5 Minute JournalClub

POST-ASH Issue 6, 2015

Phase I/II RV-WM-0426 Trial of Lenalidomide and Phase I/II Trial of Oprozomib in Relapsed/Refractory Waldenström Macroglobulinemia

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and salvage therapeutic options for the treatment of relapsed or refractory multiple myeloma (MM) and Waldenström macroglobulinemia (WM), high-risk smoldering MM (SMM) and the front-line management of AL amyloidosis from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the final efficacy and safety results from the Phase I/II 1703 study of elotuzumab in combination with lenalidomide and dexamethasone for patients with relapsed/refractory MM.
- Appraise recent clinical research findings on the effectiveness of the monoclonal anti-CD38 antibodies SAR650984 and daratumumab in combination with lenalidomide and dexamethasone in relapsed/refractory MM.
- Investigate the efficacy and safety of ibrutinib as a single agent or in combination with dexamethasone in relapsed or relapsed/refractory MM.
- Compare and contrast the benefits and risks of lenalidomide and low-dose dexamethasone with or without carfilzomib for patients with high-risk SMM.
- Analyze the role of front-line cyclophosphamide in combination with bortezomib and dexamethasone (CyBorD) in AL amyloidosis.
- Assess the safety and efficacy of the proteasome inhibitor oprozomib as a single agent in the treatment of WM.

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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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Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary.

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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: May 2015
Expiration date: May 2016

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POST-ASH Issue 6, 2015

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

Sagar Lonial, MD

One of my favorite days of the year occurs every April when the American Society of Clinical Oncology (ASCO) releases their iPlanner for the upcoming annual meeting that provides a first glimpse at the titles of all the oral abstracts that will be presented during the conference. This year my review quickly established that in the world of solid tumors there would be many highlights, including the long-awaited MARIANNE report evaluating pertuzumab and T-DM1 in HER2-positive breast cancer and a ton of impressive checkpoint inhibitor papers in lung cancer (squamous and nonsquamous), melanoma and a number of other diseases.

In terms of hematologic cancers, ASCO is always good for a few headline grabbers, and in reviewing the papers, my attention was immediately drawn to the first abstract in the multiple myeloma (MM) oral session — the Phase III ELOQUENT-2 trial in relapsed/refractory (RR) disease. The study, one of the most anticipated in MM in many years, randomized patients to lenalidomide (len)/dexamethasone (dex) alone or combined with the novel monoclonal antibody elotuzumab (elo).

This was definitely not the first time I became aware ahead of time that an important new data set was about to be presented, and as usual I was desperately curious to find out the results. About a week later I had my chance when the principal investigator, Dr Sagar Lonial, participated in a symposium we were doing as part of our always rewarding annual visit to the Oncology Nursing Society Congress. However, as usual my hopes were crushed by a strict embargo, and Sagar was a complete stone-wall Buddha sphinx, rebuffing all my attempts to squeeze the information out of him and leaving me totally clueless whether the study proved what earlier smaller trials suggested, namely that a special synergy exists between this antibody, which has no single-agent activity, and len.

