5 Minute JournalClub

Key ASH Presentations
Issue 3, 2012

Pomalidomide and Dexamethasone for Patients with 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

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


Paul G Richardson, MD

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.

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.

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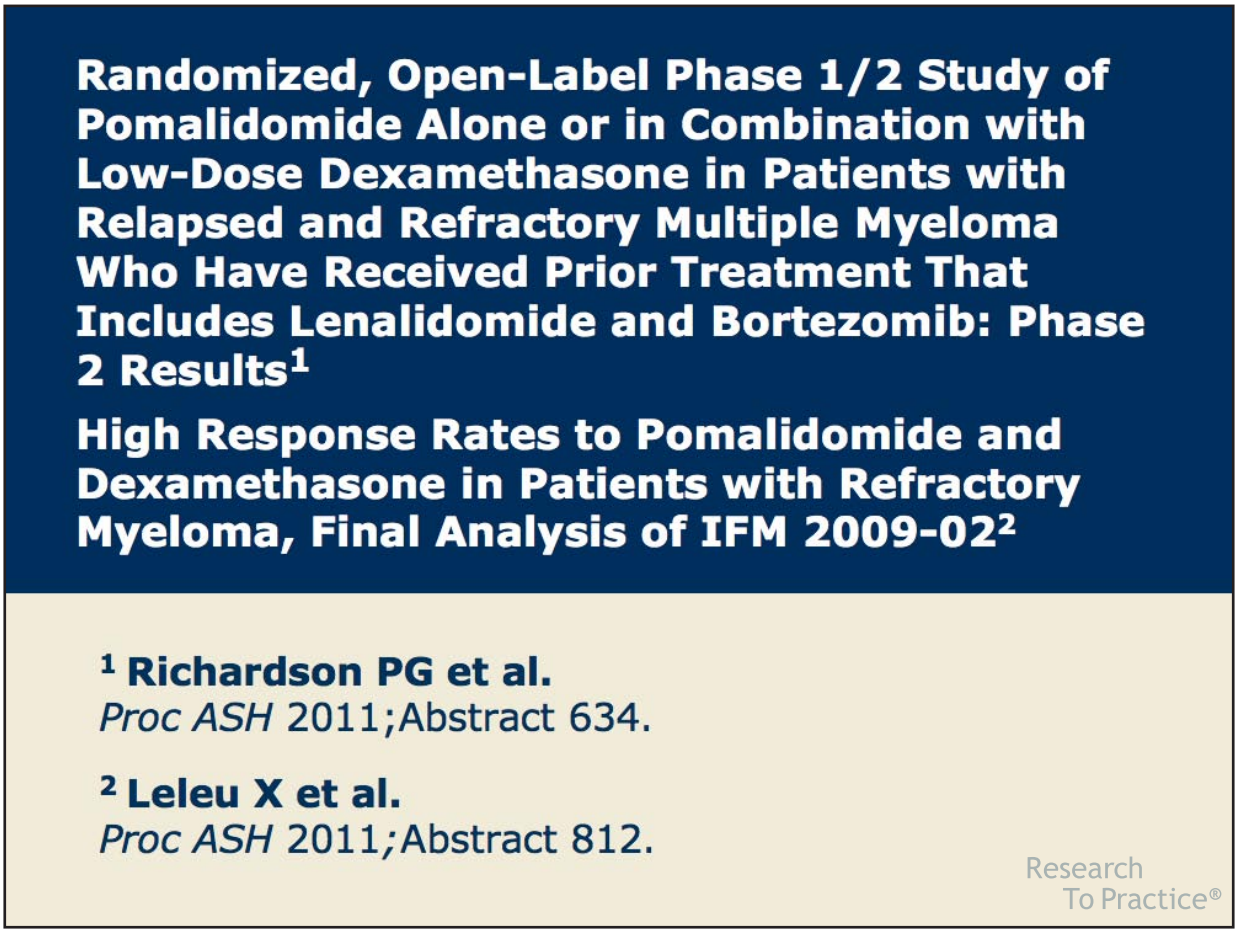
Pomalidomide and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Presentations discussed in this issue

Richardson PG et al. **Randomized, open label Phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients (Pts) with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): Phase 2 results.** *Proc ASH* 2011;**Abstract 634**.

Leleu X et al. **High response rates to pomalidomide and dexamethasone in patients with refractory myeloma, final analysis of IFM 2009-02.** *Proc ASH* 2011;**Abstract 812**.

