5 Minute JournalClub

POST-ASH Issue 5, 2013

Phase I/II Trial of MLN9708 with Lenalidomide and Dexamethasone for Treatment-Naïve 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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Dean for Research, Mayo Clinic in Arizona
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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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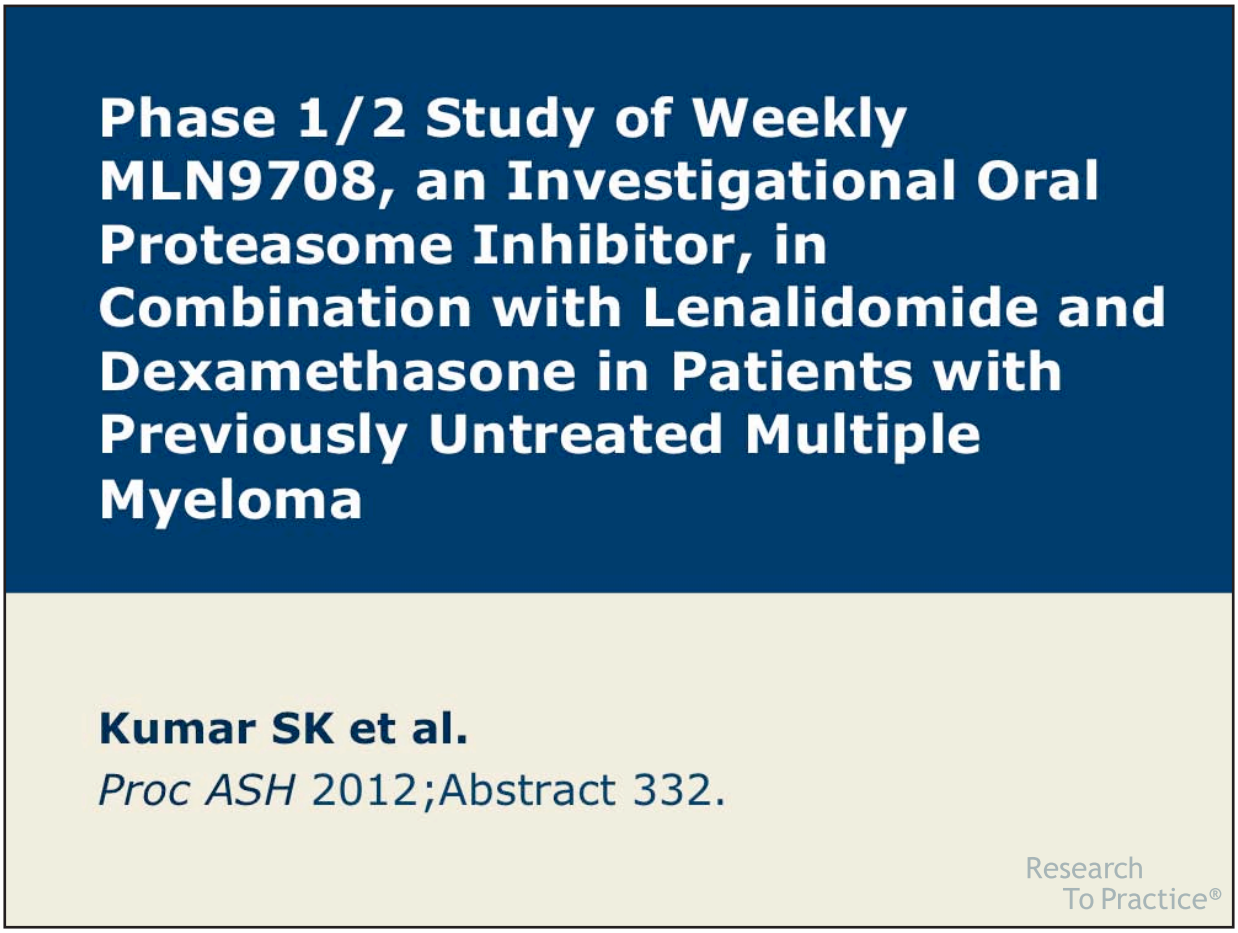
Phase I/II Trial of MLN9708 with Lenalidomide and Dexamethasone for Treatment-Naïve Multiple Myeloma

Presentation discussed in this issue

Kumar S et al. **A Phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM).** *Proc ASH* 2012;**Abstract 332**.