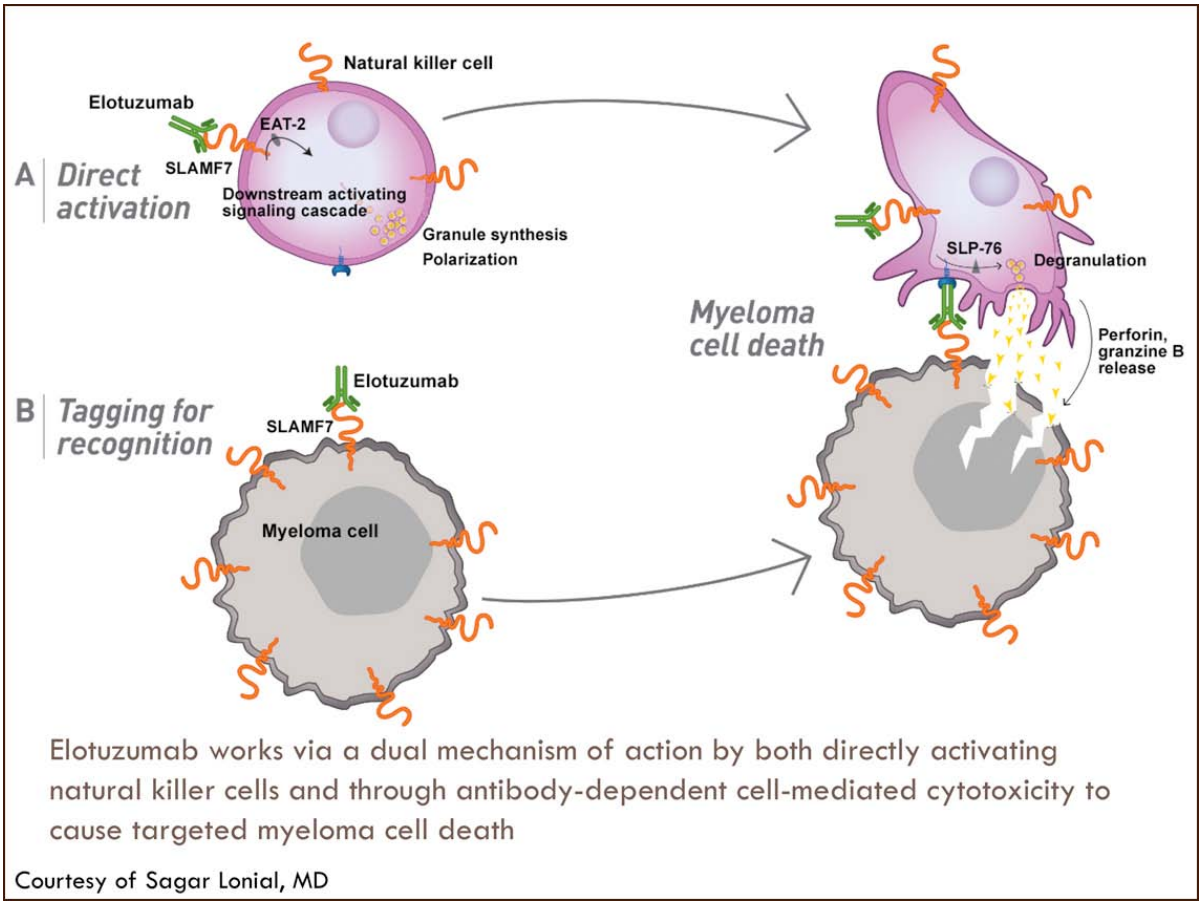
Fast forward to a week ago, when ASCO released online all but the late-breaking abstracts. My first click was to ELOQUENT-2, and to my delight, elo/len/dex resulted in a 30% reduction in the risk of disease progression and also a mortality benefit. While we most definitely need to see the data and hear Sagar and the rest of the myeloma community's take, if first impressions are any indication it could be that finally a cancer of cells that produce antibodies is soon going to have one as part of its treatment.

However, until the fun begins in Chicago, there is still much work to be done, and this issue of our American Society of Hematology (ASH) review series highlights a number of new directions in the treatment of MM, including antibodies, and several other related (at least in terms of who manages them) diseases, including Waldenström macroglobulinemia and AL amyloidosis.

