5 Minute JournalClub

Key ASH Presentations

Issue 7, 2011

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CME Information

LEARNING OBJECTIVES

- Compare and contrast the efficacy and safety outcomes with subcutaneous versus intravenous bortezomib administration in multiple myeloma.
- Counsel patients with multiple myeloma about the known benefits and risks of bortezomib when administered subcutaneously and intravenously.
- Recall the efficacy and safety outcomes with the pomalidomide/dexamethasone combination in patients with multiple myeloma refractory to both bortezomib and lenalidomide.
- Identify the two dosing schedules of pomalidomide currently under investigation in refractory multiple myeloma.
- Recall the efficacy and safety of single-agent carfilzomib in relapsed/refractory multiple myeloma.
- Recognize the role of off-target proteasome inhibition in the development of treatment-related peripheral neuropathy.

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:

Rafael Fonseca, MD
Consultant, Professor of Medicine
Mayo Clinic Arizona
Deputy Director, Mayo Clinic Cancer Center
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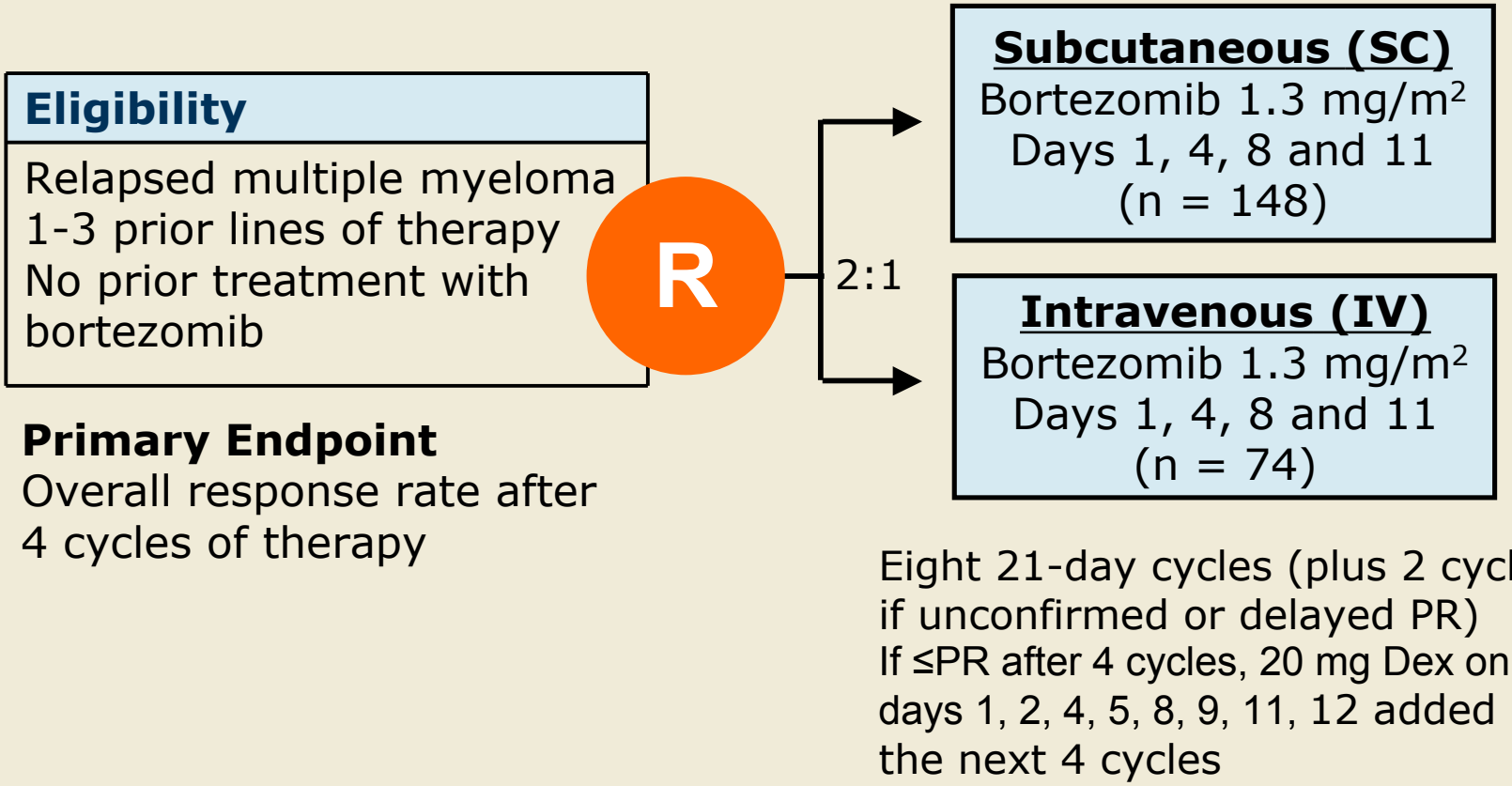
Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; *Paid Research:* Celgene Corporation, Onyx Pharmaceuticals Inc.

