Dexamethasone
Cohort 1	27 mg/m^2	3 mg	40 mg
Cohort 1 (MTD)	27 mg/m^2	4 mg	40 mg
Cohort 2	36 mg/m^2	4 mg	40 mg
Cohort 3	45 mg/m^2	4 mg	40 mg
Cohort 4	56 mg/m^2	4 mg	40 mg

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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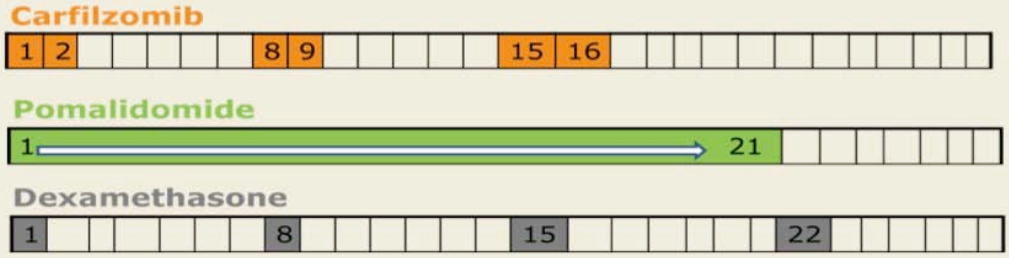
Study Schema

- 12 patients enrolled in Phase I and 20 additional patients enrolled at MTD (n = 32)
- 97% of patients had MM that was also refractory to bortezomib

Treatment cycles 1-6: 28-day cycles



- Cycles ≥7: Maintenance cycles with carfilzomib dosed on d1, 2, 15, 16; pomalidomide/dexamethasone unchanged

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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Response Rates

Response	n = 30
Overall response rate	50%
Very good partial response (VGPR)	13%
Partial response (PR)	37%
Minimal response (MR)	17%
Stable disease (SD)	23%
Progressive disease (PD)	10%

Clinical benefit rate (≥MR): 67%

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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Response Rates According to Cytogenetic Risk Status*

n (%)	High (n = 5)	Intermediate (n = 6)	Standard (n = 18)	Total (n = 29)
VGPR	0 (0%)	0 (0%)	4 (22%)	4 (14%)
PR	4 (80%)	2 (33%)	6 (33%)	12 (41%)
MR	1 (20%)	1 (17%)	3 (17%)	5 (17%)
SD	0 (0%)	2 (33%)	3 (17%)	5 (17%)
PD	0 (0%)	1 (17%)	2 (11%)	3 (10%)

* According to mSMART risk classification: high risk, 17p-positive/t(14;16); intermediate risk, t(4;14)-positive/hypodiploid; standard risk, hyperdiploid/t(11;14); FISH/cytogenetic data missing for 1 patient

Responses were preserved in patients with high-risk FISH/cytogenetics.

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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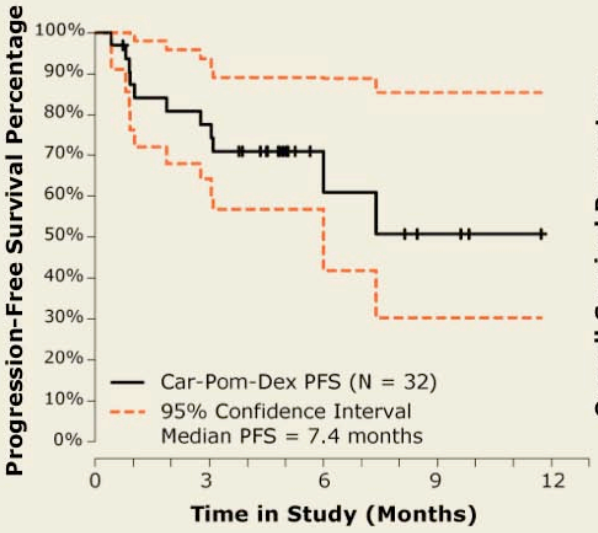
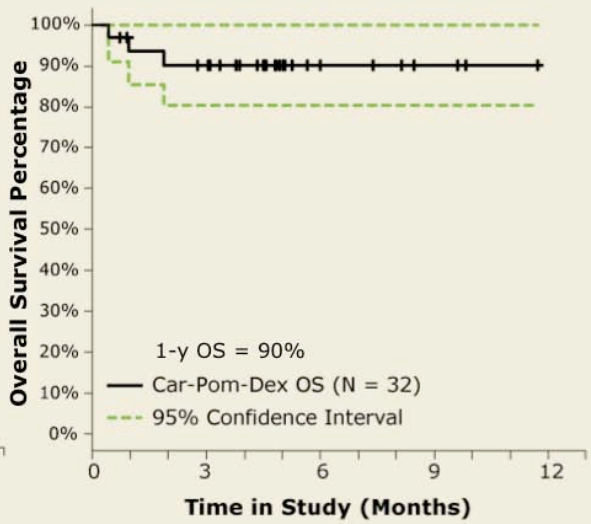
Survival Outcomes (All Patients)