Monoclonal antibodies in MM

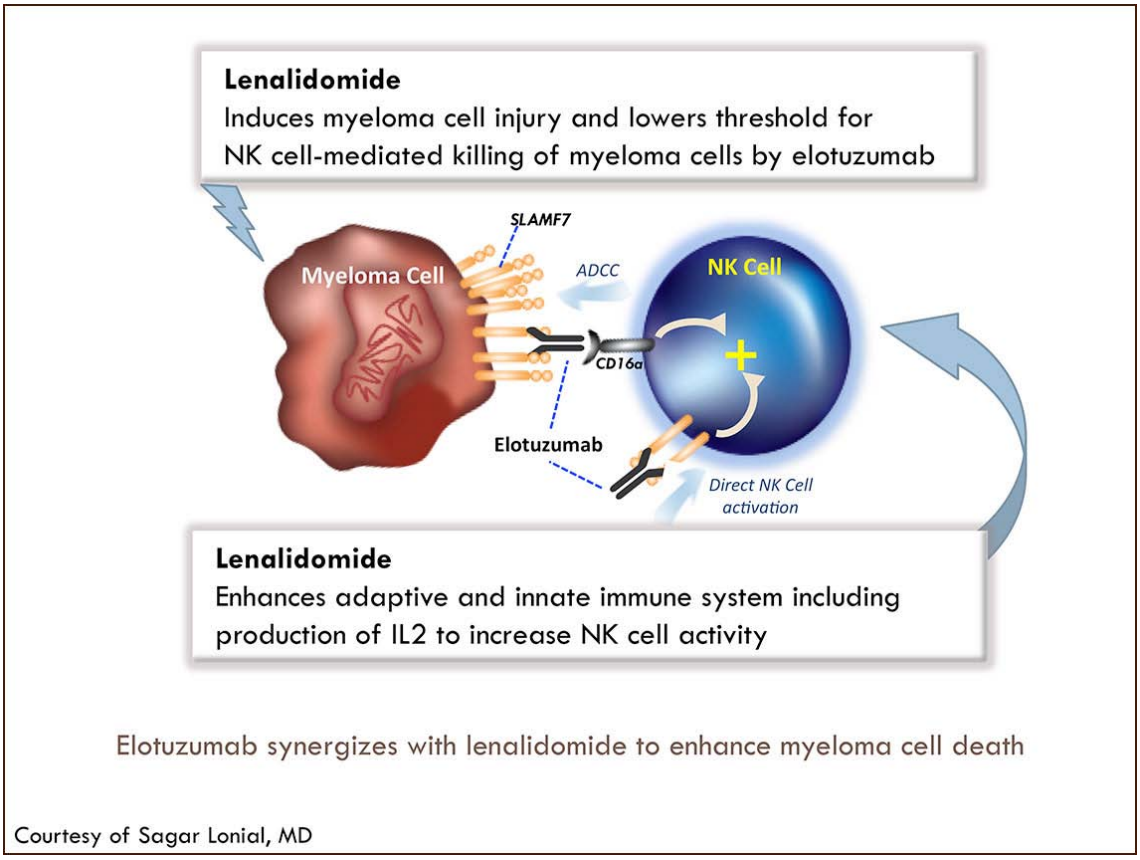
• Elo/len/dex

After years of asking investigators to explain how immunomodulating drugs work (and still not completely understanding the answer), I suspect that elo may be even more of a challenge. Signaling lymphocytic activation molecule F7 (SLAMF7) is a glycoprotein that is highly expressed on MM and natural killer (NK) cells but not on normal tissue. As a monoclonal antibody targeted against SLAMF7, elo is thought to directly activate and engage NK cells and selectively target SLAMF7-expressing MM cells for destruction.



Elotuzumab works via a dual mechanism of action by both directly activating natural killer cells and through antibody-dependent cell-mediated cytotoxicity to cause targeted myeloma cell death

Courtesy of Sagar Lonial, MD



Elotuzumab synergizes with lenalidomide to enhance myeloma cell death

Courtesy of Sagar Lonial, MD

As we learn more about the biologic basis of the apparently important synergy of len and elo, ongoing trials are evaluating this approach clinically. At ASH we saw Paul Richardson's **report of 73 patients** with RR MM who were treated with this regimen in the Phase II portion of the 1703 study, revealing similar encouraging outcomes as a prior single-arm study (response rate: 84%) with good tolerability. The bottom line now is that on Tuesday, June 2nd at 9:45 AM in the McCormick Place Convention Center, we will find out just how much it helps patients.