A Phase 3 Prospective, Randomized, International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma

Moreau P et al.

Proc ASH 2010;Abstract 312.

Phase III Multicenter Trial Schema



Primary Endpoint
Overall response rate after 4 cycles of therapy

Eight 21-day cycles (plus 2 cycles if unconfirmed or delayed PR)
If ≤PR after 4 cycles, 20 mg Dex on days 1, 2, 4, 5, 8, 9, 11, 12 added in the next 4 cycles

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Treatment Exposure

	Bortezomib SC (n = 147)*	Bortezomib IV (n = 74)
Number of Cycles (Median)	8	8
Time on Study Drug (Median)	22.57 weeks	22.57 weeks
Cumulative Bortezomib Dose (Median)	33.76 mg/m^2	31.46 mg/m^2
Patients Receiving Dexamethasone	56%	53%

* Data shown for safety population. One patient in the SC arm was not treated.

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Clinical Responses After Four Cycles

	Bortezomib SC (n = 145)	Bortezomib IV (n = 73)
Overall Response Rate[1]	42%	42%
Complete Response (CR)	6%	8%
Partial Response (PR)	36%	34%
≥Very Good PR (VGPR)	17%	16%

[1] Relative risk of overall response rate is 0.99 with 95% confidence interval of 0.71-1.37

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Additional Efficacy Outcomes

In Responding Patients	Bortezomib SC (n = 76)	Bortezomib IV (n = 38)
Time to First Response (Median)	1.4 mos	1.4 mos
Time to Best Response (Median)	1.6 mos	1.5 mos
Duration of Response (Median)	9.7 mos	8.8 mos

Intent-to-Treat Population	Bortezomib SC (n = 148)	Bortezomib IV (n = 74)
Time to Disease Progression (Median)	10.4 mos	9.4 mos
One-Year Survival Rate	72.6%	76.7%

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Select Adverse Events

	Bortezomib SC (n = 147)	Bortezomib IV (n = 74)	*p*-value
Grade ≥3 Adverse Events	57%	70%	—
Grade 3/4 Anemia	14%	12%	—
Grade 3/4 Leukopenia	8%	18%	—
Peripheral Neuropathy (All Grades)	38%	53%	0.04
Grade ≥3 Peripheral Neuropathy	6%	16%	0.03

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Author Conclusions

- The efficacy of bortezomib is similar by SC and IV administration in patients with relapsed MM.
- The PK-PD profiles of SC and IV bortezomib are similar (data not shown).
- SC administration of bortezomib appears to have an improved safety profile with respect to peripheral neuropathy compared to IV administration.
- SC administration has acceptable local tolerability (data not shown).

Moreau P et al. *Proc ASH* 2010;Abstract 312.