Progression-free survival (PFS)



Overall survival (OS)



With permission from Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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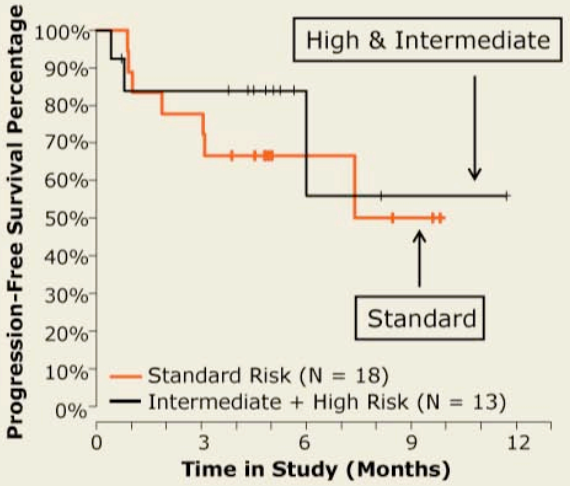
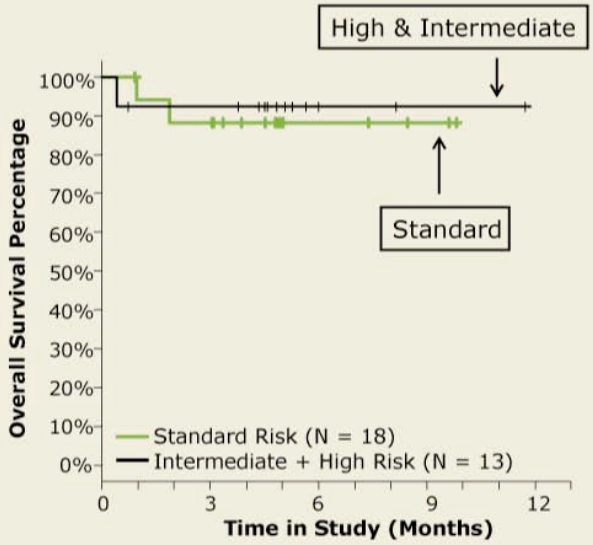
Survival According to Cytogenetic Risk Status

Progression-free survival (PFS)



Overall survival (OS)



Responses and survival were sustained and durable independent of risk status.

With permission from Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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Hematologic Adverse Events (n = 32)

Adverse event (AE)	All grades	Grade 3	Grade 4
Anemia	63%	34%	3%
Thrombocytopenia	56%	22%	6%
Neutropenia	84%	41%	16%
Febrile neutropenia	6%	6%	0%

- Low incidence of febrile neutropenia
- Hematologic toxicites were reversible and manageable
- No Grade 3 or 4 peripheral neuropathy; serious AEs: pneumonia (n = 3), pulmonary embolus (n = 1), congestive heart failure (n = 1)

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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Author Conclusions

- The MTD was carfilzomib at 20/27 mg/m^2, pomalidomide at 4 mg and dexamethasone at 40 mg in relapsed/refractory MM.
- Car-Pom-d was well tolerated with no unexpected toxicities:
  - Limited Grade 3 and 4 nonhematologic AEs were observed, and no Grade 3 or 4 peripheral neuropathy was observed (data not shown).
- Combination therapy with Car-Pom-d was highly active in this patient population with heavily pretreated relapsed or refractory MM.
- Car-Pom-d produced encouraging preserved response rates and survival outcomes independent of FISH/cytogenetic risk status.
- Enrollment is ongoing in a Phase II trial within the Academic Myeloma Consortium (NCT01464034).

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

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Investigator Commentary: A Phase I/II Trial of Carfilzomib, Pomalidomide and Dexamethasone for Relapsed or Refractory MM

Pomalidomide (Pom) was recently granted accelerated FDA approval for the treatment of MM in patients whose disease has progressed during or after treatment with bortezomib and an IMiD. In that setting, carfilzomib achieved a response rate (RR) of about 20% to 24% with a duration of response of 8 months and an OS of 15 months. After the accelerated approval of carfilzomib, it has gone forward to be used with Len/dexamethasone (dex) in relapsed MM with an RR of about 55%. This provided the basis for the ongoing ASPIRE trial evaluating carfilzomib/Len/dex versus Len/dex in relapsed MM.

This was a dose-escalation Phase I trial of Pom/carfilzomib, and the MTD was actually the first dose — carfilzomib at 20-27 mg/m^2, Pom at 4 mg and dex at 40 mg. Both Pom and carfilzomib were so potent that there was no opportunity to escalate either one when combined. The RRs were higher, as one might have predicted, and at the MTD this combination was well tolerated. This study further confirms the exciting ability to combine an IMiD with a PI. Pom and carfilzomib are second-generation, more potent drugs in their classes. Even in MM that is refractory to Len and bortezomib, the combination achieved an RR of about 50% regardless of adverse cytogenetics.

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