- **Anti-CD38 antibodies with len/dex**

While elo may be first with Phase III data, among MM investigators there is perhaps even more excitement about anti-CD38 agents, particularly daratumumab (dara) and the as yet nameless SAR650984 (sar). For quite some time now on our CME programs we have been hearing about the single-agent activity of these compounds, and I can recall a number of cases with impressive responses after disease progression on multiple therapies. However, the future of MM treatment seems to be combinations, which are firmly entrenched in the induction setting and gaining traction in RR disease. Thus it is no surprise to see strategies like **the 2 featured here** of combining these antibodies with len/dex and producing very good outcomes (77% very good partial response or greater with dara/len/dex; 64.5% overall response rate with sar/len/dex).

Many investigators, including Dr Lonial, believe that depth of response is critical in MM, and the hope has been that bringing in new classes of effective agents might push the disease into a more prolonged remission, also raising the possibility of cure as a treatment goal. Much more to come.

Ibrutinib in MM

Ibrutinib has been a revelation in terms of efficacy and activity across many variants of non-Hodgkin lymphoma, and when laboratory evidence emerged regarding the activation of Bruton tyrosine kinase in MM cells, there was optimism that this drug might play an important role in the management of this disease. Unfortunately, at ASH we saw data from **a Phase II trial** evaluating ibrutinib as a single agent or in combination with dex for patients with RR MM that demonstrated modest, somewhat underwhelming activity (clinical benefit rate of 8% with single-agent ibrutinib and 25% with the combination of ibrutinib/dex). Although further research is ongoing, few are optimistic that ibrutinib in MM will be anything close to what it is in chronic lymphocytic leukemia and mantle-cell lymphoma.

High-risk smoldering MM (SMM)

Although the standard therapy for these patients continues to be observation, a variety of predictive factors identify a subgroup with at least a 75% risk of disease progression at 5 years. As such, there continues to be significant interest in whether early intervention could help improve outcomes for these patients. In this regard, in San Francisco we saw more follow-up from the **landmark Spanish Phase III QUIREDEX trial** that had previously demonstrated an important benefit with the use of len/low-dose dex. With a median follow-up of 64 months, these findings continue to be positive, revealing that progression to symptomatic disease occurred in 25% of patients who received treatment versus 85% in the control group (overall survival rate at 7 years: 94% versus 64% with a hazard ratio of 4.6 and $p = 0.001$).

The NCI group formerly led by Ola Landgren, MD, PhD decided to take things even further and evaluate a triplet regimen, in this case carfilzomib/len/dex, followed by len maintenance in patients with high-risk SMM. Among the 12 patients who received treatment in this manner, 10 became MRD-negative after 8 cycles as determined by next-generation sequencing, which, by way of indirect comparison, appears to be an even greater benefit than the approach taken by the Spanish.

Importantly, a number of ongoing studies are pursuing these encouraging leads, including a major ECOG trial chaired by Dr Lonial in an attempt to confirm the Spanish len/dex data, and it could very well be that one day soon treating high-risk SMM will become part of practice.

Cyclophosphamide/bortezomib/dex (CyBorD) in AL amyloidosis (ALA)

Based on the results from a number of smaller trials, CyBorD has become one of the most commonly used up-front regimens for the treatment of this disease. To further confirm the benefits of this approach, 2 major ALA centers in London, England and Pavia, Italy prospectively collected findings from 230 cases of patients with newly diagnosed disease who received this regimen. The result is the **largest data set ever reported** with up-front CyBorD in the disease, from which a number of important observations can be made. Notably, of 30 patients with Stage I ALA (no cardiac

involvement), 80% responded (56% complete response/very good partial response) and there were no deaths with a median of 25 months of follow-up. Median survival of all patients was 72 months.