Investigator comment on subcutaneous versus intravenous administration route for bortezomib in multiple myeloma

This is definitely exciting as it makes it more convenient for the patients, who may not have to have an IV line placed for bortezomib infusions. Based on this study, the subcutaneous route of administration of bortezomib appears to be at least as effective, if not potentially even better than, the intravenous route. The data even show a lower rate of peripheral neuropathy and ≥Grade 3 adverse events.

This opens a new door for a more convenient treatment for patients with myeloma, many of whom have difficulties with mobility and access to the clinic. Even self-administration approaches could be explored without any compromise in tolerability. Hopefully this will be adopted as a standard approach as more information comes forward.

Interview with Rafael Fonseca, MD, December 22, 2010

Pomalidomide plus Low-Dose Dexamethasone in Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies in Dual-Refractory Disease

Lacy MQ et al.

Proc ASH 2010;Abstract 863.

Background

- Pomalidomide/dexamethasone (pom/dex) regimen using a pom dose of 2 mg/day has demonstrated response rates of:
  - 63% in relapsed multiple myeloma (*JCO* 2009;27:5008)
  - 32% in a lenalidomide-refractory cohort (*Leukemia* 2010;24:1934)
- The maximum tolerated dose of pomalidomide has been determined to be 4 mg/day for 21 of 28 days (*Proc ASH* 2009;Abstract 301).
- Two sequential phase II trials were opened to evaluate the efficacy of a pom/dex regimen using different doses of pom in patients with multiple myeloma refractory to both lenalidomide and bortezomib.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

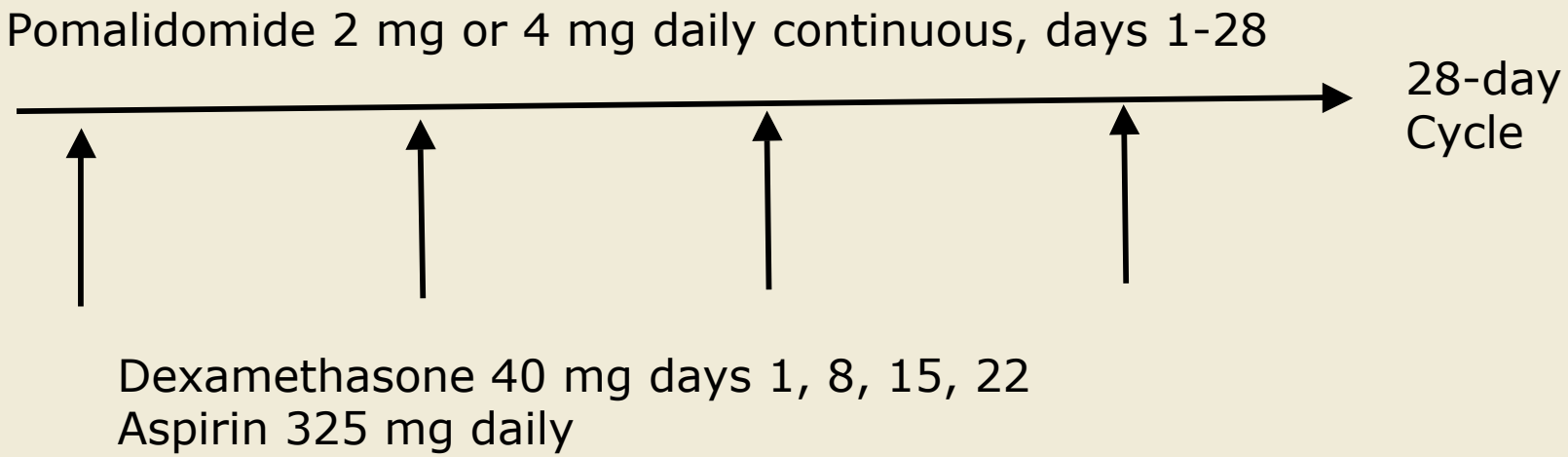
Study Methods and Objectives

- **Methods**
  - Two sequential Phase II trials opened with 35 patients each
    - May 2009 - Nov 2009: Cohort A (2 mg/day pom)
    - Nov 2009 - Apr 2010: Cohort B (4 mg/day pom)
  - Responses were assessed according to IMWG response criteria
- **Study Objectives**
  - Assess response rate and duration of remission in dual-refractory multiple myeloma
  - Assess toxicity in this patient population

