5 Minute JournalClub

POST-ASH Issue 1, 2013

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

CME Information

LEARNING OBJECTIVES

- Develop an understanding of cereblon as a mediator of immunomodulatory drug function and its correlation with the efficacy of immunomodulatory drugs in multiple myeloma.
- Compare and contrast the benefits and risks of immunomodulatory drugs in combination with other agents in the treatment of relapsed/refractory multiple myeloma.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2013/1/CME.

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:

A Keith Stewart, MBChB
Dean for Research, Mayo Clinic in Arizona
Consultant, Division of Hematology/Oncology
Vasek and Anna Maria Polak Professorship in Cancer Research
Scottsdale, Arizona

Advisory Committee: Onyx Pharmaceuticals Inc; *Consulting Agreements:* Celgene Corporation, Millennium: The Takeda Oncology Company; *Paid Research:* Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

5 MinuteJournalClub

POST-ASH Issue 1, 2013

ASH highlights: An important new IMiD is about to come on board in multiple myeloma

The rapid evolution of effective agents in multiple myeloma over the past few years has changed the face of the disease by tripling average overall survival rates from approximately 2-3 years to about 7-8 years. At ASH 2012 this inspiring march of progress continued most notably with the presentation of definitive data on the third-generation, orally administered immunomodulatory (IMiD) agent pomalidomide. These were accompanied by provocative findings on a new predictor of clinical benefit for this class of drugs and several other related data sets. Here's the bottom line:

1. Phase III trial of pomalidomide (POM)

Dr Meletios Dimopoulos' late-breaking presentation of a Phase III study comparing high-dose dexamethasone (HDD) to POM/low-dose dexamethasone (dex) in patients with a median of 5 prior treatments — including bortezomib and lenalidomide (len) for most — was maybe the most discussed practice

changer from the meeting. Among the groundbreaking results that were unveiled, perhaps the most impressive were hazard rates for both progression-free and overall survival of about 0.5 despite the fact that 29% of patients crossed over to POM after progression on HDD.

This and prior work has shown that the drug is generally well tolerated except for some myelosuppression, and as with the other IMiDs thromboprophylaxis with at least low-dose aspirin is recommended. Even without these Phase III data many believed the FDA was poised to approve POM based on impressive Phase II results in patients with extensive prior treatment, and now it seems almost certain that in the next few weeks oncologists will have access to yet another option for patients with relapsed/refractory disease, less than a year after the approval of carfilzomib.

2. Potentially promising POM combinations

ClaPD (clarithromycin, POM, dex)

One of the more pleasant-sounding myeloma acronyms is BiRD, a regimen that was pioneered by Cornell's Dr Ruben Niesvizky that combines len and dex with a fascinating and unusual ingredient, the macrolide antibiotic clarithromycin, which is purported to slow the hepatic clearance of dex and to possess immunomodulatory properties. Perhaps the lack of Phase III supporting data is why BiRD is not commonly used in practice today, and one has to wonder if these promising Phase II results will be enough to help this approach, which replaces len with POM, gain traction. Regardless, the findings provide even more validation of the substantial activity of POM.

PCP (POM, cyclophosphamide, prednisone)

For the past few years Dr Antonio Palumbo has been evaluating regimens that can be administered without complications for prolonged durations — particularly in elderly patients — because he believes the key to long-term success is long-term therapy. In that vein, PCP — an all-oral regimen that after 6 cycles drops the C and continues POM/prednisone until disease progression — not only produced impressive disease control (51% PR/CR with median PFS 10.4 months) but was also very well tolerated.

3. Cereblon (CRBN) as a marker for IMiD activity

A couple of years back Dr Keith Stewart noticed a Japanese paper in *Science* demonstrating that the clear-cut mechanism of teratogenicity for thalidomide was binding to CRBN, an adaptor protein that is part of the E3 ubiquitin ligase complex. A logical extension of this concept was the theory that this interaction was also the basis for the profound, yet somewhat obscure, antimyeloma action of IMiDs. After obtaining strong in vivo supporting evidence, Dr Stewart, his Mayo Clinic team and other sites set out to correlate CRBN levels in myeloma cells with the clinical activity of this class of agents. Two ASH papers — one in patients receiving len/dex and another in patients receiving POM/dex — moved this important initiative closer to a clinical reality by demonstrating a tripling of response and survival in individuals with higher versus lower CRBN levels. Although the ideal method to measure CRBN and the clinical applicability of these results are still being determined and debated, it seems quite plausible that in the not-too-distant future a related predictive assay will become an important part of myeloma practice.

4. IMiDs and monoclonal antibodies (moAbs)

It has always been a bit ironic that although moAbs have been utilized in a variety of solid tumors and hematologic cancers, none have been found useful in this disease, which is defined by abnormal antibody production. However, at ASH we saw evidence that this phenomenon may soon change based on encouraging data with elotuzumab (elo), which targets the CS1 antigen, and daratumumab, an anti-CD38 antibody.

Elo is farther along in development, and although it has minimal single-agent activity, there appears to be a true, perhaps immunologically based synergy with IMiDs. At ASH, data from a Phase II study of len/elo/dex demonstrated an encouraging overall response rate of 84% and a PFS of more than 18 months. Ongoing Phase III studies will soon determine the future of this regimen. Importantly, myeloma is not the only place where the intuitive concept of combining an immune modulator and a monoclonal antibody is being explored, as the “R squared” combination of len/rituximab has demonstrated impressive activity in B-cell lymphoma/CLL.

And on a related note…coming up next in this series: R squared, ibrutinib, idelalisib and the provocative question posed by Dr Bruce Cheson and others — Was ASH 2012 the beginning of the end of chemotherapy in indolent lymphoma and CLL?

Neil Love, MD
Research To Practice
Miami, Florida

Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study

Dimopoulos MA et al.

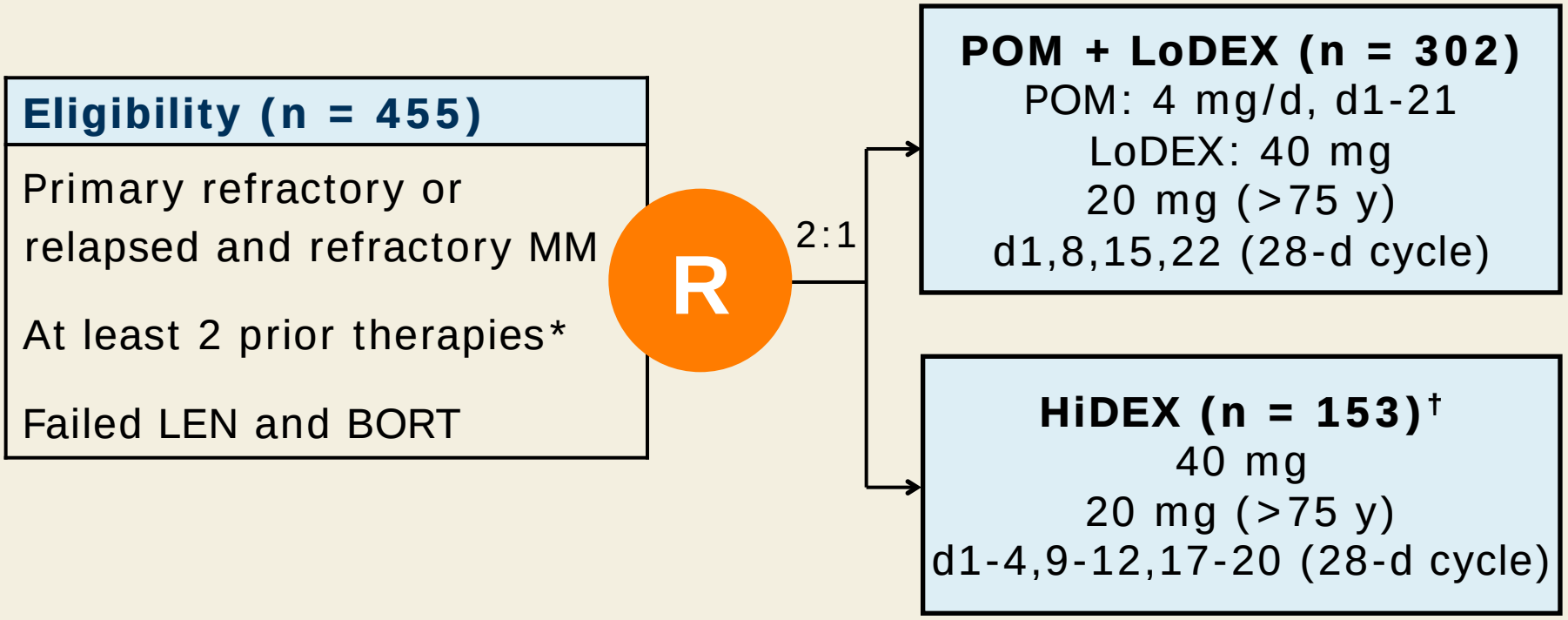
Proc ASH 2012;Abstract LBA-6.

