5 Minute JournalClub

Key ASH Presentations

Issue 3, 2012

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CME Information

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.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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:

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Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)[1]

Final Results from the Bortezomib-Naïve Group of PX-171-004, a Phase 2 Study of Single-Agent Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma[2]

[1] **Jakubowiak AJ et al.**
Proc ASH 2011;Abstract 631.

[2] **Vij R et al.**
Proc ASH 2011;Abstract 813.

Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)

Jakubowiak AJ et al.
Proc ASH 2011;Abstract 631.

Background

- Carfilzomib is a next-generation proteasome inhibitor that selectively and irreversibly binds to its target, resulting in sustained inhibition in the absence of off-target effects.
- In relapsed and/or refractory MM, the combination of carfilzomib (CFZ) with lenalidomide (Len) and low-dose dexamethasone (Dex) (CRd) has shown very promising efficacy: 78% ≥PR , 40% ≥VGPR, 24% CR/nCR (Wang et al, ASCO 2011).
- In a Phase I/II study of newly diagnosed MM, the regimen was well tolerated and very active with 96% ≥PR, 70% ≥VGPR and 55% CR/nCR (Jakubowiak et al, ASH 2010).
- This study presents results after enrollment in the Phase II portion of the Phase I/II trial of CRd in MM.

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Methods

Accrual: 53 (Closed)

Eight 28-day cycles

CFZ: IV on days 1, 2, 8, 9, 15, 16
20 mg/m^2, 27 mg/m^2 (Phase I), 36 mg/m^2 (Phase I and II)
LEN: Days 1-21, 25 mg PO
Dex: Cycles 1-4/5-8, 40/20 mg PO weekly

- Achieved ≥PR → stem cell collection (SCC) and autologous stem cell transplant (ASCT) after 4 cycles
- ASCT patients offered continued CRd treatment after SCC
- After 8 cycles, pts received 28-d maintenance cycles of CFZ on d1, 2, 15, 16 + LEN on d1-21 + weekly Dex at tolerable dose at end of cycle 8

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Response to CRd by Treatment Cycles and CFZ Dose (Abstract Only)

	ORR (%)	CR/nCR (%)	≥VGPR (%)
Treatment cycles			
1+ (n = 49)	94	53	65
4+ (n = 35)	100	71	89
8+ (n = 28)	100	75	89
12+ (n = 19)	100	79	100
CFZ dose (mg/m^2)			
20 (n = 4)	100	75	100
27 (n = 13)	100	85	100
36 (n = 32)	91	38	47

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Response to CRd (Abstract Only)

Clinical parameter (n = 49)*	ORR (%)	CR/nCR (%)	≥VGPR (%)
Cytogenetics			
Normal/favorable (n = 33)	91	52	61
Unfavorable (n = 16)	100	56	75
ISS stage			
I (n = 20)	90	50	65
II (n = 16)	94	44	56
III (n = 13)	100	69	77

* Response by IMWG criteria

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Adverse Events (Abstract Only)

Event	n = 51*
Hematologic (Grade 3/4)	
Anemia	18%
Neutropenia	12%
Thrombocytopenia	10%
Nonhematologic (Grade 3/4 in ≥10%)	
Hyperglycemia	24%
Dyspnea	12%
Deep vein thrombosis/pulmonary embolism while on ASA prophylaxis	10%
Nonhematologic (all grades)	
Hyperglycemia	76%
Hypophosphatemia	61%
Infection	53%
Peripheral neuropathy (Grade 1 or 2)	24%

* As of June 30, 2011

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Author Conclusions

- CRd is highly active and well tolerated, allowing the use of full doses for an extended time in patients with newly diagnosed MM with limited need for dose modification.
- Responses are rapid and improve over time, reaching 100% ≥VGPR, and early time-to-event data are encouraging.
- These results compare favorably to the best front-line regimens in MM.

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Investigator Commentary: Front-Line Carfilzomib, Lenalidomide and Low-Dose Dexamethasone in MM

The overall response rate in the study presented by Dr Jakubowiak and his team was 94% partial response or better, which is a response rate similar to that seen with lenalidomide combined with bortezomib and dexamethasone (RVD), with which a rate of partial response or better of 100% was reported. It is also exciting that such high-quality results were seen early in the course of this study because the quality of responses may improve with longer follow-up. Importantly, the side effects appear very manageable, with a relative lack of neurotoxicity and an approximately 25% rate of treatment-emergent peripheral neuropathy overall, which is significantly less than with RVD. Conversely, the 53% incidence of infection was not unexpected in this setting, as upper respiratory infections in patients with newly diagnosed (ND) MM are common, but the 76% incidence of significant hyperglycemia is more difficult to explain. Another important side effect seen with CFZ and Rd, which was not reported with RVD, was shortness of breath at the time of drug administration or shortly thereafter. At the ASH meeting, Dr Jakubowiak suggested that this could have been due to the aggressiveness of the fluid challenge that was administered with CFZ, and this may indeed be true but the rate of approximately 12% is significant, and possibly attributable toxicity warrants some caution. Overall, however, I believe that CFZ and Rd is an outstanding combination based on current data and is very promising as we go forward in developing novel up-front 3- and 4-drug regimens for ND MM.

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

Final Results from the Bortezomib-Naïve Group of PX-171-004, a Phase 2 Study of Single-Agent Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma

Vij R et al.

Proc ASH 2011;Abstract 813.

