



Key ASH Presentations

Issue 3, 2012

Investigational Agent MLN9708 for Patients with Relapsed/ Refractory Multiple Myeloma

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

- Develop an understanding of the emerging efficacy and toxicity data with novel agents in order to inform future patients with newly diagnosed and relapsed or refractory multiple myeloma about protocol and nonprotocol options.
- Assess the clinical benefits and risks of deacetylase inhibitors in combination with proteasome inhibitors for relapsed and refractory multiple myeloma.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors for patients with relapsed or refractory and previously untreated multiple myeloma.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Sagar Lonial, MD
Professor

Vice Chair of Clinical Affairs
Director of Translational Research, B-Cell Malignancy Program
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Merck and Company Inc, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc.

Paul G Richardson, MD
Associate Professor of Medicine
Harvard Medical School
Clinical Director of the Jerome Lipper Center for Multiple Myeloma
Dana-Farber Cancer Institute
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Keryx Biopharmaceuticals Inc, Millennium: The Takeda Oncology Company, Nereus Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation.

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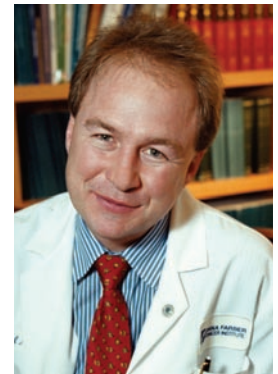
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To go directly to slides and commentary for this issue, [click here](#).

When the New England Patriots' Rob Gronkowski dived futilely for Tom Brady's final "Hail Mary" pass in Sunday night's Super Bowl, I flipped off the TV and sat down with my notes from a recent conversation with Gronk's Boston neighbor Dr Paul Richardson, a dynamic Englishman from Surrey and a profoundly knowledgeable member of Dana-Farber's powerhouse myeloma team. Dr Richardson can always be counted on to contribute a plethora of ASH papers and presentations (he had 6 orals in December), and this was part of the reason I wanted his take on the hottest new myeloma data emerging at the conference. Our recent 90-minute breathless run through the happenings was mainly focused on emerging and currently unapproved agents, and as is always the case with myeloma nowadays, there was a lot to talk about.



Paul G Richardson, MD

1. **Carfilzomib**

As Dr Richardson was the lead investigator on the landmark front-line Phase II trial of RVD (lenalidomide, bortezomib, dex), I was particularly interested in his perspective on Dr Andrzej Jakubowiak's second presentation of data on the so-called CRd regimen (lenalidomide, carfilzomib, low-dose dex) also in this setting. Like RVD, CRd was shown to have response rates approaching 100%, so perhaps it was to be expected that our conversation quickly led to a review of the toxicity profile of this irreversible proteasome inhibitor. While Dr Richardson noted the impressive reduced risk of peripheral neuropathy (PN), he also commented on 2 other somewhat unexpected side effects of CRd, specifically dyspnea (12% of patients) that may be cardiac related due to fluid challenge and renal impairment and hyperglycemia (76%) that may be greater than would be expected from corticosteroids alone. Regardless, Dr Richardson thinks CRd may become a critical alternative for many patients up front, but right now he, like most investigators, believes carfilzomib clearly offers an important alternative in later-line disease.

2. **MLN9708**

Dr R called this oral boronic acid peptide proteasome inhibitor similar to bortezomib "the myeloma news of the meeting" and labeled the related ASH data set evaluating the agent up front combined with len/dex as "a knockout...huge." This once- or twice-weekly pill causes some skin toxicity but no PN, and when combined with len/dex as an all-oral up-front regimen, responses were observed in all 15 patients. Similarly, Dr Richardson presented data in the relapsed setting where useful activity was seen "even in the ninth inning," and it seems likely that MLN9708 will soon get a catchier moniker and quickly move forward in development.

3. [Pomalidomide](#)

This third-generation IMiD already has an impressive safety and efficacy track record, and significant responses have been observed in patients with disease progressing on lenalidomide and/or thalidomide. At ASH, more encouraging data were reported that further illustrate the striking activity of this agent alone or with dex and shed light on potential dosing strategies that might be appropriate for younger patients (continuous) and older, more frail individuals (3 weeks on, 1 week off). Either way it's a therapy most investigators — including Dr R — are ready to use if approved.