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Treatment Schema

Eligibility
Previously treated multiple myeloma
Resistant/refractory to both lenalidomide and bortezomib
≥1 prior regimen; no upper limit on number of previous regimens



If no response after 2 cycles, or if progression, then pomalidomide dose could be increased to 4 mg/day in the 2 mg cohort.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Efficacy Assessment

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Confirmed Response (≥PR)	26%	26%
≥Minimal Response	49%	40%
Time to Response (Median)	1 month	1.7 months
Duration of Response	12 months	Not attained
Survival Rate at 6 Months	78%	69%

≥MR in patients from both subgroups (N = 62) considered to be at high risk was 33%.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Select Adverse Events

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Grade 3/4 Neutropenia	49%	66%
All Grades Neuropathy (Possibly attributed to pomalidomide)	20%	29%
Grade 3/4 Neuropathy (Possibly attributed to pomalidomide)	0%	3%
Thromboembolic Events	9%	6%

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Author Conclusions

- Pomalidomide/dexamethasone has significant activity in heavily pretreated myeloma refractory to lenalidomide and bortezomib.
- Responses are rapid with median time to response within 2 months.
- Toxicity is manageable at both dose levels and consists primarily of neutropenia, but rate is higher at the 4-mg continuous dose.
- No evidence for dose response; responses appear similar with both dose levels.
- Effective in patients at high risk.
- Studies ongoing to assess whether pom starting dose of 4 mg for 21 of 28 days is equally efficacious while producing less toxicity.

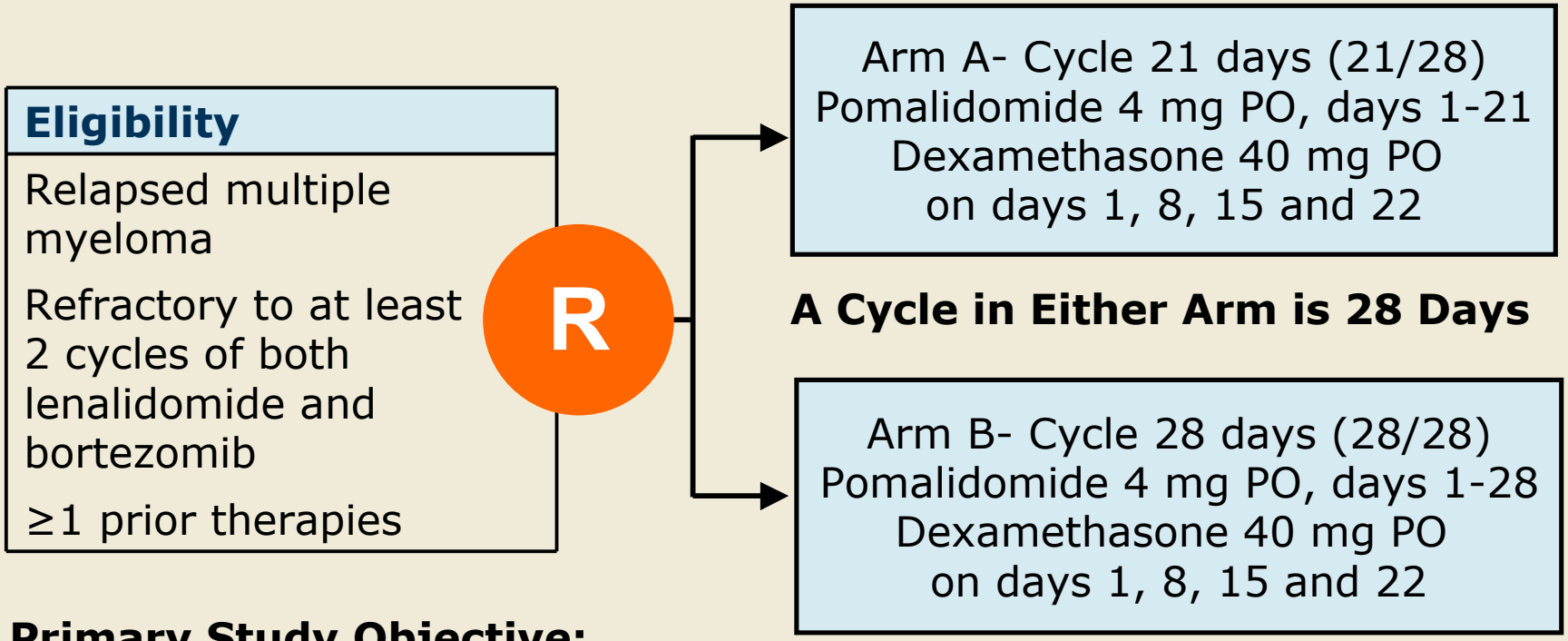
Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Phase 2 Randomised Open Label Study of 2 Modalities of Pomalidomide plus Low-Dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02