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)



Randomized, Open-Label Phase 1/2 Study of Pomalidomide Alone or in Combination with Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib: Phase 2 Results

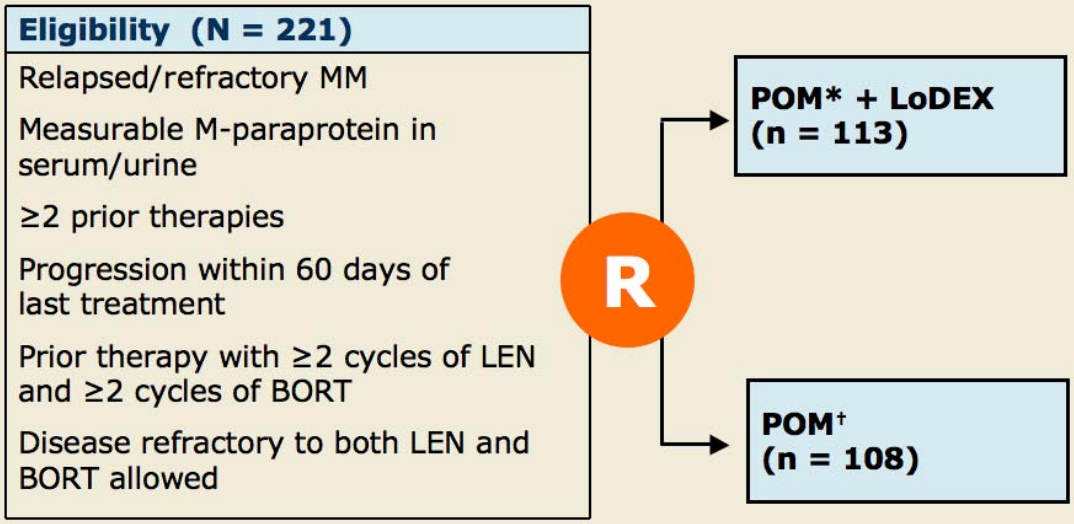
Richardson PG et al.

Proc ASH 2011;Abstract 634.

Background

- Pomalidomide (POM) is a potent oral immunomodulatory agent with significant antimyeloma activity in vitro (*Blood* 2000;96:2943).
- POM has demonstrated promising activity in patients with relapsed/refractory multiple myeloma (RRMM) (*J Clin Oncol* 2004;22:3269).
- When combined with low-dose dexamethasone (LoDEX), POM has clinical efficacy in patients with RRMM previously treated with lenalidomide (LEN) and/or bortezomib (BORT) (*Blood* 2011;118:2970).

Study Design



* POM: 4 mg/day on days 1–21 of a 28-day cycle
† Addition of LoDEX allowed for patients experiencing disease progression (n = 61)

Richardson PG et al. *Proc ASH* 2011;Abstract 634.

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Efficacy

Outcome	POM (n = 108)	POM + LoDEX (n = 113)
Overall response rate		
Overall population	13%	34%
Refractory to LEN and BORT	16%	30%
Median duration of response		
Overall population	8.5 mo	7.9 mo
Refractory to LEN and BORT	8.3 mo	6.5 mo
Median progression-free survival		
Overall population	2.7 mo	4.7 mo
Refractory to LEN and BORT	2.0 mo	3.9 mo
Median overall survival		
Overall population	14.0 mo	16.9 mo
Refractory to LEN and BORT	12.7 mo	13.7 mo

Richardson PG et al. *Proc ASH* 2011;Abstract 634.

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Grade 3/4 Adverse Events

Event (≥5% patients)	POM (n = 107)	POM + LoDEX (n = 112)
Neutropenia	45%	38%
Thrombocytopenia	21%	19%
Anemia	17%	21%
Pneumonia	8%	19%
Fatigue	8%	10%

- No Grade 3/4 peripheral neuropathy
- Grade 3/4 thromboembolic events: 4% with POM + LoDEX, 3% with POM alone
- Discontinuation due to AEs: 12% with POM alone, 6% with POM + LoDEX

Richardson PG et al. *Proc ASH* 2011;Abstract 634.

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Author Conclusions

- POM with or without LoDEX demonstrates promising efficacy in patients with advanced MM who have received multiple prior therapies and whose disease is refractory to both LEN and BORT.
- POM + LoDEX exhibits synergistic activity and is generally well tolerated.
- POM + LoDEX produces consistent and durable response rates regardless of prior therapy and refractoriness, with favorable progression-free survival and encouraging median overall survival (16.9 months).
- POM + LoDEX is being investigated in Phase III trials and as part of combination treatments, including with bortezomib.

Richardson PG et al. *Proc ASH* 2011;Abstract 634.

