5 Minute JournalClub

POST-ASH Issue 1, 2013

Updated Results of a Phase II Study of Elotuzumab/Lenalidomide/ Low-Dose Dexamethasone for Relapsed/Refractory MM

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Develop an understanding of 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.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: January 2013
Expiration date: January 2014

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POST-ASH Issue 1, 2013

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

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

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?

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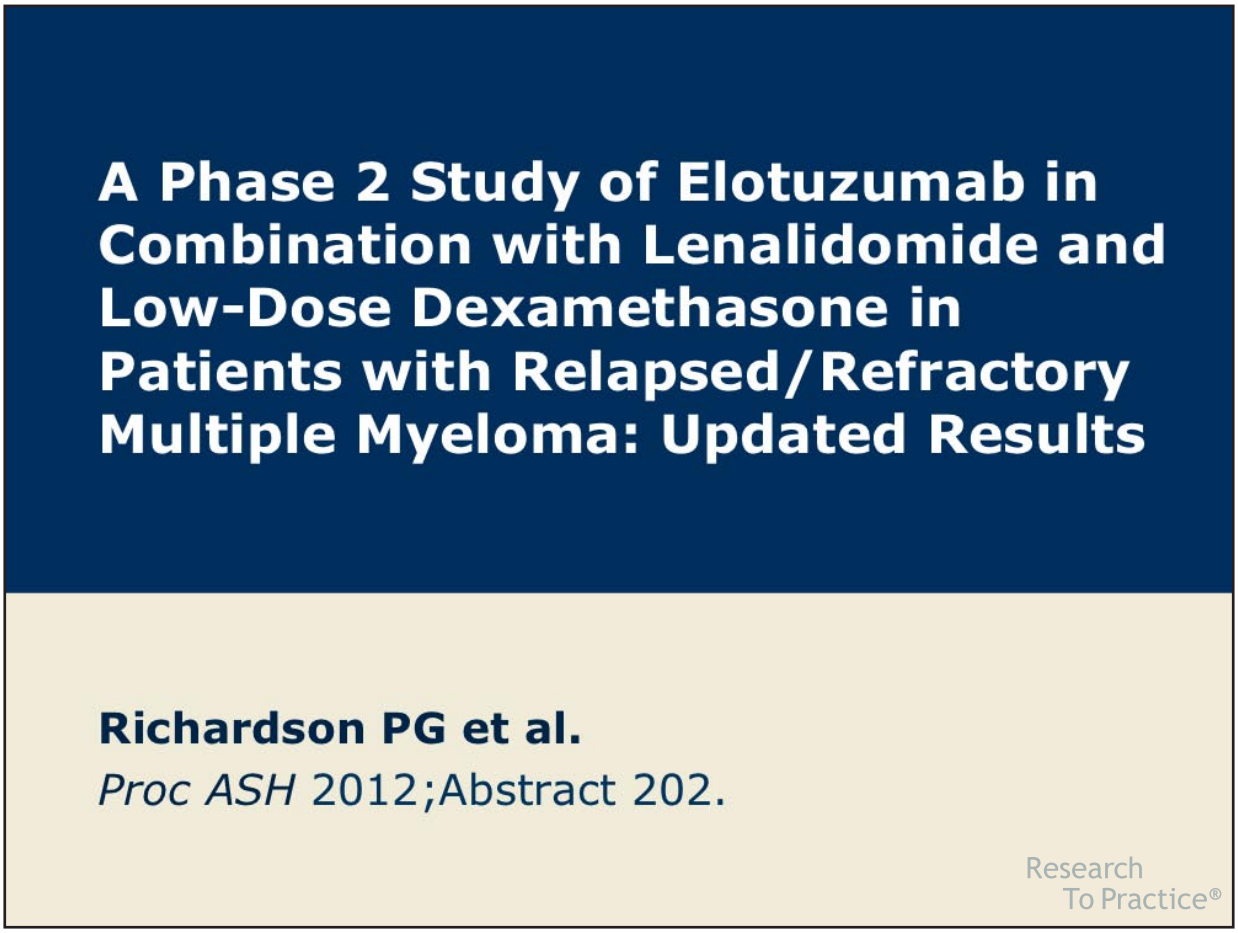
Updated Results of a Phase II Study of Elotuzumab/ Lenalidomide/Low-Dose Dexamethasone for Relapsed/ Refractory MM

Presentation discussed in this issue

Richardson PG et al. **A Phase 2 study of elotuzumab (Elo) in combination with lenalidomide and low-dose dexamethasone (Ld) in patients (pts) with relapsed/ refractory multiple myeloma (R/R MM): Updated results.** *Proc ASH* 2012;**Abstract 202**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with A Keith Stewart, MBChB (1/9/13)



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.