However, it appears that cardiac stage was the main determinant of survival, and patients with advanced heart disease (defined as those with N-terminal pronatriuretic peptide type B >8,500 ng/L) had poor outcomes, although 37% did achieve a response and seemed to fare better overall. The key takeaway from this data set is that due to the high clonal response and excellent outcome in early-stage ALA, CyBorD remains a preferred induction option and further research is needed to determine whether autologous stem cell transplant should be initiated as part of up-front treatment.

Novel agents in Waldenström macroglobulinemia (WM)

On January 29, 2015, ibrutinib became the first ever agent approved by the FDA for the management of WM. This significant milestone, along with emerging data indicating the activity of a number of other established and novel therapeutics, has breathed new life and interest into the treatment of this rare disease. At ASH we saw several examples of work attempting to move the field forward, including a Phase I/II trial evaluating **single-agent len** in 17 patients with RR WM. Thirty-six percent of these individuals responded to therapy, and with a median follow-up of 36 months, 35% of patients had a progression-free survival greater than 24 months.

Similarly, we also saw data from a Phase Ib/II trial evaluating the oral proteasome inhibitor oprozomib, which, like its intravenous cousin carfilzomib, appears to have significant efficacy in this disease. Notably, responses were observed in 5 of 7 patients refractory to bortezomib, and treatment was reasonably well tolerated, although some of the gastrointestinal toxicity that has plagued this agent was observed. To potentially eliminate this troubling side effect there is great interest in evaluating an extended-release formulation of the agent in both MM and WM.

Next, on the final issue of our ASH series, we check out papers on non-Hodgkin lymphoma, including the evaluation of anti-CD20 maintenance treatment in mantle-cell lymphoma.

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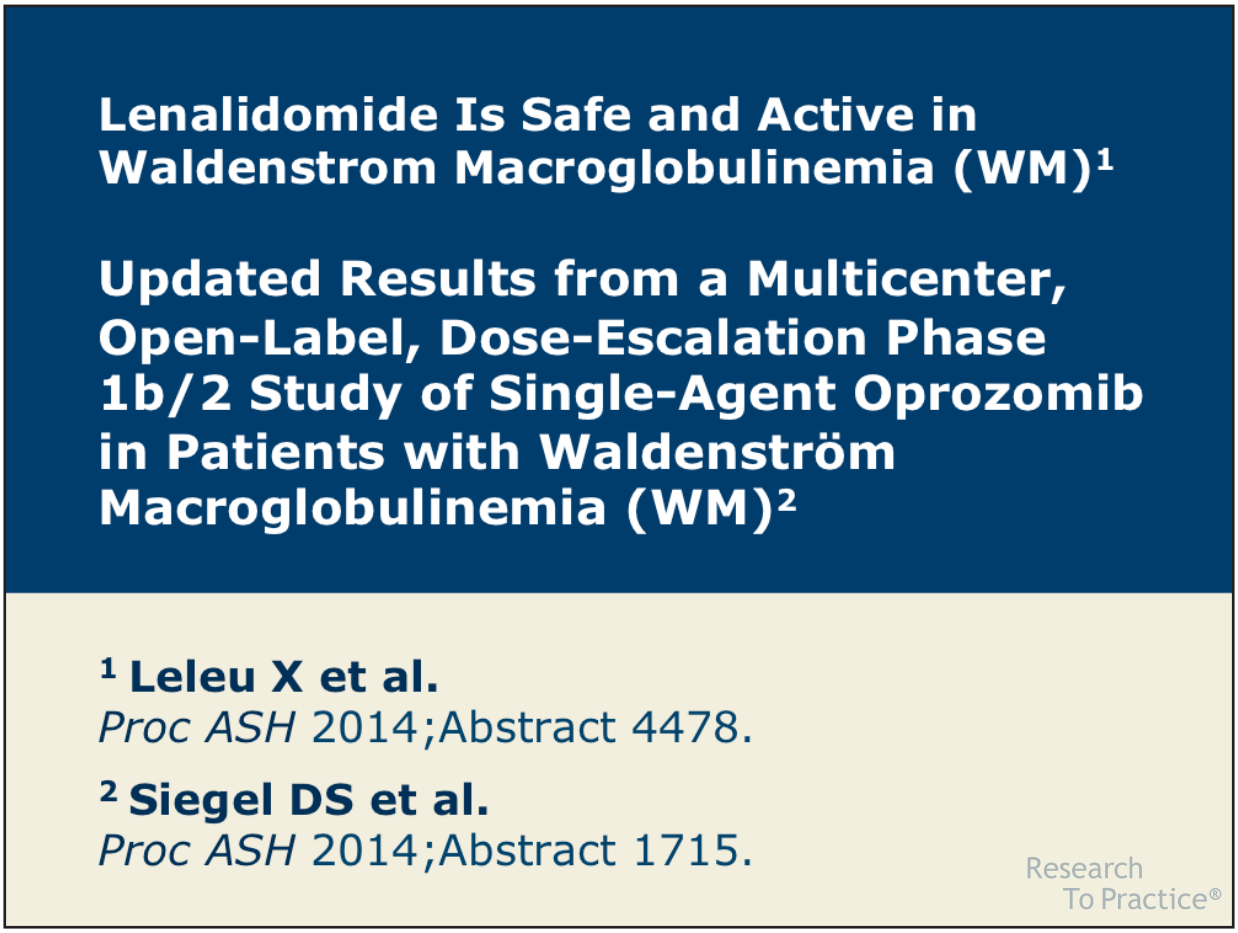
Phase I/II RV-WM-0426 Trial of Lenalidomide and Phase I/II Trial of Oprozomib in Relapsed/Refractory Waldenström Macroglobulinemia