Background

- Patients with lenalidomide (LEN)- and bortezomib (BORT)-refractory multiple myeloma (MM) have few treatment options, and high-dose dexamethasone (HiDEX) is commonly used as salvage therapy.
- Pomalidomide (POM), an oral immunomodulatory agent, has potent direct antimyeloma activity, inhibits stromal cell support and modulates the immune response (*Leukemia* 2010;24(1):22).
- POM + LoDEX (low-dose dexamethasone) has demonstrated clinical efficacy in patients with relapsed or refractory MM treated with LEN and/or BORT (*Blood* 2011;118(11):2970).
- **Study objective**: To evaluate POM + LoDEX versus HiDEX in patients with LEN- and BORT-refractory MM.

Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Phase III MM-003 Trial Design



* Including ≥2 consecutive cycles of LEN and BORT, alone or in combination

† Patients experiencing disease progression on HiDEX could receive POM on companion MM-003C trial

Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Patient Characteristics

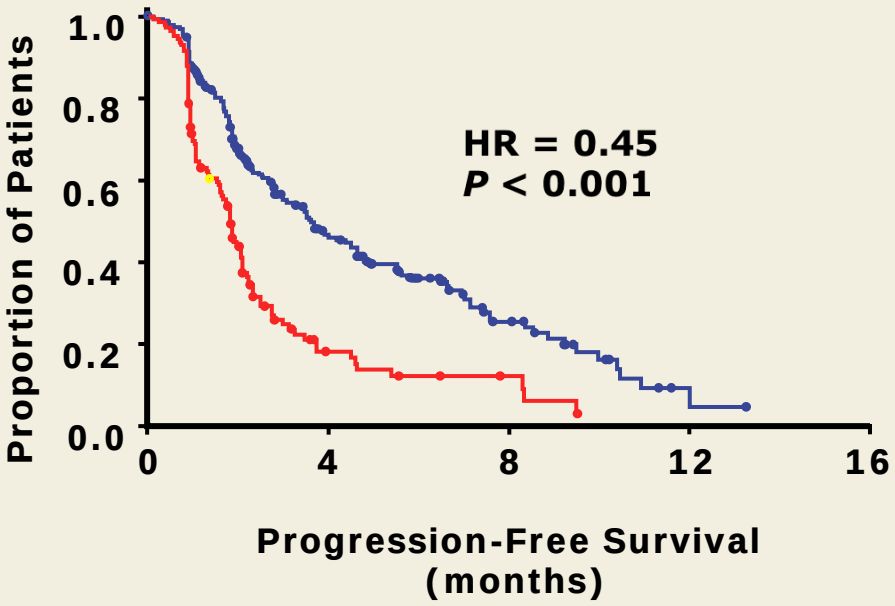
Patient characteristic	POM + LoDEX (n = 302)	HiDEX (n = 153)
Median number of prior therapies, n (range)	5 (1-14)	5 (2-17)
LEN refractory	93%	90%
BORT refractory	78%	77%
LEN and BORT refractory	73%	71%

Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Primary Endpoint: Progression-Free Survival

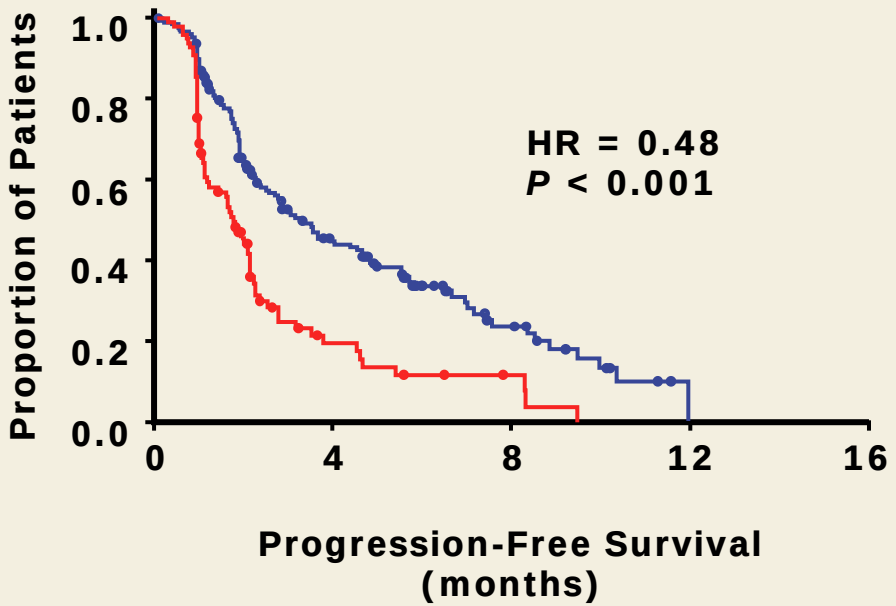
ITT population

	Median PFS
POM + LoDEX (n = 302)	3.6 months
HiDEX (n = 153)	1.8 months



Patients refractory to LEN and BORT

	Median PFS
POM + LoDEX (n = 221)	3.2 months
HiDEX (n = 108)	1.7 months

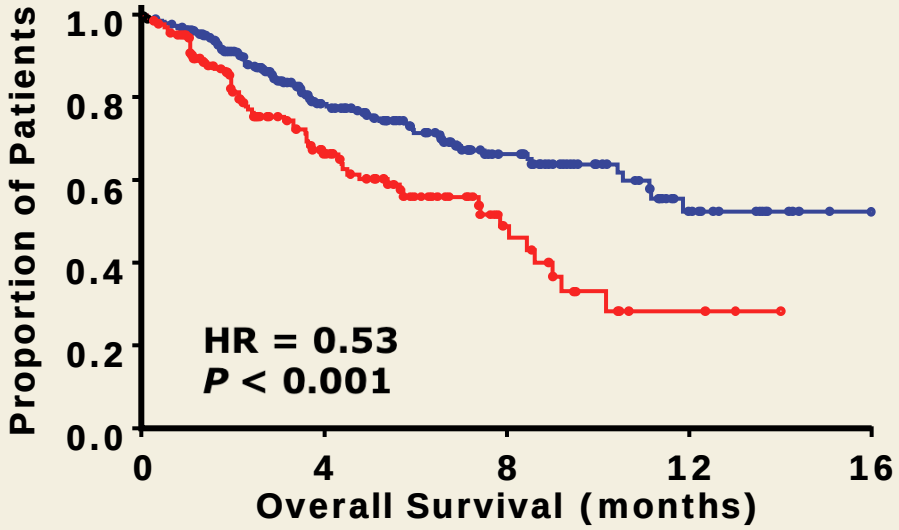


With permission from Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Secondary Endpoint: Overall Survival

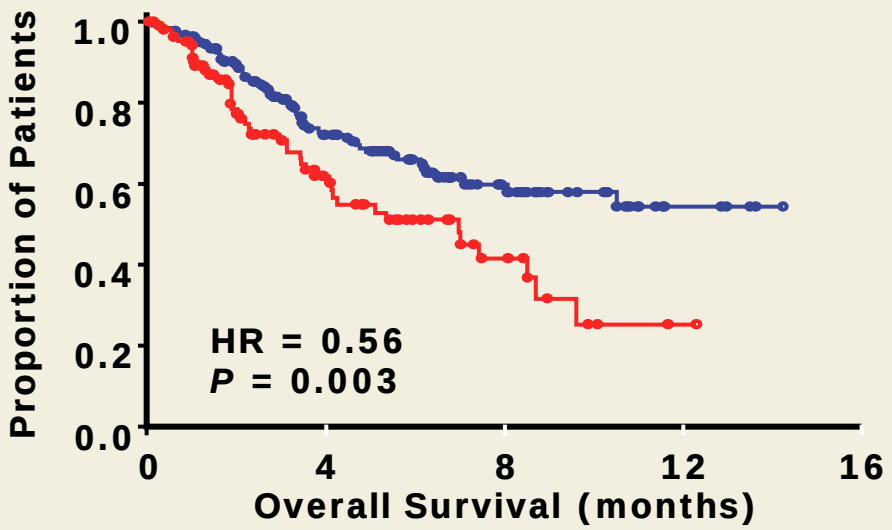
ITT population

	Median OS
POM + LoDEX (n = 302)	Not Reached
HiDEX (n = 153)	7.8 months



Patients with LEN- and BORT-refractory MM

	Median OS
POM + LoDEX (n = 221)	Not Reached
HiDEX (n = 108)	7.4 months



29% of patients received POM after progression on HiDEX.