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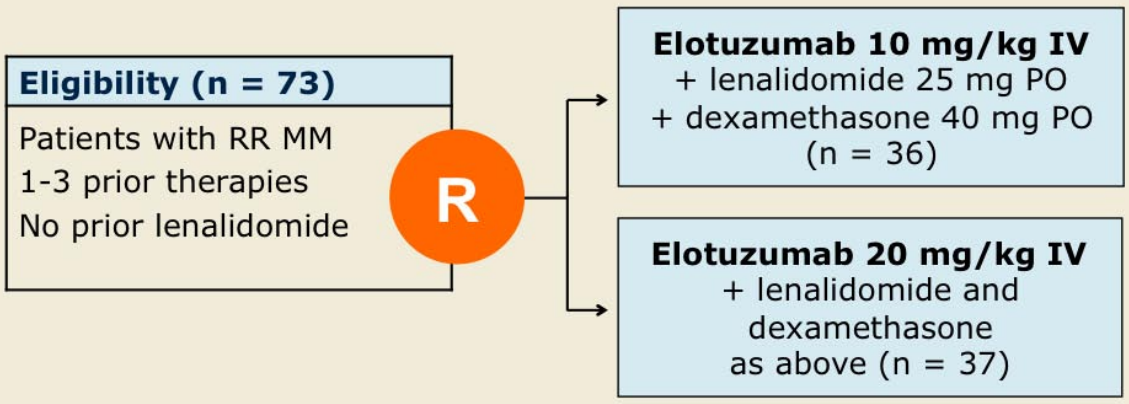
Phase II (Study 1703) Trial Design



- **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.

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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.

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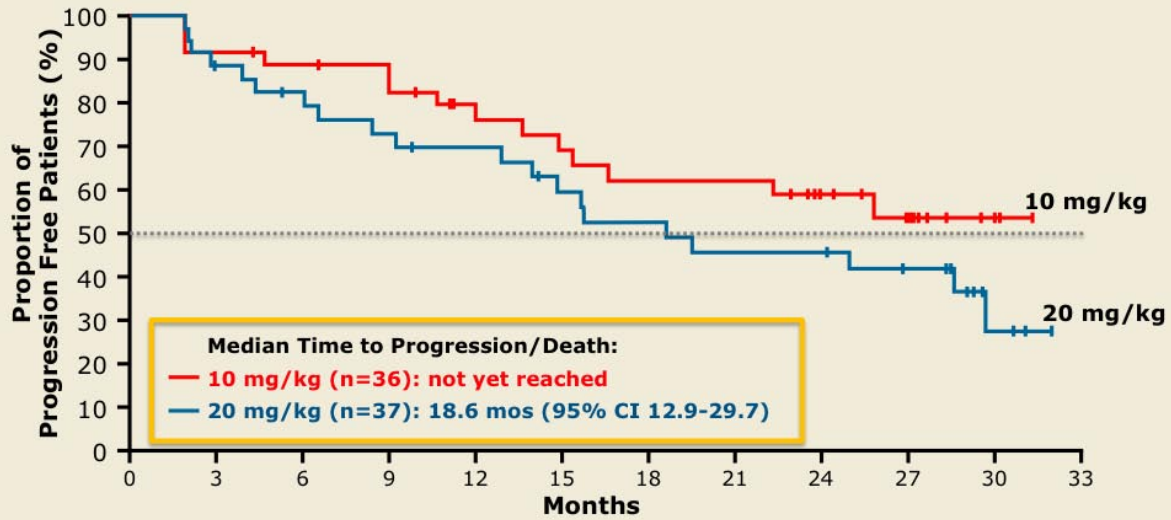
PFS



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.

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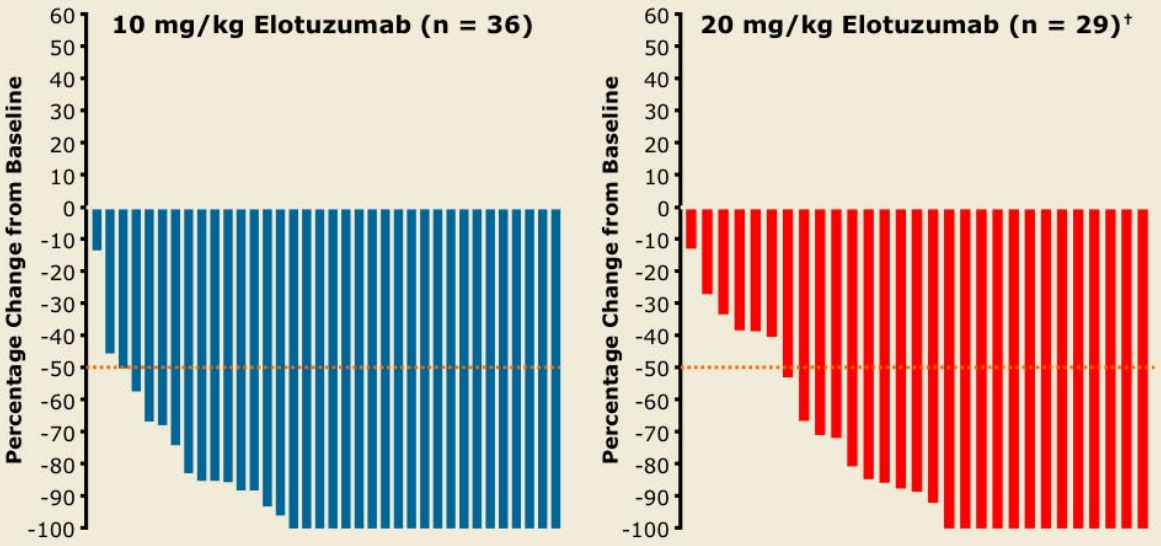
Efficacy: Maximum Percent Reduction in Serum M Protein*



* 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.

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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.

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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

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