4. [Elotuzumab](#)

At ASH, Dr Sagar Lonial presented an intriguing data set on this humanized monoclonal antibody targeting human CS1, a cell surface glycoprotein that is highly expressed in more than 95% of patients with myeloma. Elotuzumab acts primarily through NK cell-mediated ADCC that may be compromised because of underlying immune dysfunction in myeloma, but in vitro work suggests synergistic activity when combined with the immune modulator lenalidomide. In this Phase II study in relapsed/refractory disease the elotuzumab/lenalidomide/low-dose dex combination was well tolerated and highly active (82% response rate) and as such has now moved into Phase III testing.

5. [HDAC inhibitors](#)

Data sets with vorinostat and panobinostat (both in combination with bortezomib) were reported at ASH, and although Dr Richardson and others believe there is a future role for this approach, the optimal doses, schedules and partner agents have yet to be defined. Next we journey back to the solid tumor world and investigator perspectives on daily management of a common tumor that could dearly benefit from some myeloma-like progress...cancer of the pancreas.

Neil Love, MD

[Research To Practice](#)

Miami, Florida

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

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Investigational Agent MLN9708 for Patients with Relapsed/Refractory Multiple Myeloma

Presentations discussed in this issue

Richardson PG et al. **Investigational agent MLN9708, an oral proteasome inhibitor, in patients (Pts) with relapsed and/or refractory multiple myeloma (MM): Results from the expansion cohorts of a Phase 1 dose-escalation study.** *Proc ASH 2011*; **Abstract 301**.

Kumar S et al. **Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results from a Phase 1 Dose-Escalation Study.** *Proc ASH 2011*; **Abstract 816**.

Berdeja JG et al. **Phase 1/2 study of oral MLN9708, a novel, investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM).** *Proc ASH 2011*; **Abstract 479**.

Slides from presentations at ASH 2011 and transcribed comments from recent interviews with Sagar Lonial, MD (1/25/12) and Paul G Richardson, MD (1/24/12)

The Investigational Agent MLN9708, an Oral Proteasome Inhibitor, in Patients with Relapsed and/or Refractory Multiple Myeloma (MM): Results from the Expansion Cohorts of a Phase 1 Dose-Escalation Study¹

Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results from a Phase 1 Dose-Escalation Study²

Phase 1/2 Study of Oral MLN9708, a Novel, Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)³

¹ **Richardson PG et al.**
Proc ASH 2011; Abstract 301.

² **Kumar S et al.**
Proc ASH 2011; Abstract 816.

³ **Berdeja JG et al.**
Proc ASH 2011; Abstract 479.

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The Investigational Agent MLN9708, an Oral Proteasome Inhibitor, in Patients with Relapsed and/or Refractory Multiple Myeloma (MM): Results from the Expansion Cohorts of a Phase 1 Dose-Escalation Study

Richardson PG et al.

Proc ASH 2011;Abstract 301.

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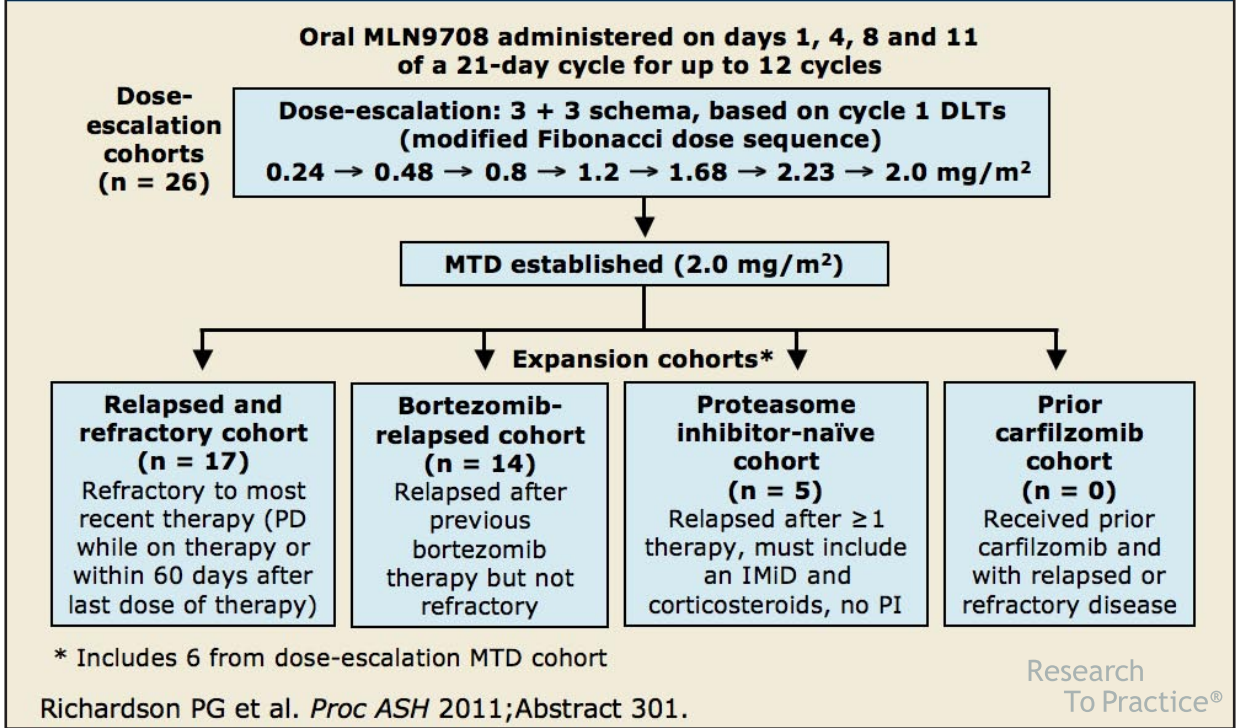
Background