With permission from Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Select Adverse Events (AEs)

Grade 3/4 AEs	POM + LoDEX (n = 300)	HiDEX (n = 149)
Hematologic		
Neutropenia	42%	15%
Febrile neutropenia	7%	0%
Anemia	27%	29%
Thrombocytopenia	21%	24%
Nonhematologic		
Infections	24%	23%
Hemorrhage	3%	5%

Any grade AEs of interest — VTE: POM + LoDEX (3%), HiDEX (2%); peripheral neuropathy: POM + LoDEX (12%), HiDEX (11%)

Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Author Conclusions

- POM + LoDEX significantly improved PFS and OS versus HiDEX for patients with MM.
- Equal benefit was observed in patients with LEN- and BORT-refractory disease.
- In heavily pretreated patients, POM + LoDEX was generally well tolerated.
- POM + LoDEX should be considered as a new treatment option for patients with LEN- and BORT-refractory MM.

Dimopoulos MA et al. *Proc ASH* 2012;Abstract LBA-6.

Investigator Commentary: A Phase III Trial of Pomalidomide and Low-Dose Dexamethasone in Relapsed or Refractory MM

Pomalidomide is the third immunomodulatory drug to be investigated in addition to thalidomide and lenalidomide. It had been studied in Phase II trials in patients with lenalidomide-resistant disease and yielded a 30% or better response rate, fairly consistently, in that setting.

The current study was a fairly large Phase III trial, conducted mostly in Europe, in a patient population with highly refractory MM. The results demonstrated a longer duration of remission and most importantly an overall survival advantage for patients who received pomalidomide and dexamethasone compared to dexamethasone alone. These findings should expedite approval for pomalidomide, perhaps for when the first-line agents are no longer active.

All of the clinical studies of pomalidomide for MM have been conducted for patients with disease progression on lenalidomide either through intolerance or through relapsed and/or refractory disease. So I believe that would be the setting in which it is likely to be approved and the patient population in whom I would be most likely to use it.

Interview with A Keith Stewart, MBChB, January 9, 2013

ClaPD (Clarithromycin, Pomalidomide, Dexamethasone) Therapy in Relapsed or Refractory Multiple Myeloma

Mark TM et al.

Proc ASH 2012;Abstract 77.

Background

- The addition of clarithromycin was previously reported to enhance antimyeloma activity of lenalidomide/dexamethasone in the up-front treatment of multiple myeloma (MM) (*Blood* 2008;111(3):1101).
- Pomalidomide is an immunomodulatory agent with a significant response rate in combination with dexamethasone for patients with relapsed/refractory MM (*J Clin Oncol* 2009;27(30):5008).
- Initial results suggested that clarithromycin may enhance pomalidomide/dexamethasone activity in relapsed or lenalidomide-refractory MM (*Proc ASCO* 2012;Abstract 8036).
- **Study objective**: To examine the efficacy and tolerability of ClaPD in relapsed/refractory MM.

Mark TM et al. *Proc ASH* 2012;Abstract 77.

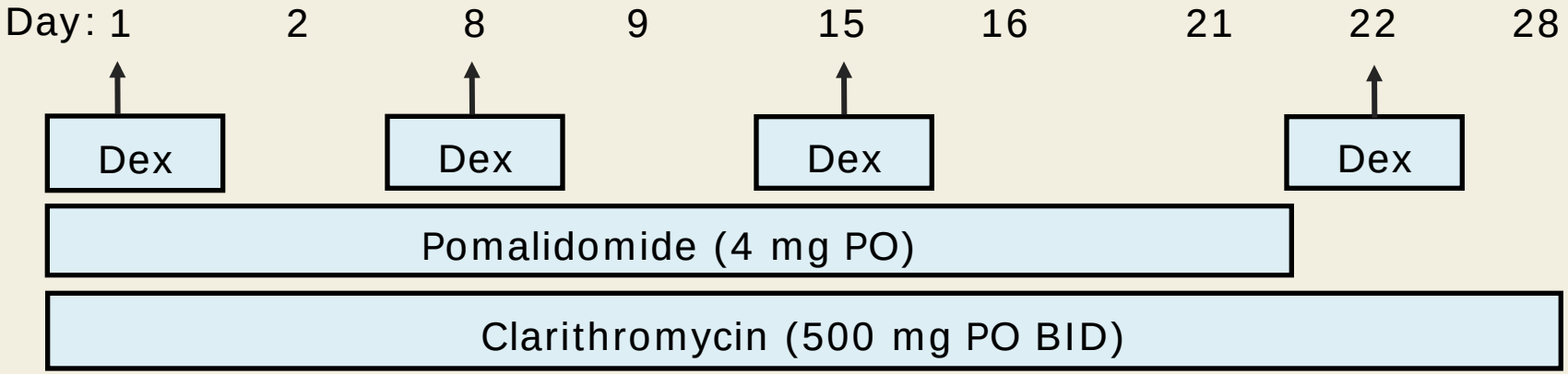
Phase II Trial Design

Eligibility (n = 100)

Relapsed* or refractory† MM

≥3 prior lines of therapy

1 prior line of therapy must have included lenalidomide



Dex = dexamethasone (40 mg PO)

* Relapsed: Previously treated myeloma that progresses and requires initiation of salvage therapy but does not meet the definition of refractory MM

† Refractory: Disease that is nonresponsive on therapy or progresses within 60 d of last therapy

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Best Response Rates (Median Follow-Up: 9.6 Months)

	n = 98*
Overall response rate (≥PR)	57%
Stringent CR (sCR)	6%
Very good PR (VGPR)	17%
Partial response (PR)	34%
Minimal response (MR)	9%
Clinical benefit rate (≥MR)	66%

* Patients who completed ≥1 cycle of ClaPD

- Median time to PR = 1 cycle; median time to best response = 2 cycles

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Best Response by Treatment History

	R refractory (n = 83)	V refractory (n = 82)	RV refractory (n = 72)
ORR (≥PR)	63%	56%	54%
sCR	7%	6%	7%
VGPR	16%	16%	13%
PR	34%	34%	35%
MR	10%	10%	11%
CBR (≥MR)	67%	65%	65%

R = lenalidomide; V = bortezomib; CBR = clinical benefit rate

Mark TM et al. *Proc ASH* 2012;Abstract 77.

PFS by Cytogenetic Risk and Prior Treatment History

- Median PFS for all patients (n = 100): 8.67 mo

PFS by subset analysis	HR	*p*-value
Standard (n = 41) vs high risk (n = 55)	1.23	0.448
R-relapsed (n=15) vs R-refractory (n=85)	1.00	0.995
V-relapsed (n = 16) vs V-refractory (n = 84)	1.09	0.806
RV-nonrefractory (n = 26) vs RV-refractory (n = 74)	1.35	0.307

HR = hazard ratio; RV-nonrefractory = not refractory to both lenalidomide and bortezomib

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Adverse Events*

Occurring in ≥10% of patients	Grade 3	Grade 4
Anemia	21%	4%
Thrombocytopenia	17%	16%
Neutropenia	33%	14%
Lymphopenia	31%	6%
Febrile neutropenia	2%	1%
Pulmonary embolism	1%	—
Deep vein thrombosis	4%	—

* Three patients withdrew due to Grade 3 fatigue (n = 1), Grade 4 muscular weakness (n = 1) and Grade 4 neutropenic sepsis (n = 1).