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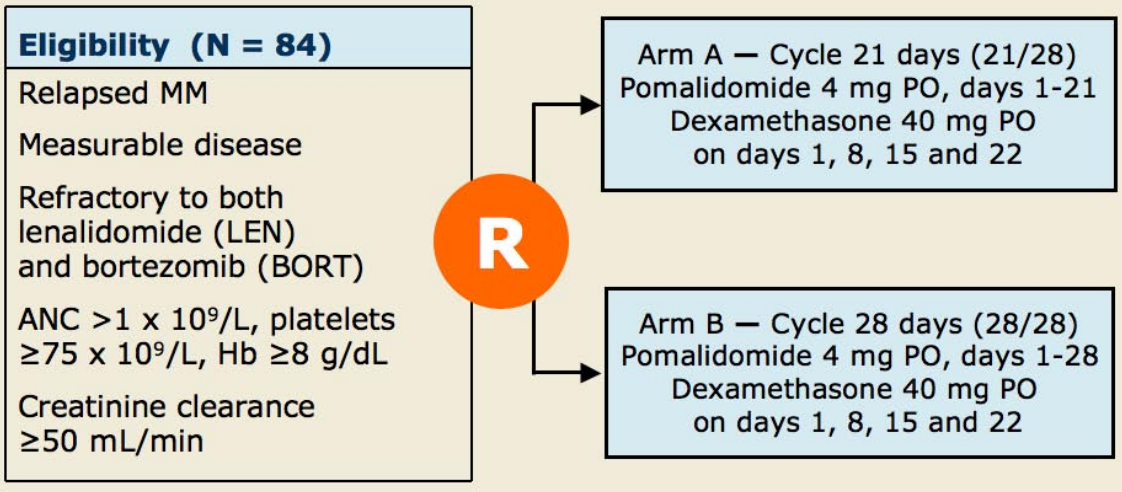
High Response Rates to Pomalidomide and Dexamethasone in Patients with Refractory Myeloma, Final Analysis of IFM 2009-02

Leleu X et al.

Proc ASH 2011;Abstract 812.

Study Design



Primary Study Objective:
Response rate (≥PR) in either arm according to IMWG criteria

Leleu X et al. *Proc ASH* 2011;Abstract 812.

Efficacy

Outcome	Arm A (n = 43)	Arm B (n = 41)
Overall response rate		
Overall population	35%	34%
Refractory to LEN and BORT	34%	28%
Median duration of response		
Overall population	10.5 mo	7.2 mo
Median progression-free survival		
Overall population	9.1 mo (HR = 1.18, p = 0.5875)	
Refractory to LEN and BORT	3.8 mo (HR = 0.89, p = 0.6814)	

HR = hazard ratio; median follow-up = 11.3 mo

Leleu X et al. *Proc ASH* 2011;Abstract 812.

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Adverse Events (AEs)

Event	Arm A (n = 43)	Arm B (n = 41)
Serious AEs	33%	41.5%
Any Grade 3/4 AEs	91%	83%
Blood/lymphatic system disorders	72%	71%
Anemia	33%	32%
Neutropenia	63%	56%
Thrombocytopenia	28%	24%
General disorders and administration site conditions	23%	27%
Asthenia	14%	5%

Leleu X et al. *Proc ASH* 2011;Abstract 812.

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Author Conclusions

- The combination of pomalidomide and dexamethasone is safe and effective in patients with MM resistant or refractory to BORT and LEN.
- The combination of pomalidomide and dexamethasone is effective regardless of subgroup and refractoriness to prior therapy.
- Pomalidomide 4 mg 21/28 days + dexamethasone appeared superior to pomalidomide 4 mg 28/28 days + dexamethasone considering duration of response and treatment duration, in view of a similar safety profile.

Leleu X et al. *Proc ASH* 2011;Abstract 812.

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Investigator Commentary: Pomalidomide/Dexamethasone for MM Refractory to Both Lenalidomide and Bortezomib

This randomized Phase II study reported by Dr Leleu and colleagues compared 2 schedules of pomalidomide of either continuous dosing or 3 weeks on and 1 week off. Although the response rates were the same, the duration of response was strongly in favor of the 3 weeks on, 1 week off schedule. This important trial appears to validate the current schedule of 3 weeks on and 1 week off in this population because of better tolerability and improved patient outcome.

After pomalidomide is, as we hope, approved, these data would mean, for example, that I might dose continuously for robust, healthy patients with relapsed/refractory MM for whom response is key and low counts and other potential side effects are less of a concern, based primarily on the studies from the Mayo Clinic evaluating this approach. Conversely, I would favor administering pomalidomide 3 weeks on, 1 week off for most other patients, in particular for frailer patients with relapsed/refractory MM, based on this work and our own experience in the multicenter MM-002 pomalidomide study in relapsed/refractory MM.

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

Investigator Commentary: Pomalidomide/Dexamethasone for MM Refractory to Both Lenalidomide and Bortezomib

Pomalidomide to me represents an agent that one really wishes was on the market because it does have significant activity and can make a big difference to patients. A number of pomalidomide trials were presented at ASH 2011, and they consistently show that 1 of 3 patients who are resistant to lenalidomide will achieve a partial response or better with pomalidomide/dexamethasone.

Interview with Sagar Lonial, MD, January 25, 2012

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