- Proteasome inhibition is a valid anticancer strategy, as has been demonstrated with bortezomib.
- MLN9708 is an orally bioavailable, potent, reversible, specific inhibitor of the 20S proteasome, and compared to bortezomib in preclinical studies, MLN9708 demonstrated
 - Similar selectivity and potency
 - Faster dissociation from proteasome
 - Greater tissue penetration
- MLN9708 demonstrates antitumor activity in solid tumor and hematologic malignancy xenograft models, including in vivo models of MM, and is the first oral proteasome inhibitor (PI) to enter clinical investigation in MM.

Richardson PG et al. *Proc ASH 2011;Abstract 301.*

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Study Design



Safety Profile

Adverse events (AEs)	Overall cohorts (n = 56)
Any AE/drug-related AEs	98%/91%
Grade ≥3 AEs/drug-related Grade ≥3 AEs	73%/61%
Drug-related AEs in >20% of patients	
Fatigue	46%
Thrombocytopenia	39%
Nausea	30%
Diarrhea	23%
Vomiting	23%
Rash	21%
Dose reductions/discontinuance due to AEs	32%/9%

Grade ≥3 AEs in ≥2 patients: Thrombocytopenia (n = 19), neutropenia (n = 8), fatigue (n = 5), rash (n = 5), abdominal pain, anemia, hypophosphatemia and leukopenia (each n = 2)

Richardson PG et al. *Proc ASH* 2011;Abstract 301.

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Preliminary Response*

Response (n)	Overall cohorts (n = 46)
Complete response	1
Partial response	5
Minimal response	1 [†]
Stable disease up to 12.9 mo	28

* IMWG uniform criteria plus minimal response and near complete response

[†] From bortezomib-relapsed expansion cohort; 40% M-protein reduction

Richardson PG et al. *Proc ASH* 2011;Abstract 301.

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Author Conclusions

- MTD was established for MLN9708 as 2.0 mg/m² on twice-weekly dosing.
- Oral MLN9708 was generally well tolerated:
 - Infrequent (11%) peripheral neuropathy (PN), and no Grade 3 or 4 PN, was observed (data not shown).
- Pharmacokinetic/pharmacodynamic properties support continued development (data not shown).
- Preliminary data suggest activity in heavily pretreated relapsed/refractory MM, including durable responses and disease control.

Richardson PG et al. *Proc ASH* 2011;Abstract 301.