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

- The high response rates seen with the bortezomib, lenalidomide and dexamethasone regimen highlight the feasibility of combining a proteasome inhibitor with an immunomodulatory agent and a steroid for untreated multiple myeloma (MM) (*Blood* 2012;119(19):4375).
- MLN9708 is an investigational, oral, reversible proteasome inhibitor with promising antimyeloma effects and a favorable toxicity profile with low rates of peripheral neuropathy (*Proc ASCO* 2012;Abstract 8034; *Proc ASCO* 2012;Abstract 8017).
- **Objective:** Present updated results of the Phase I/II study evaluating the efficacy and safety of weekly MLN9708 in combination with lenalidomide and dexamethasone in patients with previously untreated MM.

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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Eligibility and Key Objectives

- **Eligibility:**
  - Previously untreated MM and measurable disease
  - No Grade ≥2 peripheral neuropathy or prior/concurrent deep vein thrombosis/pulmonary embolism
- **Phase I objectives:** Safety, tolerability, maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)
- **Phase II objectives:**
  - Primary: Combined complete and very good partial response (CR + VGPR) rate, safety and tolerability
  - Secondary: Overall response rate (ORR), time to response, duration of response and progression-free survival
  - Exploratory: ORR in patients with high-risk cytogenetics and minimal residual disease (MRD) status in patients achieving CR

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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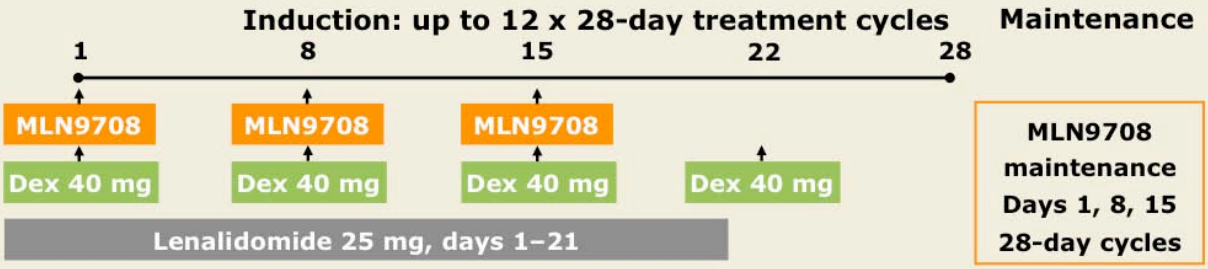
Phase I/II Study Design



- Phase I (n = 15): 4 MLN9708 dose-escalation cohorts from 1.68 to 3.95 mg/m^2, based on dose-limiting toxicities (DLTs) in cycle 1
- Phase II (n = 53):
  - 3 patients from the dose-escalation cohort, 50 patients from Phase II
  - MLN9708 at the RP2D of 4.0 mg
- Mandatory thromboprophylaxis with aspirin or low molecular weight heparin

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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Preliminary Response Data

	Phase I (n = 15)	RP2D (n = 52)	Total (n = 64)
ORR	100%	90%	92%
≥VGPR	53%	58%	55%
CR + nCR*	33%	29%	28%
CR	33%	23%	23%

* Required bone marrow confirmation per protocol

- 64 of 65 patients were evaluable for response
- Median number of cycles of MLN9708 received in Phase I and RP2D was 6 and 7, respectively
- Median time to first response (≥PR) was 1 cycle
- Median duration of response not reached
- Similar responses seen in patients with favorable and unfavorable cytogenetics