Leleu X et al.

Proc ASH 2010;Abstract 859.

IFM 2009-02 Phase II Study Schema



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

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Efficacy Assessment

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Overall Response Rate (≥PR)	42%	39%
Stable Disease	46.5%	51%
Time to Best Response	2 months	1.7 months
Time to Progression, Median*	7 months	9.7 months

* Median follow-up was 6.5 months for Arm A and 7 months for Arm B.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Select Adverse Events

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
≥Grade 3 Events	23.5%	26.5%
Percentage Hematologic Events of All ≥Grade 3 Events	66%	76%
Neuropathy	0	0
Deep Vein Thrombosis (with prophylactic treatment)	0	0

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Author Conclusions

- Pomalidomide and dexamethasone combination provides responses in patients with advanced myeloma refractory to bortezomib and lenalidomide.
- Pomalidomide 4 mg per day is well tolerated.
- Pomalidomide 4 mg per day 21 days out of 28-day cycle does not appear inferior to pomalidomide 4 mg per day continuous on 28-day cycle.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Investigator comment on pomalidomide/dexamethasone combination for multiple myeloma refractory to both lenalidomide and bortezomib

The presentation by Lacy was from a series of Phase II trials conducted at my institution. The study essentially showed that significant activity with the pomalidomide/dexamethasone combination is observed in patients who are truly refractory to both bortezomib and lenalidomide. The minor responses were as high as 49 percent, and thus support that once approved, this combination could be an alternative for patients with refractory disease.

The study by Leleu also showed that in this patient population with heavily pretreated disease, there is a significant likelihood of patients achieving responses. Regarding the specific issues of the two dosing cycles of 21/28 or 28/28, I believe it is hard to compare them right now, so I would not like to make a statement that either therapy was better. My take from this study is that even being the third IMiD® and being similar to both thalidomide and lenalidomide, pomalidomide has a different efficacy and safety profile, and in my opinion, it will soon be part of the standard armamentarium against myeloma.

Interview with Rafael Fonseca, MD, December 22, 2010

Carfilzomib: High Single-Agent Response Rate with Minimal Neuropathy Even in High-Risk Patients

Vij R et al.

Proc ASH 2010;Abstract 1938.