Study Design

Eligibility (N = 165)

Relapsed/refractory MM following 1-3 prior treatment regimens

Responsive to ≥1 prior therapy

ECOG PS 0-2

Cohort 1*: (n = 59)
20 mg/m² CFZ, cycles 1-12
Bortezomib (BOR) naïve

Cohort 2: (n = 70)
20 mg/m² CFZ cycle 1
27 mg/m² CFZ cycles 2-12
BOR naïve

CFZ = carfilzomib IV qd x 2, 3 wks (28-d cycle)

* Results in BOR-treated (n = 35) group have been previously reported

Sixty-six percent of patients in cohort 1 and 64% patients in cohort 2 were refractory to most recent therapy.

Vij R et al. *Proc ASH* 2011;Abstract 813.

Efficacy Outcomes

Outcome	Cohort 1	Cohort 2*
Overall response rate (n = 59, 67)	42%	52%
Clinical benefit rate (n = 59, 67)	59%	64%
Median duration of response (n = 25, 35)	13.1 mo	NR
Median duration of clinical benefit response (CBR) (n = 35, 43)	11.5 mo	NR
Median time to progression (n = 59, 67)	8.3 mo	NR
Median time to response (n = 25, 35)	1.0 mo	1.9 mo
Median time to CBR (n = 35, 43)	0.5 mo	0.5 mo
Median progression-free survival (n = 59, 67)	8.2 mo	NR
Median overall survival (n = 59, 67)	NR	NR
Median follow-up (n = 59, 67)	23.2 mo	13.8 mo

* Three patients not evaluable for response
NR = not reached

Vij R et al. *Proc ASH* 2011;Abstract 813.

Grade 3/4 Adverse Events

Event (≥5% patients)	Cohort 1 (n = 59)	Cohort 2 (n = 70)
Hematologic		
Lymphopenia	14%	19%
Anemia	12%	17%
Thrombocytopenia	15%	11%
Neutropenia	12%	14%
Nonhematologic		
Pneumonia	14%	11%
Fatigue	12%	1%
Dyspnea	5%	6%
Treatment-emergent neuropathy	2%	0%

Vij R et al. *Proc ASH* 2011;Abstract 813.

Author Conclusions

- Carfilzomib showed robust and durable single-agent activity in bortezomib-naïve patients with relapsed/refractory MM.
- ORR of 42%–52% and a CBR of 59%–64% were observed in 2 separate dose cohorts. These data are suggestive of a dose–response relationship and are being further evaluated in the exploratory Phase Ib/II study PX-171-007.
- The most common adverse events included fatigue, nausea, anemia, dyspnea, cough and pyrexia, and the majority of AEs were Grade 1 or 2.
- Carfilzomib was associated with minimal peripheral neuropathy.

Vij R et al. *Proc ASH* 2011;Abstract 813.

Investigator Commentary: Single-Agent Carfilzomib in Relapsed and/or Refractory MM

The PX-171-004 Phase II study by Dr Vij and colleagues showed an overall response rate of 42% in cohort 1 and 52% to CFZ in cohort 2 for patients with bortezomib-naïve relapsed MM. This is really quite encouraging because it suggests that CFZ is similar to bortezomib in terms of efficacy as monotherapy, albeit with low-dose dexamethasone administered as a premedication at the time of CFZ administration. Importantly, there was a markedly lower incidence of peripheral neuropathy and, in the context of an equivalent response rate, this is an obvious advantage. For comparison, the Phase III APEX trial recorded a similar overall response rate of 43% to bortezomib as a single agent, with the more recent Phase III study of SC bortezomib (led by Dr Moreau and colleagues) showing a rate closer to 50%, but half as much neuropathy, with the SC route of bortezomib administration having this as a clear benefit to its use.

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

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[1]

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[2]

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.

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.

