

Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma

Lacy MQ et al.

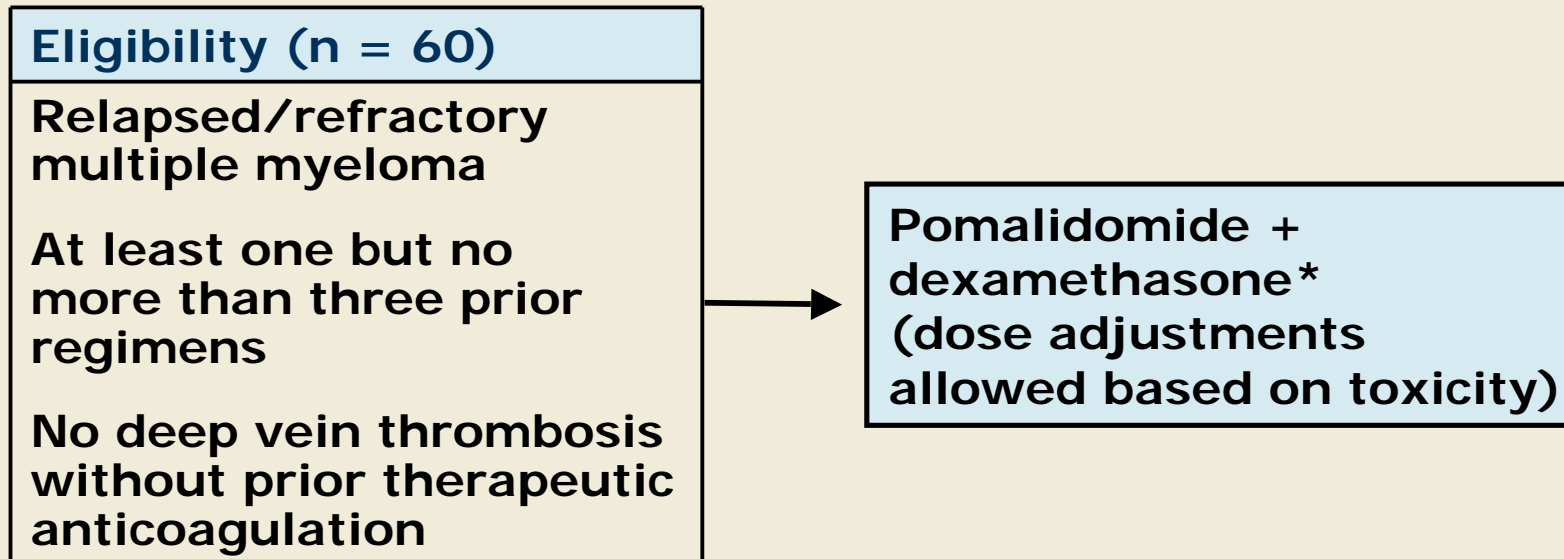
J Clin Oncol 2009; 27(30):5008-14.

Introduction

- A curative therapy for multiple myeloma (MM) does not exist and most patients relapse.
- Pomalidomide is a new immunomodulatory drug demonstrated to be highly potent in vitro (*Blood* 2006; 107: 3098; *Leukemia* 2003; 17: 41).
- Pomalidomide dosed from 1 to 5 mg/mL has been shown to be well tolerated in Phase I trials in patients with relapsed MM (*Br J Haematol* 2008; 141: 41).
- **Current study objective:**
 - Assess the efficacy and safety of pomalidomide plus dexamethasone therapy for patients with relapsed MM.

Phase II Trial of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Relapsed Multiple Myeloma

Protocol ID: NCT00558896



** Pomalidomide 2 mg/day oral, d1-28 q28 days*

Dexamethasone 40 mg/day oral, d1, 8, 15, 22 q28 days

Confirmed Responses in Patients with Refractory Disease

Response	CR	VGPR	PR	RR
Total population (n = 60)	5%	28%	30%	63%
Bortezomib refractory (n = 10)	10%	20%	30%	60%
Lenalidomide refractory (n = 20)	0%	5%	35%	40%
Bortezomib and lenalidomide refractory (n = 5)	0%	20%	40%	60%

CR = complete response; VGPR = very good partial response; PR = partial response; RR = response rate (CR + VGPR + PR)

Confirmed Responses in Patients at High Risk

Response	CR	VGPR	PR	RR
All high risk* (n = 19)	5%	27%	42%	74%
Deletion 13 (n = 4)	0%	25%	75%	100%
t(14;16) (n = 3)	0%	0%	67%	67%
17p- (n = 5)	0%	60%	40%	100%
PCLI \geq 3% (n = 8)	12.5%	25%	25%	63%

Only one patient with t(14;16) achieved stable disease.

