5 Minute JournalClub

POST-ASH Issue 1, 2013

Cereblon Expression Correlates with Efficacy of Immunomodulatory Drugs in 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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FACULTY — 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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Dean for Research, Mayo Clinic in Arizona
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Advisory Committee: Onyx Pharmaceuticals Inc; Consulting Agreements: Celgene Corporation, Millennium: The Takeda Oncology Company; Paid Research: Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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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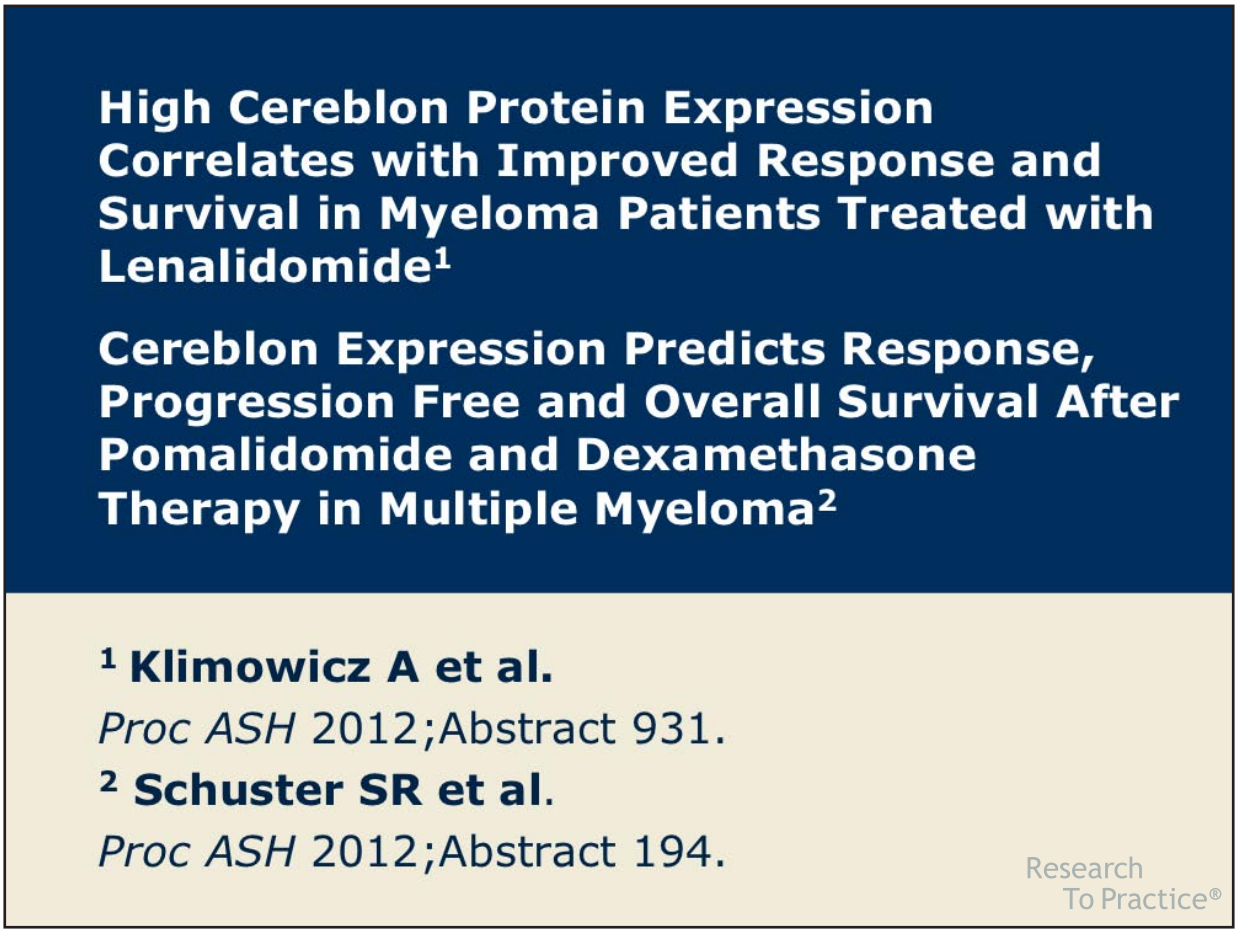
Cereblon Expression Correlates with Efficacy of Immunomodulatory Drugs in MM

Presentations discussed in this issue

Klimowicz A et al. **High cereblon protein expression correlates with improved response and survival in myeloma patients treated with lenalidomide.** *Proc ASH* 2012;**Abstract 931**.

Schuster S et al. **Cereblon expression predicts response, progression free and overall survival after pomalidomide and dexamethasone therapy in multiple myeloma.** *Proc ASH* 2012;**Abstract 194**.

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



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.

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.

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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.

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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.

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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.

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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.

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.

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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.

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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.

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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.

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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.

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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