No treatment-related mortality observed.

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Author Conclusions

- ClaPD is an effective regimen for patients with heavily pretreated relapsed or refractory MM.
- ClaPD demonstrated clinical activity in patients with advanced MM treated with multiple lines of therapies, including those with R- and V-refractory disease.
- Following treatment with ClaPD, PFS was sustained for >8 months for the majority of patients on the study and was not influenced by high-risk cytogenetics nor a history of R-, V- or RV-refractory disease.
- Overall survival was not significantly affected by high-risk cytogenetics, but a trend toward shorter survival was observed for patients with double-refractory disease (data not shown).

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Investigator Commentary: A Phase II Trial of ClaPD in Heavily Pretreated Relapsed or Refractory MM

Clarithromycin is an interesting antibiotic that Dr Niesvizky and colleagues in New York have been promoting for many years as a drug with the ability to increase response rates for patients receiving immunomodulatory drugs in combination with steroids. It appears to accentuate steroid potency, but by itself it is not particularly active. I have seen some impressive results, including this presentation, demonstrating higher response rates than one would predict without clarithromycin.

I wouldn't say that it's currently being widely used, but some of my colleagues certainly administer it frequently now. It is a well-known antibiotic that is fairly innocuous and easy to combine with other agents. So, in the absence of any Phase III testing, it seems like a reasonable addition to therapy. However, it may exacerbate steroid side effects and one needs to watch out for this. I think it is beginning to increase in popularity, is unlikely to have deleterious effects and may be beneficial.

Interview with A Keith Stewart, MBChB, January 9, 2013

Pomalidomide Cyclophosphamide and Prednisone (PCP) Treatment for Relapsed/Refractory Multiple Myeloma

Palumbo A et al.

Proc ASH 2012;Abstract 446.

Background

- The outcome of patients with multiple myeloma (MM) who are no longer responding to thalidomide, lenalidomide (LEN) or bortezomib (BORT) is poor.
- The median event-free survival for these patients is 5 months and median overall survival (OS) is 9 months (*Leukemia* 2012;26:149-57).
- Pomalidomide (POM), an oral immunomodulatory agent, has shown significant activity in relapsed/refractory patients treated with LEN and/or BORT (*Blood* 2011; 118:2970-5).
- **Study objective:** To evaluate dosing, efficacy and safety of POM-cyclophosphamide-prednisone (PCP) in patients with LEN-relapsed or LEN-refractory MM.

Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Study Design

Eligibility (N = 55)

MM relapsed* or relapsed and refractory† to LEN

Received 1-3 lines of therapy

PCP treatment

POM: 1-2.5 mg/d

Cyclophosphamide: 50 mg, every other day

Prednisone: 50 mg, every other day

Six 28-d cycles

Maintenance (until progression)

POM 2.5 mg/d

Prednisone 25 mg every other day

- Stage I: dose-limiting toxicity probability updated
  - 12 pts enrolled in Phase I treated at MTD
- Stage II: Additional 43 pts enrolled in Phase II
- 55 pts evaluable after completing at least 1 cycle

Thromboprophylaxis with aspirin or low-molecular-weight heparin in patients at high risk

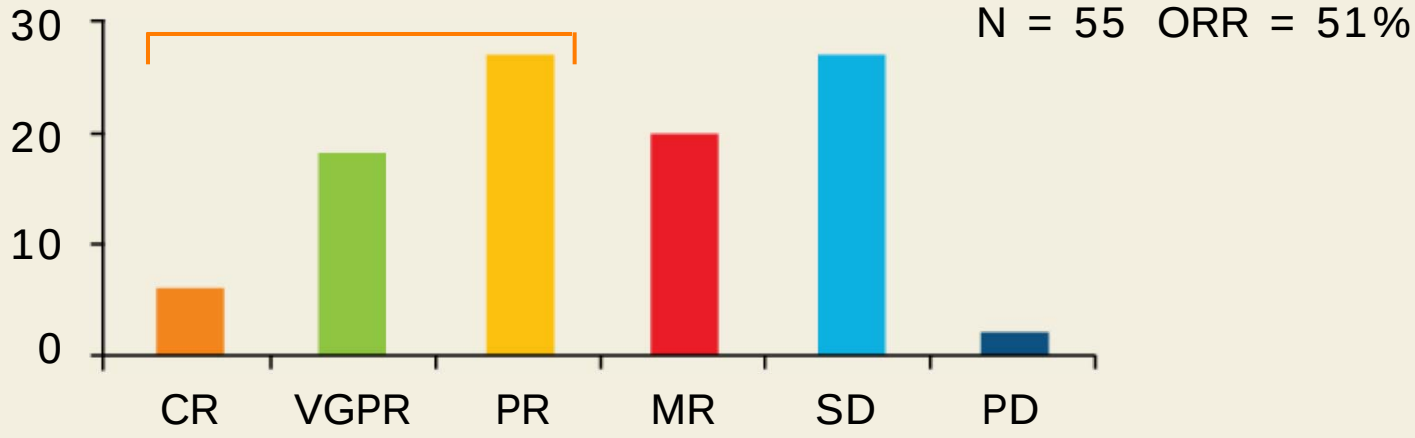
* Relapsed = previously treated MM that progressed and required initiation of salvage therapy

† Relapsed and refractory = relapsed while on salvage therapy or progressed within 60 d of most recent therapy

Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Phase II: Best Response to PCP

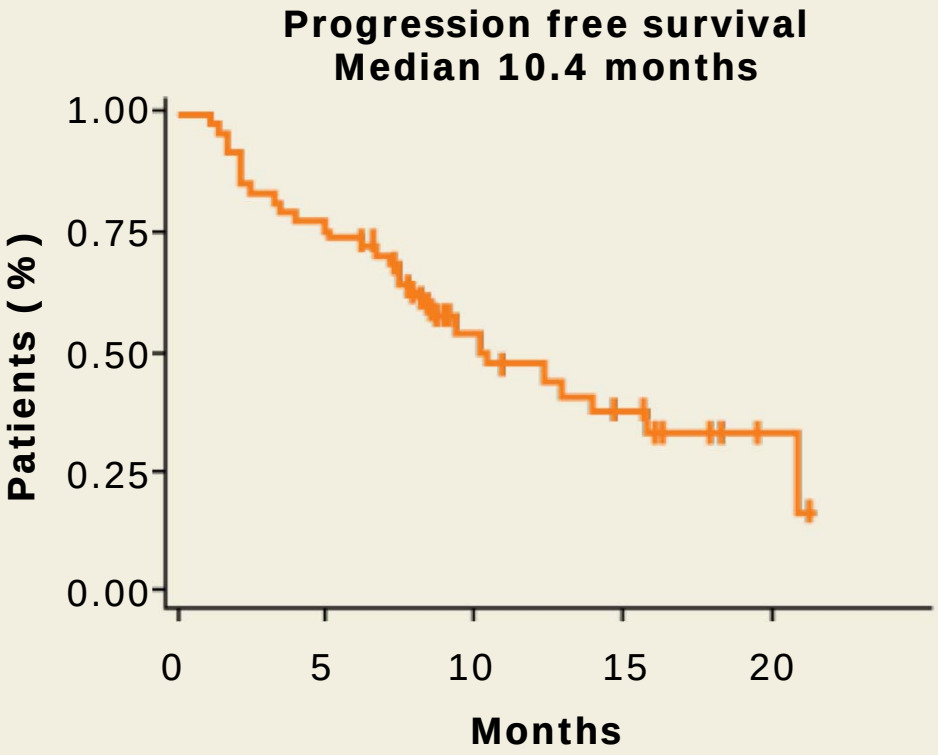
	Evaluable 2.5 mg N = 55	Refractory to lenalidomide N = 37	Relapsed after lenalidomide N = 18	Refractory to lenalidomide-bortezomib N = 16
CR	6%	5%	5%	12%
≥VGPR	24%	16%	39%	19%
≥PR	51%	46%	61%	50%
≥MR	71%	70%	72%	81%