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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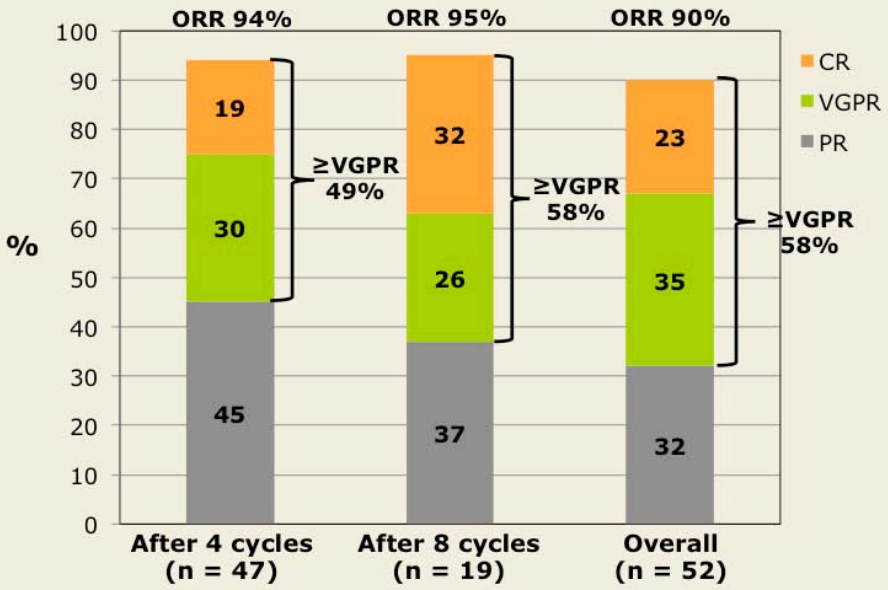
Preliminary Response Over Course of Treatment at RP2D



- Patients treated at RP2D (2.23 mg/m^2 or 4.0 mg fixed dose)
- 3 response-evaluable patients completed 12 cycles: CR (n = 2), VGPR (n = 1)

With permission from Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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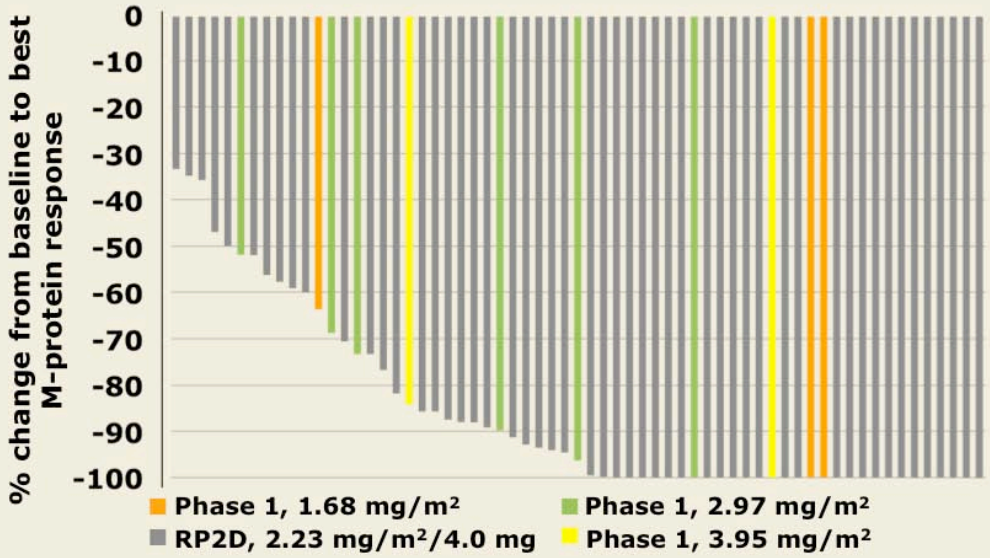
Best Percent Change in M-Protein from Baseline in Response-Evaluable Patients



- 48% of patients achieved a 100% reduction in M-protein
- Reductions were seen at multiple dose levels