Background

- Carfilzomib (CFZ) is a selective epoxyketone proteasome inhibitor that elicits potent and sustained proteasome inhibition.
- CFZ appears to lack some of the off-target activities associated with the proteasome inhibitor bortezomib, such as severe, dose-limiting peripheral neuropathy (PN) (*J Clin Oncol* 2009;27:3518).
- Durable single-agent activity with CFZ has been observed in patients with relapsed/refractory multiple myeloma (R/R MM) who have received multiple prior lines of therapy, as well as in patients with significant comorbidities *(Proc ASCO* 2009;Abstract 8504*).*

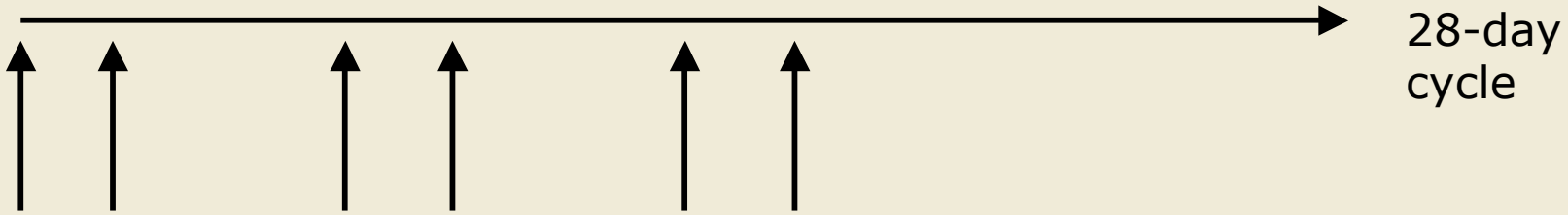
Vij R et al. *Proc ASH* 2010;Abstract 1938.

PX-171-004 Trial Schema*

Eligibility

Relapsed and/or refractory multiple myeloma, after 1-3 prior lines of therapy

Responsive (achieved minimal response or better) to standard first-line therapy



Intravenous carfilzomib on days 1, 2, 8, 9, 15, 16

Two Dose Cohorts

Cohort 1: Patients received carfilzomib 20 mg/m^2 on each administration in each cycle for up to 12 cycles

Cohort 2: Patients received carfilzomib 20 mg/m^2 on each administration in cycle 1 and at 27 mg/m^2 on each administration in subsequent cycles 2-12

*Current analysis performed on 125 patients with bortezomib-naïve disease

Vij R et al. *Proc ASH* 2010;Abstract 1938.

Efficacy Assessment

	Cohort 1 (n = 59)	Cohort 2 (n = 64)
Overall Response (OR)	42%	53%
Clinical Benefit Rate (OR + Minimal Response)	59%	63%
Duration of Response (Median)	13.1 months	Not Reached (>13 months)

Baseline Characteristics	N	Overall Response Rate
ISS Stage I or II ISS Stage III	92 19	48% 42%
Cytogenetics/FISH: Normal/Favorable Cytogenetics/FISH: Unfavorable	88 16	50% 38%

Vij R et al. *Proc ASH* 2010;Abstract 1938.

Author Conclusions

- Notable response rates for single-agent CFZ in bortezomib-naïve R/R MM.
  - 53% overall response in cohort 2
  - Durable responses
- Responses achieved with single-agent CFZ are durable.
  - Median DOR in Cohort 1: 13.1 months
  - Median DOR in Cohort 2: not yet reached (>13 months)
- The adverse (AE) profiles observed with both dosage regimens were similar and AEs were generally mild and clinically manageable (data not shown).
  - PN was infrequent and did not limit therapy, even in patients with active symptoms at baseline.
  - Fatigue, nausea, anemia, and dyspnea were the most commonly reported AEs.
  - There was no evidence of increased toxicity with increased CFZ dosage of 27 mg/m^2.
- CFZ is well tolerated for at least 12 cycles (~1 year), suggesting that prolonged administration is feasible.

Vij R et al. *Proc ASH* 2010;Abstract 1938.