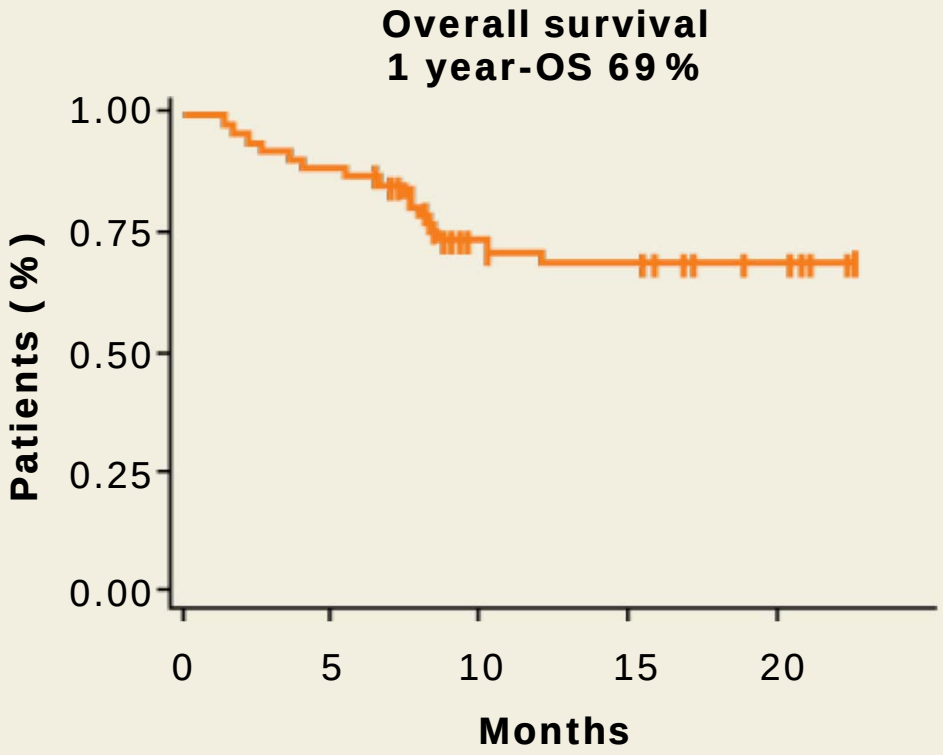


Median number of cycles: 6

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Progression-Free and Overall Survival (N = 55)

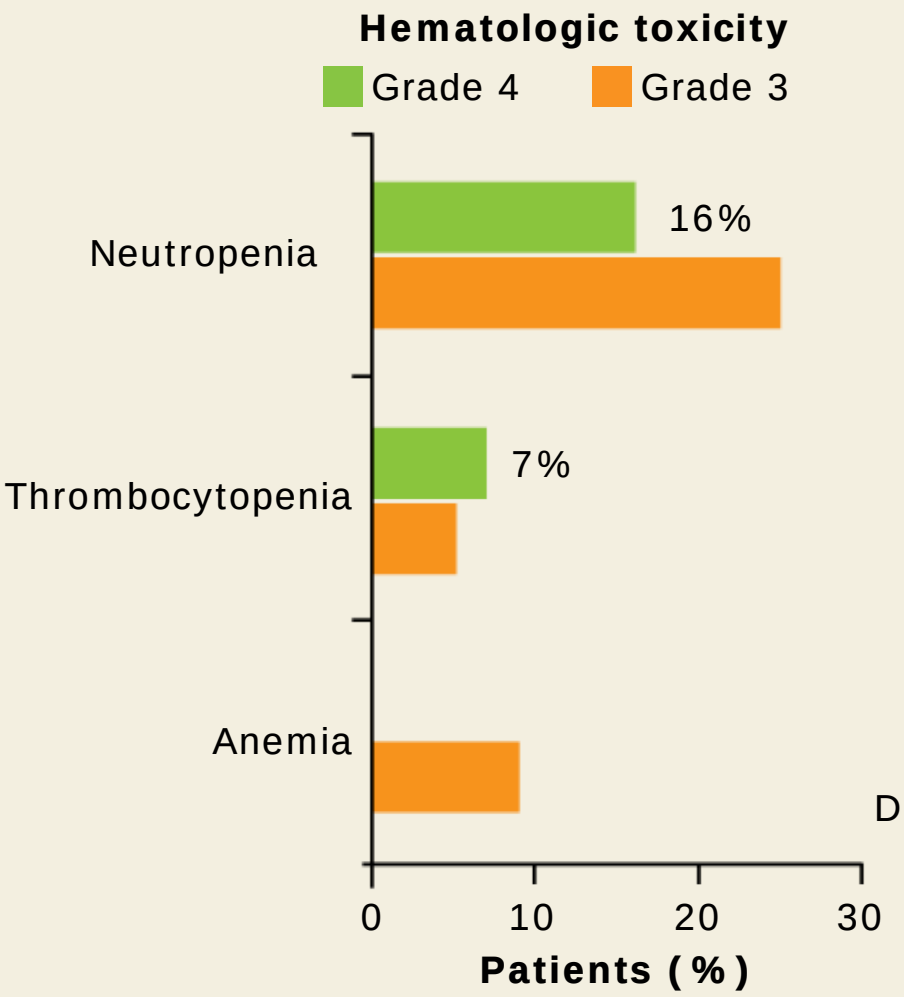


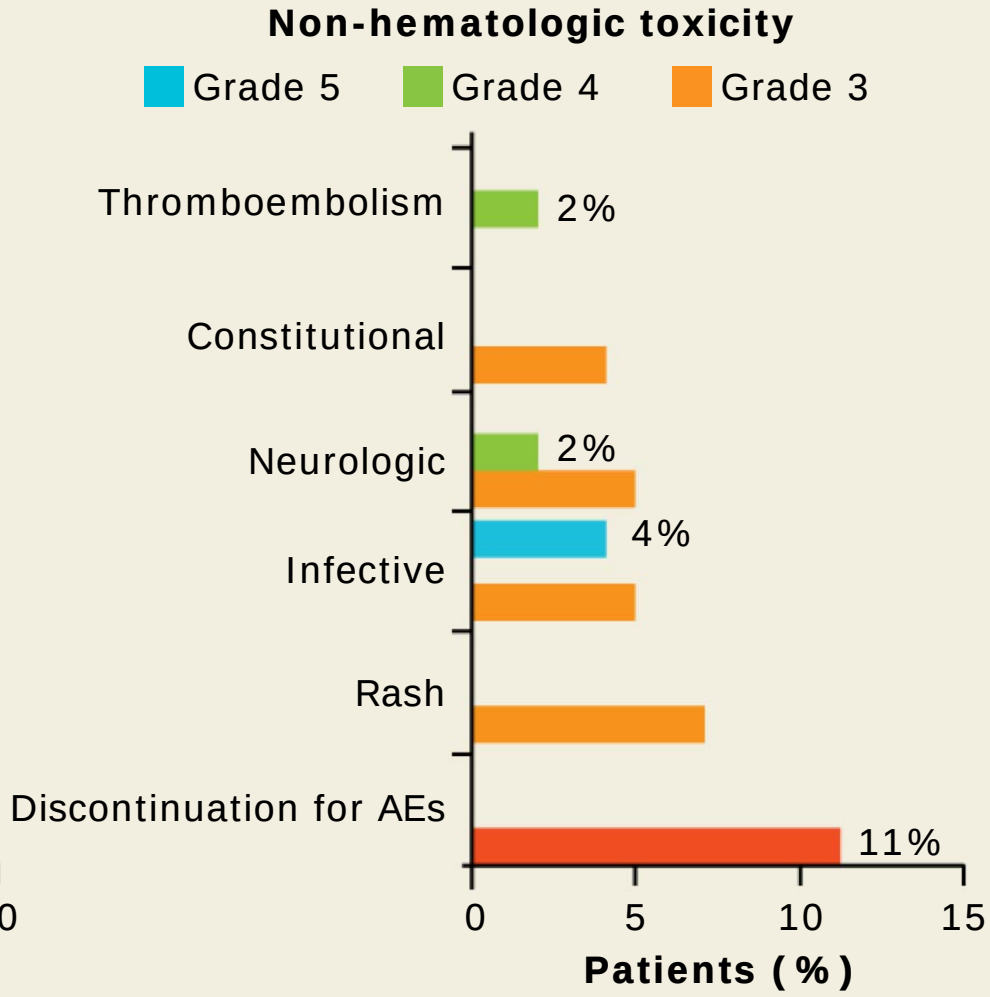


Median follow-up: 14.8 months

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Adverse Events (n = 55)





With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Author Conclusions

- The maximum tolerated dose of pomalidomide was determined to be 2.5 mg/day.
- PCP induced high response rates in patients with relapsed/refractory MM.
- The median PFS was 10.4 mo and 1-year overall survival rate was 69%.
- The main Grade 4 hematologic adverse events were neutropenia and thrombocytopenia and the main Grade 3 to 5 nonhematologic adverse events were rash and infections.
- PCP could be considered a valuable salvage option for patients with pretreated MM.