Presentations discussed in this issue

Leleu X et al. **Lenalidomide is safe and active in Waldenstrom macroglobulinemia (WM).** *Proc ASH* 2014;**Abstract 4478**.

Siegel DS et al. **Updated results from a multicenter, open-label, dose-escalation phase 1b/2 study of single-agent oprozomib in patients with Waldenstrom macroglobulinemia (WM).** *Proc ASH* 2014;**Abstract 1715**.

Slides from presentations at ASH 2014



Lenalidomide Is Safe and Active in Waldenstrom Macroglobulinemia (WM)

Leleu X et al.

Proc ASH 2014;Abstract 4478.

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Background

- Lenalidomide (LEN) has proven to be safe and effective for multiple myeloma, especially as treatment for elderly patients.
- However, in a study of patients with Waldenström macroglobulinemia (WM), the combination of LEN at 25 mg/d and rituximab resulted in clinically significant acute anemia (*Clin Cancer Res* 2009;15:355).
- The anemia did not improve in most patients when the LEN dose was reduced, and no cause was apparent for the observed anemia.
- **Study objective:** To evaluate incremental doses of single-agent LEN in patients with WM to determine the maximum tolerated dose (MTD) and possibly to determine the cause of LEN-associated anemia in patients with WM.

Leleu X et al. *Proc ASH* 2014;Abstract 4478.

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RV-WM-0426 Phase I/II Study Design

Eligibility (n = 17)

Relapsed/refractory (R/R) WM

Phase I dose escalation

LEN (PO daily) 21/28-day cycle
15 to 20 then 25 mg x 1 year
Cohorts of 3-6 patients

Phase II

LEN (PO daily) 21/28-day cycle
MTD of 15 mg*
(n = 9)

- **Primary endpoint:** LEN MTD determination

* At LEN dose of 20 mg, 2 patients had dose-limiting toxicities. Therefore, the MTD was established at 15 mg/d.

Leleu X et al. *Proc ASH* 2014;Abstract 4478 (Abstract only).

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Baseline Patient Characteristics

Characteristic	n = 17
Median age (range)	69 years (48-81)
Male/female	70%/30%
IPSS Grade 3	53%
Median hemoglobin level	11.2 g/dL
Median M spike level	26.5 g/L
Prior exposure to rituximab	47%
Prior transplant	None

Leleu X et al. *Proc ASH* 2014;Abstract 4478 (Abstract only).