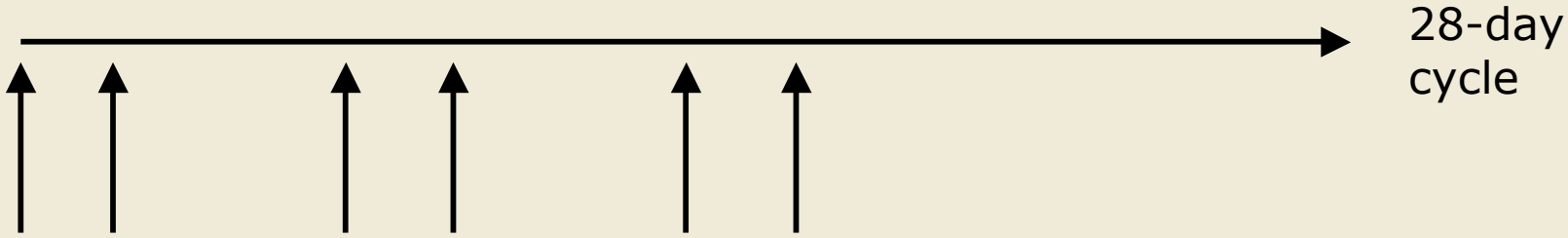
Baseline Peripheral Neuropathy Does Not Impact the Efficacy and Tolerability of the Novel Proteasome Inhibitor Carfilzomib (CFZ): Results of a Subset Analysis of a Phase 2 Trial in Patients with Relapsed and Refractory Multiple Myeloma (R/R MM)

Martin T et al.

Proc ASH 2010;Abstract 3031.

PX-171-003-A1 Trial Schema

Eligibility (N = 266)
Relapsed/refractory multiple myeloma



Intravenous carfilzomib: 20 mg/m^2 on days 1, 2, 8, 9, 15, 16 in cycle 1 and thereafter 27 mg/m^2 for up to cycle 12 on days 1, 2, 8, 9, 15, 16 of the respective cycles

Patients completing 12 cycles were eligible for an extension study

Subset analysis performed on patients with baseline Grade 1-2 peripheral neuropathy [PN] (206/266; 77%)

Martin T et al. *Proc ASH* 2010;Abstract 3031.

Efficacy Assessment (from Abstract)

Response Category (n = 202)*	CFZ
Overall Response Rate	24%
Clinical Benefit Rate (≥Minimal Response)	36%

***Responses in the subset of patients with baseline PN were nearly identical to those seen in the full study population**

	Overall Cohort (n = 266)	Baseline PN Cohort (n = 202)
Duration of Response (Median)	7.4 months	7.4 months
Duration of Minor Response (Median)	6.3 months	6.3 months

Martin T et al. *Proc ASH* 2010;Abstract 3031.

Select Safety Events (from Abstract)

Grade 3/4 Neutropenia	9%
All Grades New Onset PN	15%
Grade 3/4 New Onset PN	0.4%

Martin T et al. *Proc ASH* 2010;Abstract 3031.

Author Conclusions

- Analysis of the subset of patients (77%) with active Grade 1-2 peripheral neuropathy demonstrates that baseline PN has no impact on depth or durability of responses or on the tolerability of carfilzomib in heavily pretreated patients with relapsed refractory MM.
- New or worsening PN is very uncommon.
- Paresthesias and dysesthesia were generally infrequent and mild (data not shown).
- Carfilzomib can be administered to patients with baseline PN with little risk of exacerbation.
- Prolonged therapy is possible in this patient population.

Martin T et al. *Proc ASH* 2010;Abstract 3031.

Investigator Commentary: Carfilzomib for Patients with Relapsed or Refractory Multiple Myeloma

Both of these presentations show that the rate of peripheral neuropathy in patients treated with carfilzomib is quite low, and in fact there appears to be a lack of worsening in patients with pre-existing neuropathy. One more theme emerging here is the possibility that carfilzomib, like bortezomib, may be particularly important for patients who have unfavorable cytogenetic findings.

Although these studies are somewhat limited by the sample size, it is quite possible that carfilzomib will have a high activity as a proteasome inhibitor, with particular potential benefit for patients with high-risk disease. The presentations confirm the safety of carfilzomib in this patient population.

Interview with Rafael Fonseca, MD, December 22, 2010