Palumbo A et al. *Proc ASH* 2012;Abstract 446.

Investigator Commentary: Pomalidomide, Cyclophosphamide and Prednisone for Relapsed or Refractory MM

This study investigated a combination of pomalidomide with other agents currently used in the relapsed and relapsed/refractory setting. Cyclophosphamide and prednisone are known to have good and durable activity in patients who have experienced relapse.

The current study defined the appropriate doses of all 3 drugs. It also showed that the combination was well tolerated and yielded a response rate of 51%, as opposed to the 25% to 30% rate observed with pomalidomide and steroids alone. This study builds on others with pomalidomide and demonstrates that it can be combined safely and successfully with durable responses in some patients.

One of the advantages with this regimen is that all the drugs can be administered orally. This would be an attractive combination for patients who are elderly or for those who have to travel. It appears that pomalidomide will soon be approved.

Interview with A Keith Stewart, MBChB, January 9, 2013

High Cereblon Protein Expression Correlates with Improved Response and Survival in Myeloma Patients Treated with Lenalidomide

Klimowicz A et al.

Proc ASH 2012;Abstract 931.

Background

- Cereblon (CRBN), an adaptor protein of an E3 ubiquitin ligase complex, is a primary target of thalidomide teratogenicity (*Science* 2010;327:1345-50).
- CRBN expression is an essential requirement for immunomodulatory drug (IMiD)-mediated cytotoxicity in multiple myeloma (MM) cells *in vitro* (*Blood* 2011;118(18): 4771-9)
- **Study objective**: To confirm the association between CRBN protein expression and the clinical response to lenalidomide (LEN) in patients with MM.

Klimowicz A et al. *Proc ASH* 2012;Abstract 931.

Study Methods (Abstract Only)

- Patients with newly diagnosed or relapsed/refractory MM treated with LEN and dexamethasone in MM-009, MM-016 and MM-020 Phase III trials (n = 42)
- Pretreatment bone marrow biopsies used to construct tissue microarrays (TMAs)
- Fluorescence immunohistochemistry performed using a polyclonal anti-CRBN antibody
- Digital images from TMA slides analyzed with AQUA analysis software to determine CRBN AQUA scores or protein expression (average CRBN pixel density within CD138-positive cells)
- CRBN AQUA scores standardized on the Z-distribution
- Kaplan-Meier survival analysis generated based on CRBN normalized AQUA Z scores; bottom (Q4) and top (Q1-3) quartiles defined as CRBN low or high groups, respectively

Klimowicz A et al. *Proc ASH* 2012;Abstract 931.

Response Rates and Survival Outcomes with LEN (Abstract Only)

	N = 42
Response	
Complete response (CR)/near CR	31%
Partial response	50%
Minimal response (MR)	9.5%
Progressive disease	9.5%
Survival	
Median progression-free survival (PFS)	19.5 mo
Median overall survival (OS)	28.7 mo

Median follow-up = 22.4 mo

Klimowicz A et al. *Proc ASH* 2012;Abstract 931.

Association between CRBN Expression and LEN Response or Survival (Abstract Only)

	CRBN low	CRBN high	*p*-value
PFS	5.6 mo	19.7 mo	0.008
OS	11.4 mo	30.5 mo	0.033
Failure to respond (≤MR) to LEN	54.5%	16.1%	—

- In univariate Cox regression analysis, CRBN protein expression was significantly associated with PFS (HR = 0.322; p = 0.012) and OS (HR = 0.323; p = 0.044).
- CRBN expression remained an independent predictor of PFS (HR = 0.161; p = 0.01), but not OS, when ISS and cytogenetics were included in multivariate analysis.

Klimowicz A et al. *Proc ASH* 2012;Abstract 931.

Author Conclusion

- Using an automated, observer-independent and fully quantitative approach, this study confirms the association between cereblon protein expression and response to LEN in MM.

Klimowicz A et al. *Proc ASH* 2012;Abstract 931.

Cereblon Expression Predicts Response, Progression Free and Overall Survival After Pomalidomide and Dexamethasone Therapy in Multiple Myeloma

Schuster SR et al.

Proc ASH 2012;Abstract 194.

Background

- Recently, it was demonstrated that the expression of cereblon (CRBN) is the major mediator of IMiD action (*Leuk Lymphoma* 2012;Epub ahead of print).
  - Low CRBN expression correlates with drug resistance in MM cell lines and primary MM cells.
  - CRBN functions, at least in part, through interferon regulatory factor 4 (IRF4), a critical factor for myeloma cell survival.
  - In addition, IRF4 is downregulated by IMiD therapy.
- **Study objective**: To assess potential clinical correlation between CRBN expression and response to IMiD therapy.

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Study Methods (Abstract Only)

- Retrospective analysis of 148 patients with MM whose tumor samples had been tested for CRBN expression by gene expression profiling (GEP) prior to treatment with IMiD-based therapies.
  - Patients treated with different combination therapies in the University of Arkansas Medical School (UAMS) GEP database were also screened.
- Optimal gene expression cutoffs for survival were determined using the Contal and O'Quigley methods:
  - Cutoff for progression-free survival (PFS) = 1.18443.
  - Cutoff for overall survival (OS) = 1.17816.

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Differences in CRBN Expression Levels by GEP (Abstract Only)

- There were no significant differences in CRBN expression among MGUS, smoldering MM, untreated symptomatic MM and normal plasma cells.
- Within the genetic subtypes of MM CRBN levels were:
  - Significantly higher in hyperdiploid MM (median 1.26).
  - Significantly lower in translocation/cyclin D (TC) class D2 MM (median 0.76).
  - Average for 4p16 tumors (median 0.97).
- Examination of patients treated with multiagent regimens in the UAMS GEP database showed no correlation between CRBN expression and survival.
- Subsequent analyses focused on patients treated with a single-agent IMiD with low-dose dexamethasone (Dex).

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Response Rates for 53 Patients with MM Treated with Pomalidomide/Dex (Abstract Only)

N = 53*	Gene expression level		
	<0.81	0.81-0.90	>0.9
Partial response	0%	19%	33%

* Patients with relapsed/refractory MM (RR MM) were homogenously treated with pomalidomide (2-4 mg/d) and Dex (40 mg/week).

- Response rates varied significantly based on CRBN gene expression level.

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Survival Outcomes for Patients with RR MM Treated with Pomalidomide/Dex (Abstract Only)

N = 53	CRBN expression level		
	Lowest quartile*	Top 3 quartiles*	*p*-value
PFS	3.0 months	8.9 months	0.0006
OS	9.1 months	27.2 months	0.01

* Cutoff values: 25% = 0.889687; 50% = 1.026542; 75% = 1.211133

- There was a positive correlation between CRBN expression and clinical outcome (PFS and OS).
- However, CRBN mRNA level is primarily a reflection of CRBN gene copy number.
- Higher CRBN levels can serve as a surrogate marker for low-risk disease because trisomy 3 is common in hyperdiploid, good prognosis MM and CRBN is required for IMiD function.

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Author Conclusions (Abstract Only)

- There was a correlation between CRBN expression and clinical response to IMiD and Dex therapy.
- The level of expression of CRBN is predictive of survival outcomes.
- CRBN expression is a potential predictive biomarker of response to an IMiD-containing regimen.