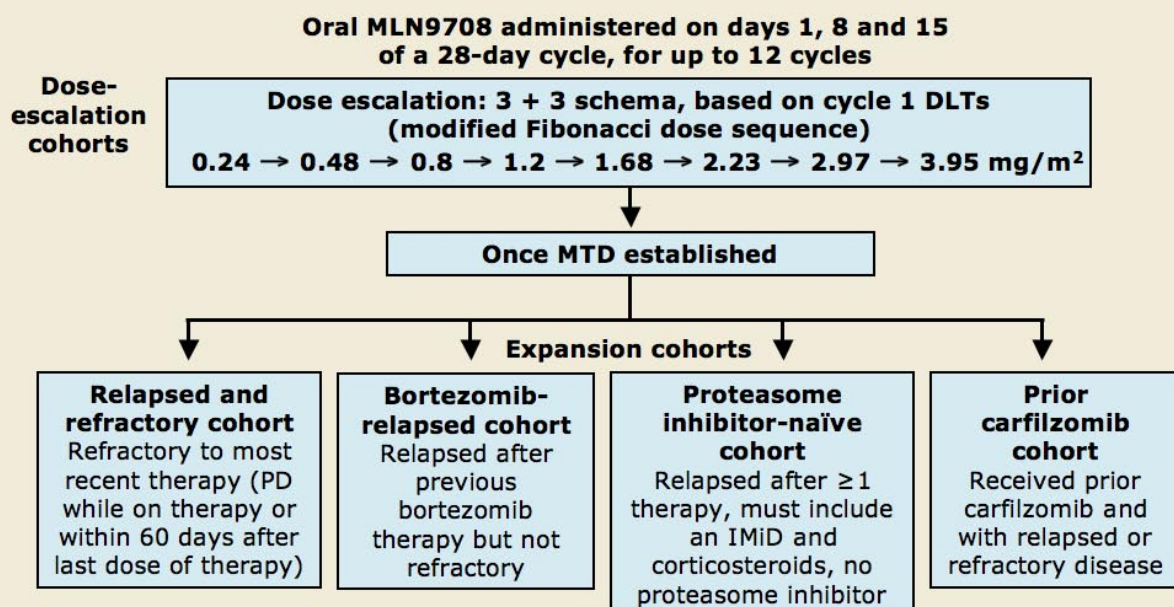
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Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results from a Phase 1 Dose-Escalation Study

Kumar S et al.

Proc ASH 2011;Abstract 816.

Study Design



Kumar S et al. *Proc ASH 2011;Abstract 816.*

Drug-Related Adverse Events (>10% of Patients)

Adverse event, n (%)	(N = 32)
Fatigue	10 (31)
Thrombocytopenia	10 (31)
Nausea	9 (28)
Diarrhea	8 (25)
Peripheral neuropathy (PN)*	3 (9)

* Patients had Grade 1 PN at baseline. No Grade ≥ 3 PN reported with oral MLN9708.

- Dose reductions and treatment discontinuation due to adverse events occurred for 6 and 2 patients, respectively.
- One patient died on study due to elevated creatinine related to disease progression.

Kumar S et al. *Proc ASH* 2011;Abstract 816.

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Efficacy Summary

- Eighteen patients were available for response.
- One patient achieved a VGPR:
 - Patient received 4 prior lines of therapy.
 - Response occurred after cycle 3 and patient remains in response at cycle 5.
- One patient has achieved a PR at 2.97 mg/m²:
 - Patient received 4 prior lines of therapy.
 - Duration of response is 3.7 months.
- Eight patients have achieved SD that has been durable for up to 9.5 months.

Kumar S et al. *Proc ASH* 2011;Abstract 816.

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Author Conclusions

- Current data suggest that MLN9708 on a once-weekly schedule is generally well tolerated with manageable toxicity:
 - No significant neuropathy was observed
 - AEs appear limited compared to twice-weekly dosing
- The MTD for weekly dosing has been determined as 2.97 mg/m².
- Pharmacokinetics and pharmacodynamics properties support continued development (data not shown):
 - Terminal half-life of 7 days supports weekly dosing
 - Linear pharmacokinetics with dose (0.8-3.95 mg/m²)
- MLN9708 shows early signs of antitumor activity in this heavily pretreated population with prior exposure to lenalidomide/thalidomide and bortezomib.

Kumar S et al. *Proc ASH* 2011;Abstract 816.

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Investigator Commentary: Novel Proteasome Inhibitor MLN9708 for Relapsed and/or Refractory MM

MLN9708 clearly demonstrates activity in patients with relapsed/refractory multiple myeloma. Whether MLN9708 can overcome bortezomib resistance is less clear, but the agent does have activity in patients who were previously bortezomib sensitive.