** Two patients had two high-risk factors; PCLI = plasma cell labeling index*

Conclusions

- The pomalidomide plus low-dose dexamethasone combination was highly active as a treatment for relapsed/refractory MM.
 - RR in patients with refractory MM: 63%
 - RR in patients with high-risk MM: 74%
- Toxicity was mild and consisted mainly of Grade 3/4 neutropenia (data not shown).
- Additional Phase II trials are planned with this treatment combination to better define response rates in patients with lenalidomide- and bortezomib-refractory MM.

Faculty Comments

DR GIRALT: Pomalidomide is a new immunomodulator that is highly potent in vitro against multiple myeloma and is evaluated in this Phase II study in combination with low-dose dexamethasone.

The combination is highly active in relapsed myeloma, and responses are observed across the board, even in patients who had experienced progression on lenalidomide and bortezomib combinations and in those with high-risk disease by cytogenetics. Toxicity is mild and consists mainly of Grade III or IV neutropenia.

Faculty Comments (Continued)

DR ORLOWSKI: Pomalidomide was administered once a day with weekly dexamethasone and with aspirin for thromboprophylaxis. Of 60 patients who were enrolled, 38 patients or 63 percent achieved a response.

Responses were observed in 40 percent of patients with lenalidomide-refractory disease and 60 percent of patients with disease that was refractory to both bortezomib and lenalidomide. This will be a great drug to have in the relapsed and/or refractory setting after therapy with bortezomib or one of the other immunomodulatory drugs.

**PX-171-004, an Ongoing
Open-Label Phase II Study of
Single-Agent Carfilzomib (CFZ)
in Patients with Relapsed or
Refractory Myeloma (MM):
Updated Results from the
Bortezomib-Treated Cohort**

Siegel D et al.

Proc ASH 2009; Abstract 303.

Introduction

- CFZ may provide greater, more sustained proteasomal inhibition than bortezomib (BTZ):
 - CFZ overcomes BTZ resistance in vitro (Blood 2007;110:3281).
 - Durable responses and disease control were observed in a Phase II study for progressive MM (ASCO 2009;Abstract 8504).
- **Current study objective:**
 - Evaluate patient responses by IMWG criteria from the bortezomib-treated cohort of the PX-171-004 study
 - Primary objective: Overall response rate (ORR), defined as \geq partial response

Phase II Study of CFZ for Relapsed or Refractory MM (BTZ-Treated Cohort)

Protocol ID: PX-171-004

Eligibility

Relapsed/refractory MM (<25% response or progressed during therapy)

1-3 prior treatment regimens



BTZ-treated cohort (n = 35)

CFZ 20 mg/m² IV bolus
Days 1, 2, 8, 9, 15 and 16
q 28 days up to 12 cycles

Efficacy of CFZ Therapy in BTZ-Treated Cohort (n = 33*)

Complete response	1 (3%)
Very good partial response	1 (3%)
Partial response (PR)	4 (12%)
Minimal response (MR)	4 (12%)
Stable disease ≥ 6 weeks	13 (39%)
ORR (\geq PR) = 18%; CBR (\geq MR) = 30%; disease control = 70%	

Duration of \geq MR = 9.0 mo; duration of \geq PR = 10.6 mo

*Median TTP = 5.3 mo at 11.5-month follow-up; * Evaluable patients*

Select \geq Grade 3 Adverse Events*

Anemia	5 (14%)
Neutropenia	4 (11%)
Thrombocytopenia	2 (6%)
Pneumonia	2 (6%)
Dyspnea	2 (6%)
Upper respiratory infection	2 (6%)

* Includes related and nonrelated Grade 3 or 4 events in >5% of patients

Conclusions

- CFZ (20 mg/m²) achieves durable responses and disease control in patients with MM despite prior bortezomib treatment.
 - 18% ORR; 70% disease control; TTP = 5.3 mo
- Adverse events are mild and manageable.
 - Tolerability permits long-term treatment — 23% completed 12 cycle protocol (~ 1 year therapy; data not shown).
 - Peripheral neuropathy is rare, mild and does not limit therapy despite preexisting symptoms (data not shown).
- These data support the continuing evaluation of CFZ as a treatment option for MM.
 - Ongoing Phase II trial (PX-171-003 A1, n = 269) is further studying this agent in relapsed and refractory MM.

Faculty Comments

DR GIRALT: Another new agent that we hope will come soon to the clinic is carfilzomib. These data suggest that single-agent carfilzomib is well tolerated and effective in patients who have experienced progression on prior bortezomib.

It will be an important addition to our clinical armamentarium against relapsed and refractory multiple myeloma.

Faculty Comments (Continued)

DR ORLOWSKI: Carfilzomib is a second-generation proteasome inhibitor and causes irreversible proteasome inhibition as bortezomib causes reversible proteasome inhibition. The data presented are from a cohort of patients who had relapsed or refractory disease. The median number of prior regimens was three: All had received bortezomib therapy and 77 percent had received lenalidomide or thalidomide.

The overall response rate was 18 percent in this heavily pretreated group, and the median duration of response was 10.6 months. The neuropathy rate was low with no Grade IV neuropathy and Grade III neuropathy in only 2.9 percent of the patients.