Schuster SR et al. *Proc ASH* 2012;Abstract 194.

Investigator Commentary: Cereblon Expression Correlates with Response and Survival with Immunomodulatory Drugs in MM

We have used immunomodulatory drugs in the past without being able to predict who will respond to treatment. The response rate to these agents in relapsed MM is in the 30% to 60% range, depending on how the disease has progressed.

It was previously reported that the binding target of thalidomide was a protein called cereblon. Subsequently, work conducted by my laboratory and others demonstrated that this is also the protein that is responsible for the ability of IMiDs to kill myeloma cells.

The 2 current studies investigated whether the expression level of cereblon in tumor cells could be used as a biomarker for outcome in patients who received either pomalidomide or lenalidomide. Both studies, using either immunohistochemistry or gene expression profiling, demonstrated that the level of cereblon was predictive of response. Importantly, it was also predictive of progression-free and overall survival. This is the first step on the road to developing a biomarker for responsiveness to these drugs. In the future, we may have a bone marrow-based assay to determine who will respond to IMiDs.

Interview with A Keith Stewart, MBChB, January 9, 2013

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

Richardson PG et al.

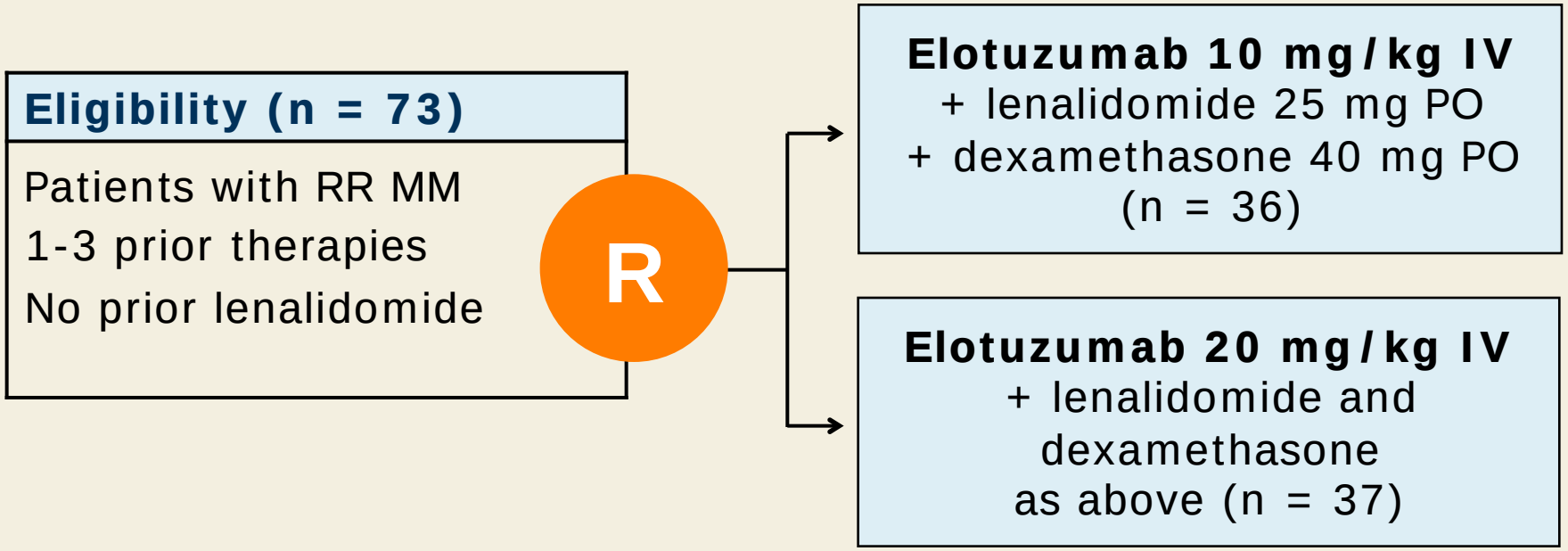
Proc ASH 2012;Abstract 202.

Background

- Elotuzumab (Elo) is a humanized monoclonal antibody directed against the human CS1 antigen, which is highly expressed on the surface of multiple myeloma (MM) cells.
- A Phase I study of Elo in combination with lenalidomide and low-dose dexamethasone demonstrated a high response rate in patients with relapsed/refractory MM (RR MM) (*JCO* 2012;30(16):1953).
- Also, lenalidomide in combination with dexamethasone is beneficial in the treatment of RR MM (*N Engl J Med* 2007;357(21):2133).
- **Study objective**: To determine the efficacy and safety of Elo in combination with lenalidomide and low-dose dexamethasone in RR MM.

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Phase II (Study 1703) Trial Design



- **Primary endpoint:** Objective response rate (ORR)
- **Secondary endpoints include:** Progression-free survival (PFS) and safety
- Premedication (30–60 min prior) included: IV methylprednisolone (50 mg) or IV dexamethasone (8 mg), IV or PO diphenhydramine (25-50 mg), IV rantidine (50 mg) and acetaminophen (650-1,000 mg PO)

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

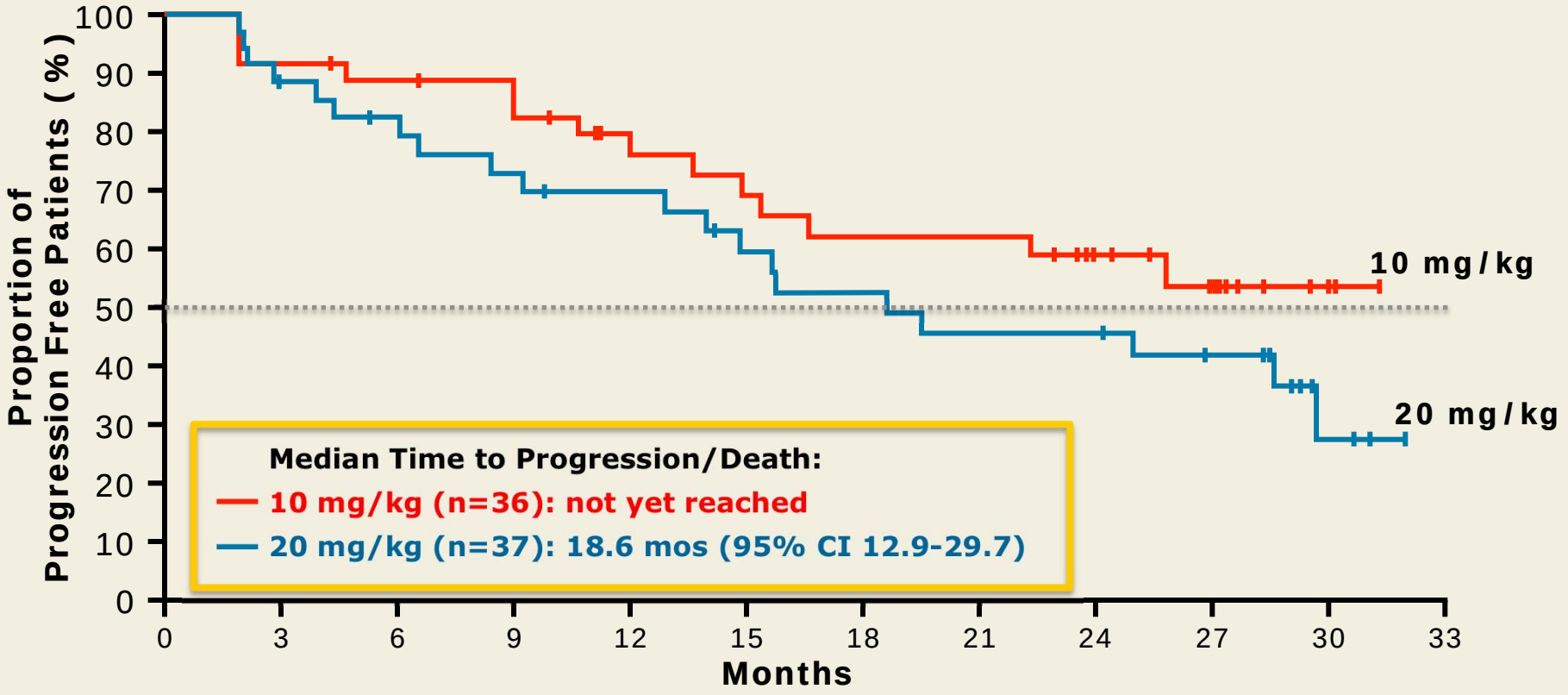
Best Response Rates

All patients	Elo (10 mg/kg) (n = 36)	Elo (20 mg/kg) (n = 37)	Total (n = 73)
ORR (≥PR)	92%	76%	84%
CR/stringent CR	14%	11%	12%
VGPR	47%	38%	43%
PR	31%	27%	29%
<PR	8%	24%	16%
By no. of prior therapies	**Elo (10 mg/kg)**	**Elo (20 mg/kg)**	**Total**
ORR (≥PR)			
1 (n = 16, 17, 33)	100%	82%	91%
≥2 (n = 20, 20, 40)	85%	70%	78%