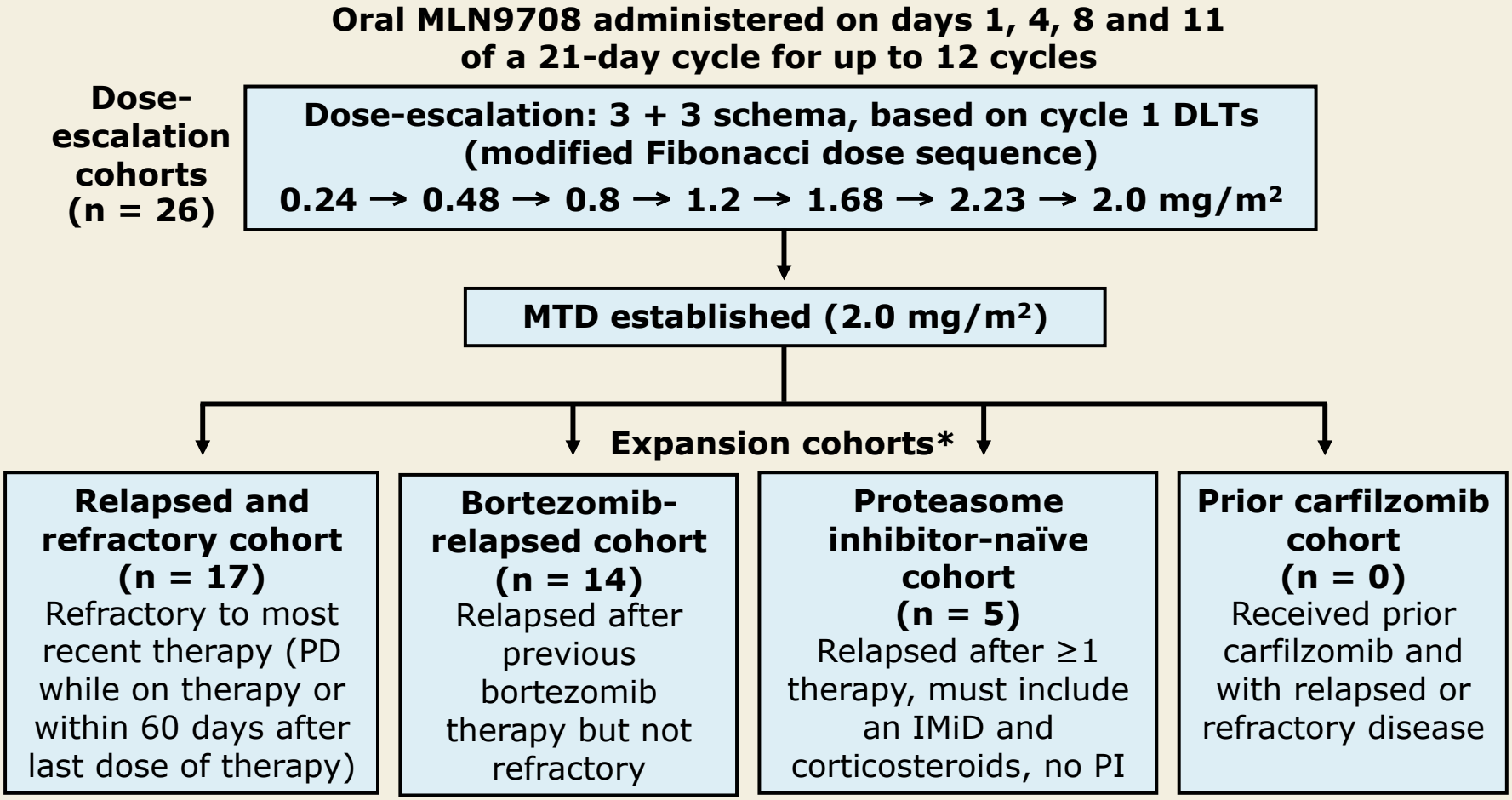
Proc ASH 2011;Abstract 301.

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.

Study Design



* Includes 6 from dose-escalation MTD cohort

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

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.

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.

Author Conclusions

- MTD was established for MLN9708 as 2.0 mg/m^2 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.

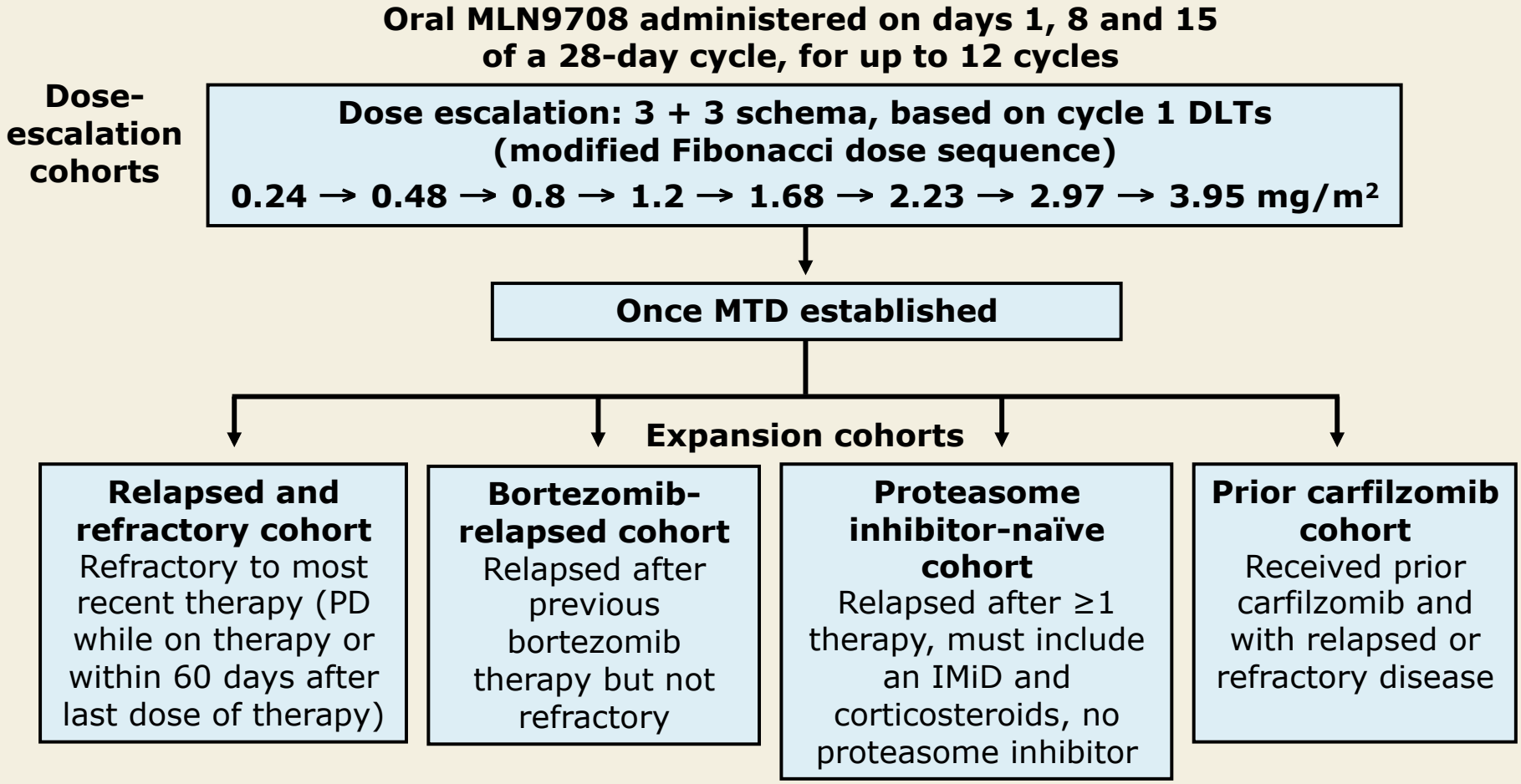
Richardson PG et al. *Proc ASH* 2011;Abstract 301.