MLN9708 in many ways is an oral version of bortezomib. What I believe separates MLN9708 from the other second-generation proteasome inhibitors is that, like bortezomib, it is a boronate. It's a structurally different molecule than carfilzomib, which is an epoxyketone. That may not make a difference one way or another to most clinicians, except that I do have patients who had anaphylaxis with bortezomib. In those patients I wouldn't consider MLN9708 because the boron is probably what yielded the allergy, and I'm using an epoxyketone, like carfilzomib, instead.

Another attractive feature of MLN9708 is that its half-life is longer than that of bortezomib. So the once-a-week schedule may be able to get you the same kind of efficacy that a twice-a-week schedule may be able to get you with bortezomib, for instance.

Interview with Sagar Lonial, MD, January 25, 2012

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Phase 1/2 Study of Oral MLN9708, a Novel, Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)

Berdeja JG et al.

Proc ASH 2011;Abstract 479.

Study Design

Eligibility: Previously untreated MM, ECOG PS 0-2, no Grade ≥ 2 PN, no prior/concurrent DVT/PE, no prior systemic MM therapy

**Phase I: Dose-escalation of oral MLN9708:
3 + 3 schema based on cycle 1 DLTs**

**Starting dose based on dose-escalation portion of twice-weekly dosing study (C16003), 33% dose increments
1.68 \rightarrow 2.23 \rightarrow 2.97 \rightarrow 3.95 mg/m²**

**Intervention: MLN9708 d1, 8, 15; Len 25 mg d1-21;
Dex 40 mg d1, 8, 15, 22 for up to twelve 28-day cycles**

Safety Profile

Event (n)	Total (n = 15)
Any AE/drug-related AEs	15/13
Grade ≥ 3 AEs/drug-related Grade ≥ 3 AEs	11/9
Grade 3/4 AEs in ≥ 4 patients	
Fatigue	0/0
Thrombocytopenia	0/1
Nausea	1/0
Diarrhea	2/0
Vomiting	2/0
Rash	2/0
Dose reductions/discontinuance due to AEs	4/1

AEs transient and manageable with standard supportive care or dose reduction/discontinuance; Grade 1 drug-related PN in 3 patients; no Grade >1 PN

Berdeja JG et al. *Proc ASH* 2011;Abstract 479.

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Preliminary Response*

Response	Patients (n = 15)
\geq Partial response (PR) through 4 cycles	100%
Complete response	4
Very good PR	5
PR	6
$\geq 50\%$ decrease in M-protein after 1 cycle [†]	14

* IMWG uniform criteria plus minimal response and near complete response

[†] One patient had 48% reduction in M-protein after 1 cycle with PR achieved after cycle 2

Berdeja JG et al. *Proc ASH* 2011;Abstract 479.

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Author Conclusions

- In the first study of oral MLN9708 administered weekly with standard-dose lenalidomide and dexamethasone in patients with previously untreated MM
 - The combination appears to be generally well tolerated, with a low rate of PN and no Grade >1 PN and rash manageable with standard supportive care, dose reduction or discontinuation
 - Preliminary evidence of antitumor activity with rapid responses was observed
- The recommended Phase II dose (RP2D) of MLN9708 in combination with a 28-day cycle of lenalidomide and dexamethasone is 2.23 mg/m² weekly
 - In Phase II, the RP2D will be converted to a fixed dose of 4 mg weekly, as supported by population pharmacokinetics analyses (*Proc ASH 2011*;Abstract 1433)

Berdeja JG et al. *Proc ASH 2011*;Abstract 479.

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Investigator Commentary: Novel Proteasome Inhibitor MLN9708 in Combination with Lenalidomide and Dexamethasone in Untreated MM

Part of the excitement at ASH 2011 was the presentation of encouraging information on the oral proteasome inhibitor MLN9708. When combined with lenalidomide and dexamethasone in the up-front setting, it resulted in a response rate of 100%. Responses to this agent as a single agent were also seen in the relapsed and refractory setting, confirming that this is an effective new second-generation proteasome inhibitor. Overall the drug has impressive response rates, especially in combination, manageable side effects and no significant neurotoxicity.

Interview with Paul G Richardson, MD, January 24, 2012

In my opinion, MLN9708 brings 2 things to the table. First, the neuropathy signal is quite low in comparison to bortezomib. Second, it is an oral agent. We have the possibility of having a completely oral proteasome inhibitor/IMiD therapy for patients with newly diagnosed disease, which I believe is a significant step forward.

Interview with Sagar Lonial, MD, January 25, 2012

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