PR = partial response; CR = complete response; VGPR = very good PR

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

PFS

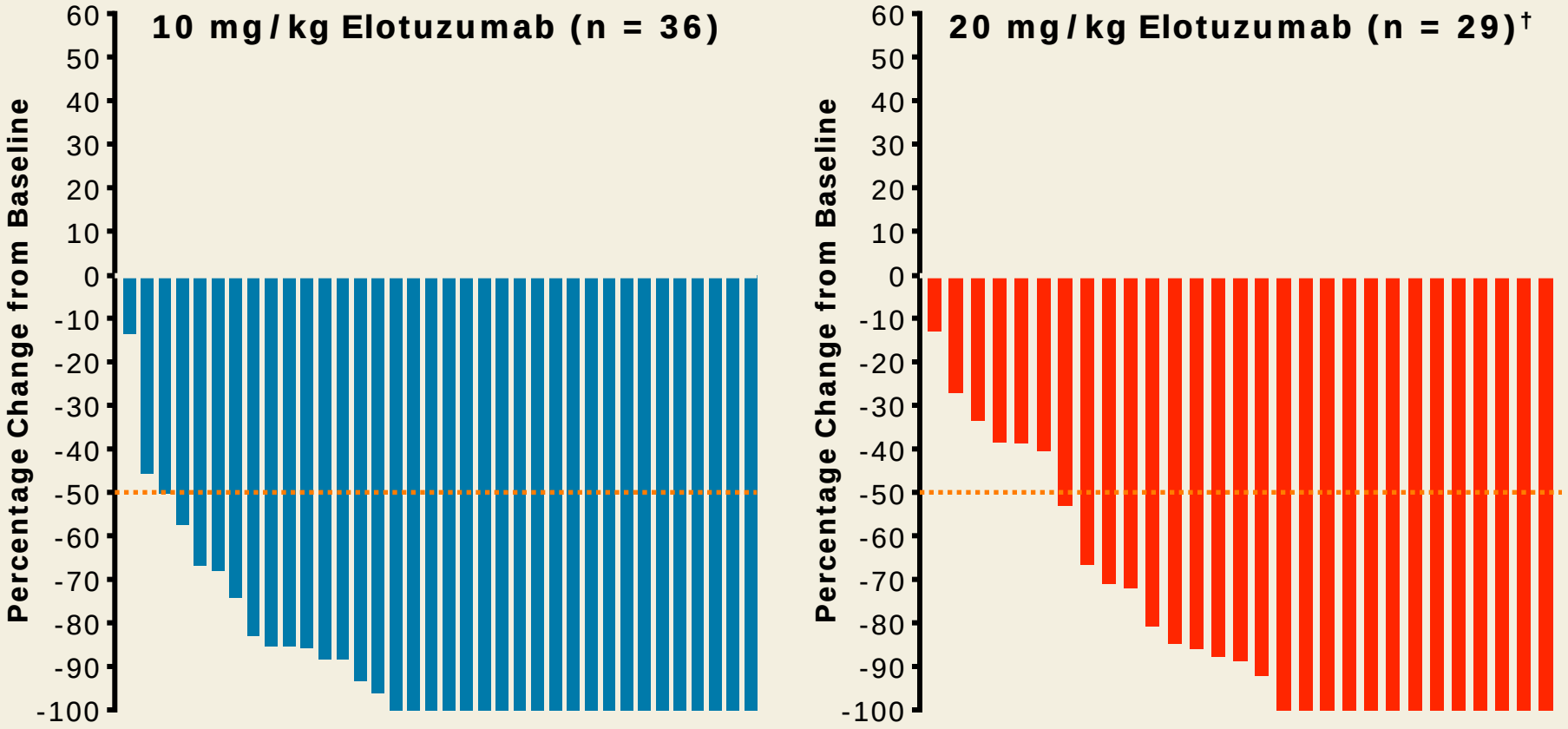


At a median follow-up of 20.8 months, median PFS has not been reached in the 10 mg/kg arm.

- For patients treated with 1 prior therapy, median PFS was 29.7 months.
- For patients treated with ≥2 prior therapies, median PFS was 19.5 months.

With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Efficacy: Maximum Percent Reduction in Serum M Protein*



* Maximum percentage decrease from baseline to 60 days after permanent discontinuation of elotuzumab or start of new line of MM therapy

† 8 patients without measurable disease (baseline and all on-study serum M protein levels <0.5 g/dL) were not included.

With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Select Adverse Events

Grade 3 or 4 (≥5%)	Elo (10 mg/kg) (n = 36)	Elo (20 mg/kg) (n = 37)
Diarrhea	8%	5%
Anemia	14%	14%
Thrombocytopenia	17%	16%
Lymphopenia	25%	14%
Neutropenia	17%	19%
Hypokalemia	8%	3%
Pneumonia	8%	5%

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Author Conclusions

- Treatment with either 10 or 20 mg/kg of elotuzumab with lenalidomide and low-dose dexamethasone resulted in high ORR for patients with relapsed or refractory MM.
  - Overall ORR in both treatment arms: 84%
  - Overall ORR in both treatment arms for patients who had received only 1 prior therapy: 91%
- Median PFS: Not reached at 20.8-mo median FU for patients randomly assigned to receive 10 mg/kg of elotuzumab; 18.6 mo for the elotuzumab 20-mg/kg group.
- Elotuzumab with lenalidomide/dexamethasone was generally well tolerated at both treatment doses.
  - Most common Grade 3/4 adverse events were lymphopenia, neutropenia and thrombocytopenia.

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Future Directions

- Two Phase III trials of 10-mg/kg elotuzumab and lenalidomide/dexamethasone are ongoing:
  - ELOQUENT–1 in previously untreated MM (CA204-006; NCT01335399)
  - ELOQUENT–2 in RR MM (CA204-004; NCT01239797)
- Additional trials of elotuzumab in MM are ongoing:
  - Bortezomib + dexamethasone ± elotuzumab in RR MM (CA204-009; NCT01478048)
  - Elotuzumab + thalidomide + dexamethasone in RR MM (CA204-010; NCT01632150)
  - Elotuzumab in high-risk smoldering MM (CA204-011; NCT01441973)
  - Elotuzumab + lenalidomide/dexamethasone in MM with impaired renal function (CA204-007; NCT01393964)
- Additional combination studies are planned.

Richardson PG et al. *Proc ASH* 2012;Abstract 202.

Investigator Commentary: A Phase II Trial of Elotuzumab with Lenalidomide/Dexamethasone in Relapsed/Refractory MM

We do not currently have a clinically successful monoclonal antibody for the treatment of MM. Elotuzumab is furthest along in clinical studies, and it looks as if it may be active. In combination with lenalidomide and low-dose dexamethasone, elotuzumab yields high response rates. In this large Phase II trial, one might expect a response rate of about 65% but elotuzumab demonstrated response rates of approximately 80% to 90%, depending on the dose employed. That in itself was impressive. However, the new and important finding from this study was that the PFS was at least 18 months for patients receiving the 3-drug regimen, although a PFS of about 1 year would have been anticipated. This seems to be much higher than one would have predicted with lenalidomide and dexamethasone alone.

So I have a lot of hope for this monoclonal antibody. Notably, this study is now in Phase III testing.

Interview with A Keith Stewart, MBChB, January 9, 2013