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.

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/m^2:
  - 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.

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/m^2.
- 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/m^2)
- 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.

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

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 → 2.23 → 2.97 → 3.95 mg/m^2

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

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

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/discontinuation; Grade 1 drug-related PN in 3 patients; no Grade >1 PN

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

Preliminary Response*

Response	Patients (n = 15)
≥Partial response (PR) through 4 cycles	100%
Complete response	4
Very good PR	5
PR	6
≥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.

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/m^2 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.

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

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[1]

High Response Rates to Pomalidomide and Dexamethasone in Patients with Refractory Myeloma, Final Analysis of IFM 2009-02[2]

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

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

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).

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

Study Design

Eligibility (N = 221)

- Relapsed/refractory MM
- Measurable M-paraprotein in serum/urine
- ≥2 prior therapies
- Progression within 60 days of last treatment
- Prior therapy with ≥2 cycles of LEN and ≥2 cycles of BORT
- Disease refractory to both LEN and BORT allowed

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POM* + LoDEX (n = 113)

POM† (n = 108)

* 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.

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.

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.

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.

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

Eligibility (N = 84)

- Relapsed MM
- Measurable disease
- Refractory to both lenalidomide (LEN) and bortezomib (BORT)
- ANC >1 x 10^9/L, platelets ≥75 x 10^9/L, Hb ≥8 g/dL
- Creatinine clearance ≥50 mL/min

R

Arm A — Cycle 21 days (21/28)
Pomalidomide 4 mg PO, days 1-21
Dexamethasone 40 mg PO
on days 1, 8, 15 and 22

Arm B — Cycle 28 days (28/28)
Pomalidomide 4 mg PO, days 1-28
Dexamethasone 40 mg PO
on days 1, 8, 15 and 22

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.

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.

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.

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

A Phase 2 Study of Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

Lonial S et al.

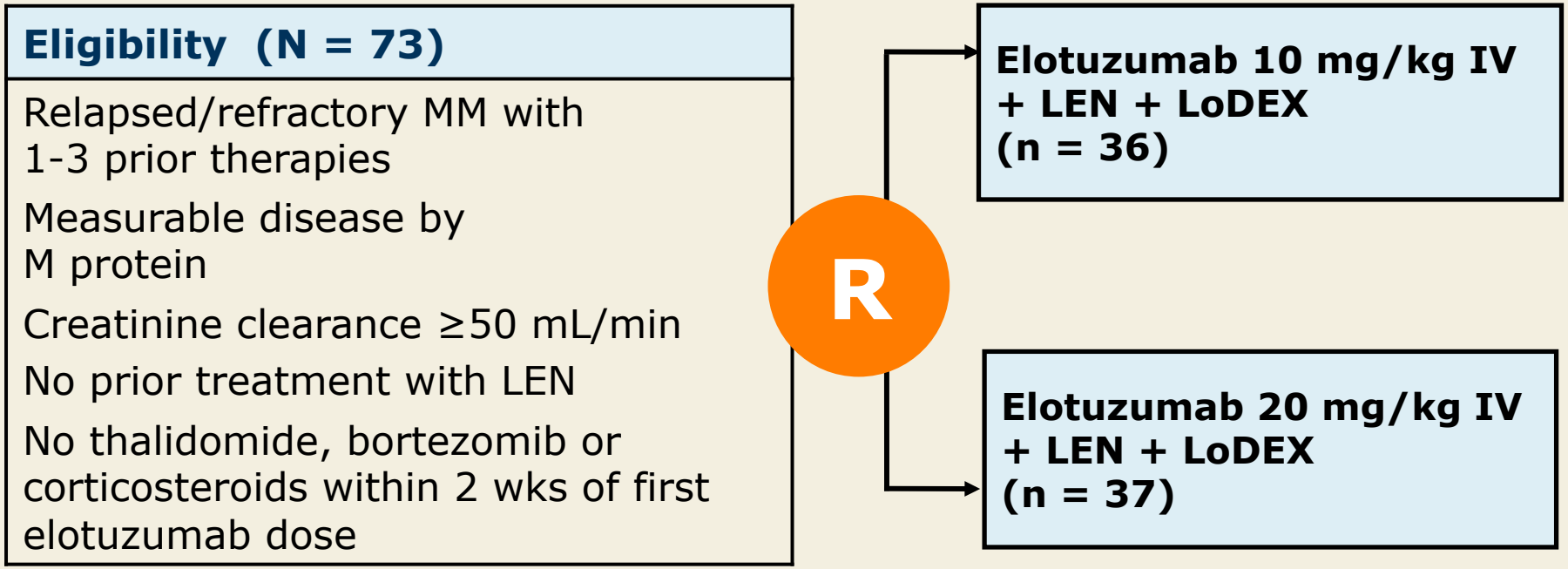
Proc ASH 2011;Abstract 303.