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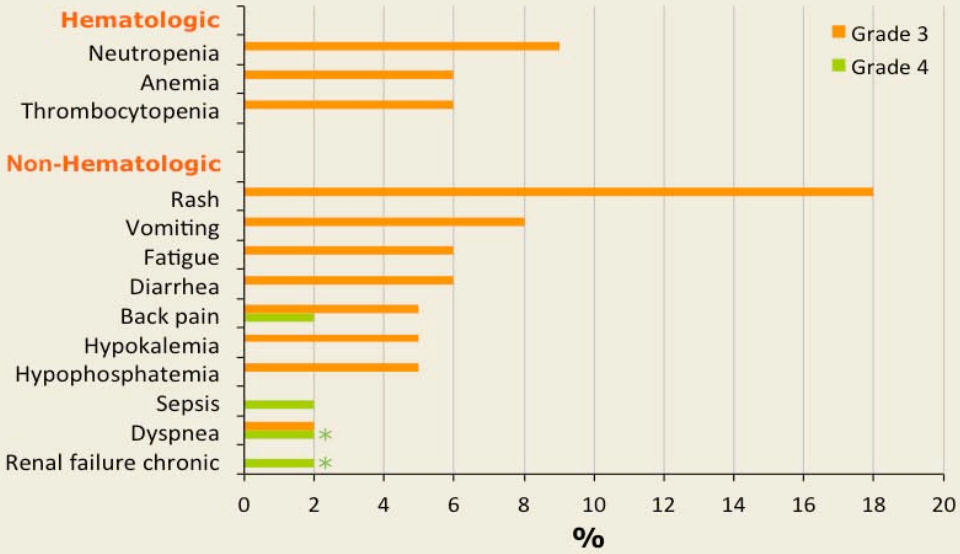
Select Grade 3 (≥5%) and Grade 4 Adverse Events (N = 65)



* Occurred in the same patient

- 1 patient treated at RP2D (4.0 mg) died on study, possibly treatment related

With permission from Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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Peripheral Neuropathy (PN)

- Treatment-emergent PN: 21 (32%) patients; 2 patients had PN at baseline
- PN was Grade 1 in the majority of patients: 13 (20%)
- Grade 2 PN reported in 6 (9%) patients
- Grade 3 PN reported in 2 (3%) patients
  - Both patients off study
  - PN has resolved in 1 and reduced to Grade 1 in the other

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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Author Conclusions

- The all-oral combination of weekly MLN9708, lenalidomide and dexamethasone appears to be generally well tolerated with limited PN.
- The primary endpoint of the study was met, suggesting antitumor activity at the RP2D.
  - 92% of patients had achieved ≥PR, including a ≥VGPR rate of 55% and a CR rate of 23% at a median drug exposure of 6 months.
  - Responses increased with number of cycles and deepened over time.
  - 88% of patients achieving CR who were evaluable for MRD status were confirmed as MRD-negative (data not shown).
- A Phase III trial of MLN9708 with lenalidomide/dexamethasone for relapsed and/or refractory MM is currently enrolling (NCT01564537), and a Phase III trial of MLN9708 with lenalidomide/dexamethasone in previously untreated MM is being planned.

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

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Investigator Commentary: Phase I/II Study of MLN9708 with Lenalidomide and Dexamethasone in Untreated MM

MLN9708 is similar to bortezomib in terms of its structure and predicted activity. This study demonstrated an impressive 90% response rate with a complete remission rate higher than 20%. These results are slightly better than lenalidomide/dexamethasone and approach the type of results seen with bortezomib/lenalidomide and dexamethasone in the same patient population. The advantages of MLN9708 are that it is an oral inhibitor, as opposed to subcutaneous or intravenous bortezomib, it elicits high response rates and it does not have significant toxicity, with a low rate of neuropathy. If we had a completely oral regimen that we could offer patients, this regimen could be a game changer.

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

The idea of combining a proteasome inhibitor with an immunomodulatory drug is exciting. This study of MLN9708 with lenalidomide/dexamethasone showed almost universal responses and good tolerability. I believe if the results continue to be promising, we are likely to have an all-oral regimen to treat multiple myeloma in the future.

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

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