Background

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- CS1 is highly expressed on >95% of MM cells (*Blood* 2008;112:1329; *Mol Cancer Ther* 2009;8:2616).
- The mechanism of action of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- In an MM xenograft mouse model, the combination of elotuzumab and lenalidomide significantly reduced tumor volume compared to either agent alone (*Mol Cancer Ther* 2009;8:2616).

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Study Schema



LEN = lenalidomide 25 mg; LoDEX = low-dose dexamethasone 40 mg

A premedication regimen of methylprednisolone/dexamethasone, diphenhydramine, ranitidine and acetaminophen was administered 30-60 min prior to each elotuzumab infusion.

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Best Response (IMWG Criteria)

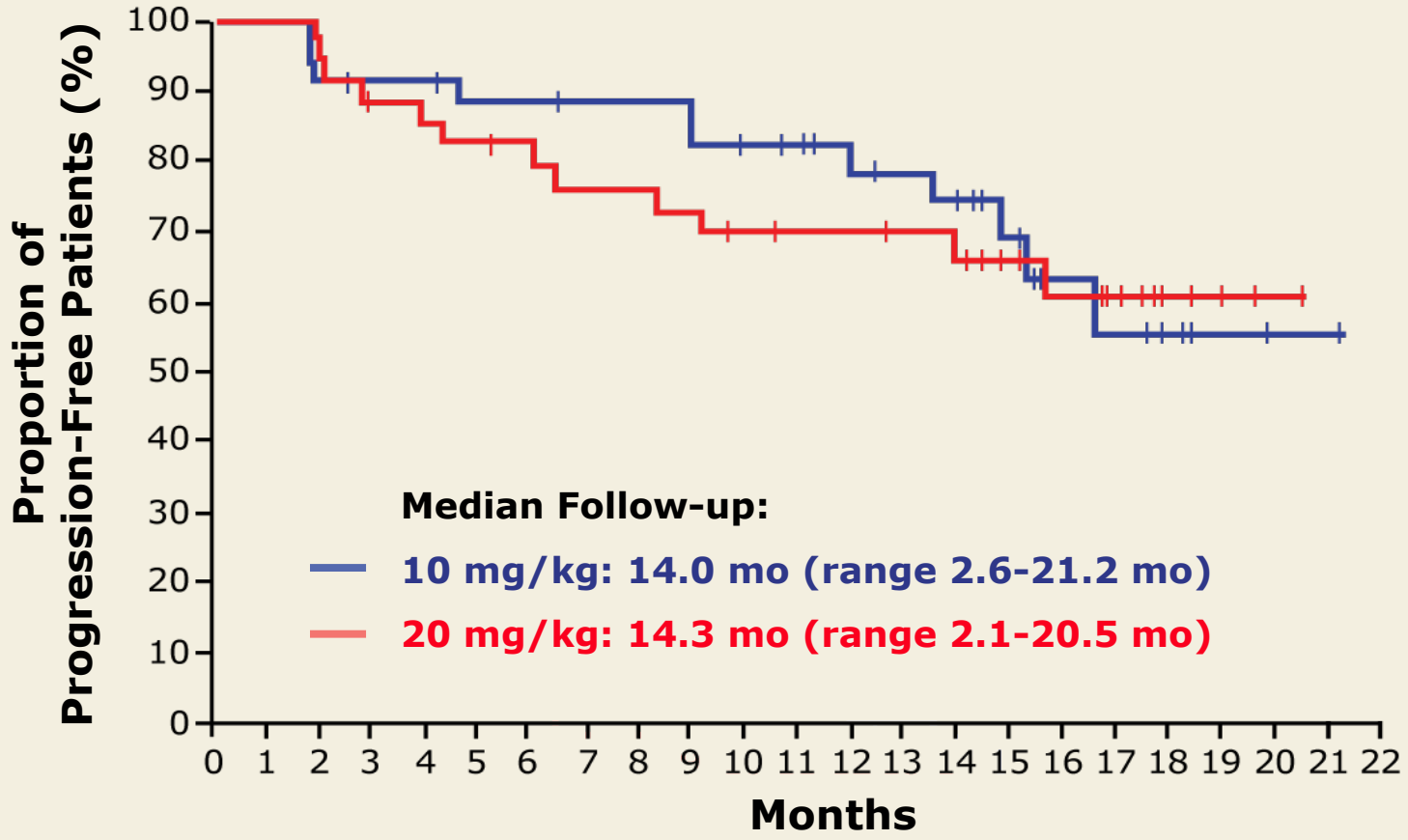
Clinical parameter	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 37)	Total (N = 73)
ORR (≥PR)	92%	73%	82%
CR/stringent CR	14%	11%	12%
VGPR	39%	32%	36%
PR	39%	30%	34%
<PR	8%	27%	18%
ORR with # prior therapies	**(n = 16)**	**(n = 17)**	**Total (n = 23)**
One prior therapy	100%	82%	91%
Two prior therapies	85%	65%	75%

ORR = objective response rate; PR = partial response; CR = complete response; VGPR = very good partial response

Median time to response = 1 mo (range, 0.7-5.8); median time to best response = 2.2 mo (range, 0.7-17.5)

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Progression-Free Survival



At a median follow-up of 14.1 months, the median PFS was not reached. PFS rate was 75% (elotuzumab 10 mg/kg) and 65% (elotuzumab 20 mg/kg).

With permission from Lonial S et al. *Proc ASH* 2011;Abstract 303.

Select Treatment-Emergent Adverse Events (AEs)

Event	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 37)	Total, Gr 3/4 only (N = 73)
Muscle spasms	53%	57%	3%
Diarrhea	56%	51%	5%
Fatigue	53%	43%	7%
Anemia	36%	27%	11%
Neutropenia	31%	22%	16%
Thrombocytopenia	31%	19%	16%
Lymphopenia	28%	19%	16%

One patient had Grade 5 pneumonia complicated by cellulitis and sepsis leading to multiorgan failure.

Peri-infusion AEs (all grades) reported in 67% of patients.

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Author Conclusions

- Elotuzumab plus LEN and LoDEX has a high ORR in relapsed and relapsed/refractory MM (all patients = 82%, elotuzumab 10 mg/kg = 92% and elotuzumab 20 mg/kg = 73%).
- At a median follow-up of 14.1 months, the median PFS was not reached (elotuzumab, 10 mg/kg = 65% and 20 mg/kg = 75%).
- The combination was generally well tolerated:
  - Most common Grade 3/4 treatment-emergent AEs were neutropenia (16%), thrombocytopenia (16%) and lymphopenia (16%).
  - The premedication regimen decreased the incidence and mitigated severity of infusion reactions.
- Two Phase III trials of elotuzumab 10 mg/kg plus LEN and LoDEX for previously untreated and relapsed/refractory MM are ongoing (NCT01335399, NCT01239797).

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Investigator Commentary: Novel Humanized Monoclonal Antibody Elotuzumab for Relapsed and/or Refractory MM

I was the principal investigator of this study, but I believe this agent represents a completely new approach for us in myeloma. Treatment with monoclonal antibodies has permeated all of oncology fairly well. The problem in myeloma has been that even when a good target exists, the immune function may be limiting the ability of an antibody to be effective in treatment. The target can be ligated with an antibody, but if the natural killer cells and others are not available to induce antibody-dependent, cell-mediated cytotoxicity, an antibody-coded cancer cell can continue to act.

I believe that the administration of LEN both enhances the immune function and improves the efficacy of the monoclonal antibody.

Interview with Sagar Lonial, MD, January 25, 2012

VANTAGE 095: An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination with Bortezomib in Patients with Relapsed or Refractory Multiple Myeloma[1]

Phase II Study of the Pan-Deacetylase Inhibitor Panobinostat in Combination with Bortezomib and Dexamethasone in Relapsed and Bortezomib-Refractory Multiple Myeloma (PANORAMA 2)[2]

Update on a Phase III Study of Panobinostat with Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: PANORAMA 1[3]

[1] **Siegel DS et al.**
Proc ASH 2011;Abstract 480.

[2] **Richardson PG et al.**
Proc ASH 2011;Abstract 814.

[3] **San-Miguel JF et al.**
Proc ASH 2011;Abstract 3976.

VANTAGE 095: An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination with Bortezomib in Patients with Relapsed or Refractory Multiple Myeloma

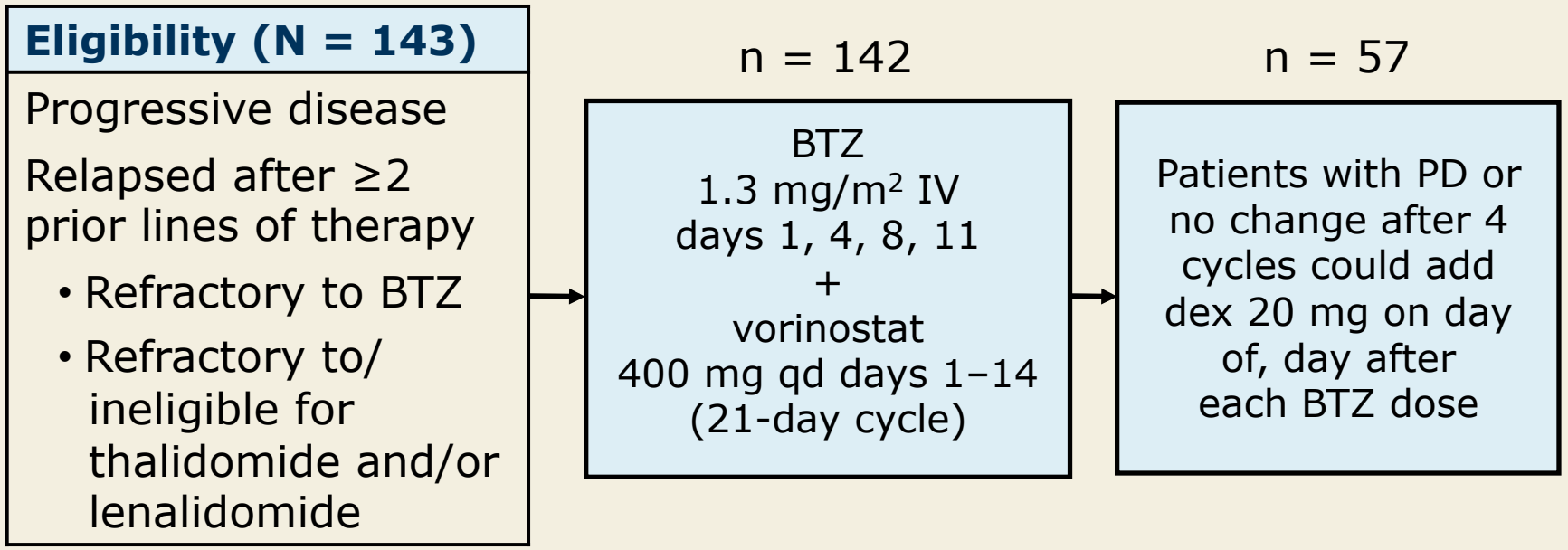
Siegel DS et al.
Proc ASH 2011;Abstract 480.

Background

- Despite the significant advances in multiple myeloma (MM) treatment in the past decade, all patients eventually experience relapse from successive treatment regimens with progressively shorter response durations (*Blood* 2007;110:3557).
- Outcomes are poor for patients who received multiple therapies and whose disease is relapsed and refractory following bortezomib and lenalidomide, with the estimated median survival being approximately 9 months (*Haematologica* 2010;Abstract 0376).
- Epigenetic changes, such as acetylation of histone or nonhistone proteins, are recognized as important factors in cancer development.
- Vorinostat is a histone deacetylase (HDAC) inhibitor that blocks the enzymatic activity of HDAC1, HDAC2, HDAC3, and HDAC6.

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

VANTAGE 095: Study Design



Primary Endpoint: Overall response rate (ORR)

Secondary endpoints: Overall survival (OS), progression-free survival, time to progression, duration of response (DOR), safety

BTZ = bortezomib; PD = progressive disease; Dex = dexamethasone

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Efficacy (IMWG criteria)

Baseline factor (N = 136)*	ORR	CBR	OS
Prior lines of therapy			
<5 (n = 72)	18%	35%	10.9 mo
≥5 (n = 64)	17%	30%	11.4 mo
Previous BTZ regimens			
1 (n = 65)	18%	37%	11.7 mo
>1 (n = 71)	17%	28%	10.8 mo
Previous IMiD regimens			
≤2 (n = 85)	22%	38%	11.2 mo
>2 (n = 50)	10%	24%	10.9 mo

Median overall survival = 11.2 mo
Median progression-free survival = 3.13 mo

* Six patients missing post-baseline assessment
CBR = clinical benefit rate

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Select Adverse Events (AEs)

Adverse event (N = 142)	Any grade	Grade 1/2	Grade 3/4
Hematologic (≥20%)			
Anemia	52%	14%	38%
Thrombocytopenia	70%	2%	68%
Neutropenia	37%	5%	32%
Nonhematologic (≥25%)			
Nausea	57%	50%	7%
Diarrhea	54%	37%	17%
Fatigue	49%	36%	13%
Vomiting	37%	33%	4%
Pyrexia	27%	23%	4%

- Other AEs of interest: Neuropathy, Grade 1/2 = 20%, Grade 3/4 = 2%; febrile neutropenia, Grade 3/4 = 4%
- Deaths due to AE = 4%, deaths due to drug-related AE < 1%

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Author Conclusions

- The combination of vorinostat and bortezomib is active in patients whose disease is considered refractory to prior bortezomib and IMiDs:
  - ORR = 17%; CBR by IMWG criteria = 31%
  - Median DOR of 6.3 months (CBR)
- The median OS was 11.2 months with a 2-year OS rate of 32%.
- The combination is generally well tolerated in patients with heavily pretreated disease, with 27% of patients completing ≥8 cycles.
- The combination of vorinostat and bortezomib may offer a new treatment option for patients with heavily pretreated, double-refractory myeloma.

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Phase II Study of the Pan-Deacetylase Inhibitor Panobinostat in Combination with Bortezomib and Dexamethasone in Relapsed and Bortezomib-Refractory Multiple Myeloma (PANORAMA 2)

Richardson PG et al.

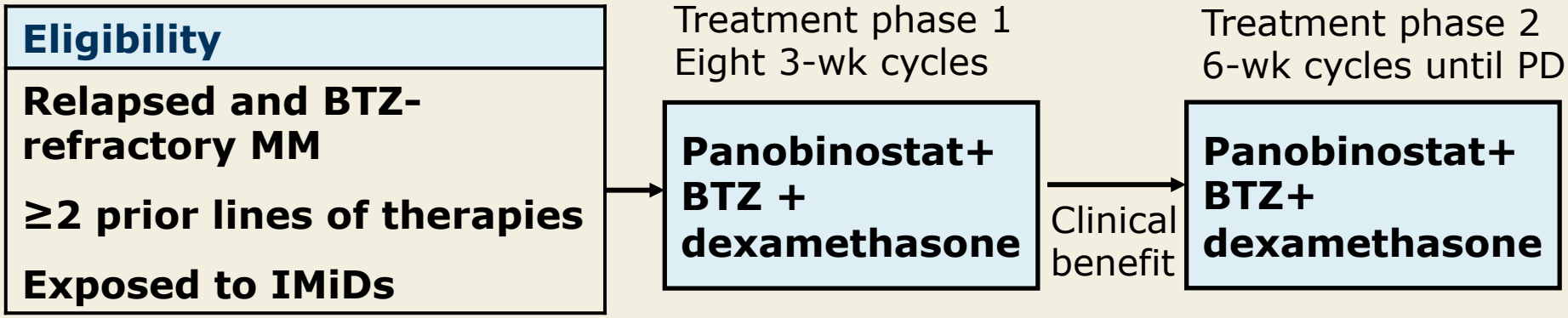
Proc ASH 2011;Abstract 814.

Background

- The proteasome inhibitor bortezomib (BTZ) and the immunomodulatory drug (IMiD) lenalidomide are commonly used for multiple myeloma (MM) treatment (*N Engl J Med* 2003;348:2609; *N Engl J Med* 2007;357:2123)
- Patients with MM refractory to both BTZ and IMiDs have a very poor prognosis (*Leukemia* 2012;26:149)
- Panobinostat is a potent pan-deacetylase inhibitor that increases acetylation of proteins involved in multiple oncogenic pathways (*Cancer Lett* 2009;280:233).
- Panobinostat and BTZ have synergistic antimyeloma activity via targeting of the aggresome and proteasome pathways (*Blood* 2006;108:3441).
- In a Phase Ib trial, the combination of panobinostat and BTZ demonstrated efficacy in patients with MM, including in a subset of patients with disease refractory to BTZ therapy (European Hematology Association 2011;Abstract 0314).
- **Current study objective**: Conduct a single-arm, open-label, Phase II study evaluating the efficacy and safety of panobinostat, BTZ and dexamethasone in patients with BTZ-refractory MM.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

PANORAMA 2 Study Design and Baseline Characteristics



Baseline characteristics	N = 55
Median age (years)	61
ECOG performance status 0-1/2/missing (%)	93/5/2
Median prior regimens	4
Median prior BTZ regimens	2
Prior autologous stem cell transplant (%)	35

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Preliminary Response Data

Best confirmed response*	N = 55
Overall response	29%
Complete response (CR)	—
Near complete response (nCR)	4%
Partial response (PR)	25%
Minimal response (MR)	20%
Clinical benefit (CR + nCR + PR + MR)	49%
Very good partial response	6%

* Confirmed at 6 wk
- Responses typically observed after 1-2 cycles
- Stable disease: 2 patients; progressive disease: 10 patients

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Select Adverse Events

Adverse events (n = 51)	All	Grade 3/4
Thrombocytopenia*	63%	53%
Fatigue	63%	16%
Diarrhea	57%	14%
Anemia	37%	16%
Nausea	59%	6%
Neutropenia	20%	12%
Hypotension	18%	6%
Pneumonia	16%	14%

* Thrombocytopenia managed with dose reduction/interruption.

- Treatment-emergent peripheral neuropathy (24% overall) was generally mild, only 2% Grade 3/4.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Author Conclusions

- Panobinostat synergizes with BTZ in recapturing responses in patients with heavily pretreated, BTZ-refractory MM.
  - Clinical benefit rate = 49%
  - Treatment ongoing in 17 patients
- The combination of panobinostat and BTZ is generally well tolerated.
  - Most common hematologic Grade 3/4 AEs proved manageable with dose interruption/reduction.
- This study and the Phase III PANORAMA 1 trial will further define the role of panobinostat combined with BTZ and dexamethasone in the care of patients with MM.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Update on a Phase III Study of Panobinostat with Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: PANORAMA 1

San-Miguel JF et al.
Proc ASH 2011;Abstract 3976.

PANORAMA 1 Study Design

Target Accrual: 672 (Closed)

Eligibility

Relapsed/refractory MM

1-3 prior lines of therapy

Prior BTZ therapy allowed

BTZ-refractory MM (failure to achieve minimal response or disease progression within 60 days of last BTZ-containing regimen) not permitted

Treatment phase 1
BTZ twice wkly

Panobinostat + BTZ + DEX 3-wk cycles x 8

Clinical benefit

Treatment phase 2
BTZ once wkly

Panobinostat + BTZ + DEX 6-wk cycles x 4

Placebo+ BTZ + DEX

Primary endpoint: Progression-free survival

Secondary endpoint: Overall survival

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Adverse Events (Abstract Only)

Adverse events*	All grades	Grade 3/4
Diarrhea	36%	10%
Thrombocytopenia	41%	29%
Anemia	24%	10%
Fatigue	24%	9%
Neutropenia	12%	8%
Peripheral neuropathy	19%	3%

* n = 267 patients who received 1 dose of treatment

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Author Conclusions

- Preliminary analysis of pooled safety data (blinded) from the first 267 patients treated in PANORAMA 1 demonstrated no new or unexpected AEs.
- The results of PANORAMA 1 along with PANORAMA 2 will help determine the potential role of panobinostat in the treatment of patients with relapsed and refractory MM.

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Investigator Commentary: Future Role of Deacetylase Inhibitors — Vorinostat and Panobinostat — in MM

Deacetylase inhibitors definitely have a role in MM treatment in my view, especially in combination, but we need to study all the agents and know where to administer them, at what dose and schedule and with what partner. Agents like vorinostat and panobinostat are in the same class, and GI side effects, fatigue and thrombocytopenia are a potential challenge with this group. Panobinostat partners very well with bortezomib in combination with dexamethasone, and efficacy has been seen even in patients with bortezomib-refractory disease, with a Phase III comparative trial approaching completion. Conversely, vorinostat is promising in combination with lenalidomide, as well as with bortezomib, although results from the Phase III VANTAGE trial were somewhat disappointing, perhaps due to difficulties with the optimal dose and schedule used for these 2 drugs in that particular study. Romidepsin is very active in combination with bortezomib, with fatigue and thrombocytopenia but not GI toxicity as dose-limiting side effects. Studies combining it with lenalidomide are now underway. Finally, an HDAC6-specific inhibitor (ACY-1215) has just entered clinical trial as a single agent and shows early promise, especially in terms of tolerability.

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