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Efficacy Summary

- Overall response (minimal response or better) on an intent-to-treat basis at LEN 15 mg/d = 36%.
  - Additionally, 2 patients had prolonged stable disease.
- A transient initial increase of the M spike (flare effect) was observed in 5 patients.
- With a median follow-up of 36 months:
  - 35% of patients have a progression-free survival >24 months.
  - 14 patients experienced disease progression, with a median time to progression of 16 months.
- One patient has died, with a 5-year overall survival of 91%.

Leleu X et al. *Proc ASH* 2014;Abstract 4478 (Abstract only).

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Adverse Event Summary

- The most common adverse event (AE ≥10%) was fatigue of at least Grade 2 reported in 50% of patients
- Grade ≥3 hematologic AEs at LEN 15 mg/d:
  - Anemia = 14%
  - Neutropenia = 43%
  - No thrombopenia was observed
- Grade ≥2 nonhematologic AEs: 78%
- Two patients with Grade 3 nonhematologic AEs: Nephrotic syndrome and cramps
- No second primary cancer or thromboembolic events were reported
- Patients requiring dose reduction: 21% (median time of 7 months)
- Patients requiring drug interruption due to AEs: 35% (median time of 4 months)

Leleu X et al. *Proc ASH* 2014;Abstract 4478 (Abstract only).

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Author Conclusions

- The MTD of LEN in R/R WM is 15 mg/d administered daily for 21 of 28 days.
- LEN is active in the treatment of R/R WM, and the safety profile appeared manageable, essentially of Grade 2 intensity.
- Future studies may investigate combinations with LEN and continuous therapeutic effect in WM at the determined MTD.

Leleu X et al. *Proc ASH* 2014;Abstract 4478 (Abstract only).

Updated Results from a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study of Single-Agent Oprozomib in Patients with Waldenström Macroglobulinemia (WM)

Siegel DS et al.

Proc ASH 2014;Abstract 1715.

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Background

- Oprozomib (OPZ) is an oral proteasome inhibitor that has shown promising activity in patients with hematologic cancer.
- An ongoing Phase Ib/II study is evaluating 2 schedules of OPZ administration (modified-release tablets) in patients with relapsed disease (*Proc ASH* 2013;Abstract 3184).
  - 18 patients included in response evaluation on OPZ 5/14 schedule (n = 13 with multiple myeloma, n = 5 with WM) and 15 patients included in response evaluation on OPZ 2/7 schedule (n = 12 with multiple myeloma, n = 3 with WM)
  - Clinical benefit rate for patients with WM = 80% (5/14 schedule) and 0% (2/7 schedule)
- **Study objective:** To report updated safety and efficacy results from the subset of patients with WM enrolled in the ongoing Phase Ib/II study of OPZ.

Siegel DS et al. *Proc ASH* 2014;Abstract 1715.

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Ongoing Phase Ib/II Study Design (NCT01416428)

Eligibility (Target: n = 364)

Hematologic cancer and relapse after ≥1 line of therapy

Phase Ib dose escalation*

2/7 schedule: OPZ PO d1, 2, 8 and 9 of 14-day cycles
5/14 schedule: OPZ PO daily d1-5 of 14-day cycles

Phase II

OPZ 240 mg PO on 5/14 schedule (initial schedule opened to enrollment)

- **Primary endpoint Phase Ib:** OPZ maximum tolerated dose (MTD) determination, safety and tolerability
- **Primary endpoint Phase II:** Best overall response rate (ORR, minimal response or better)

* Starting dose was 150 mg/d and doses were escalated in 30-mg increments; MTD determination included all 106 patients enrolled on the study.

Siegel DS et al. *Proc ASH* 2014;Abstract 1715 (Abstract only); www.clinicaltrials.gov.

Baseline Characteristics for Patients with WM

Characteristic	Phase Ib 2/7 schedule (n = 8)	Phase Ib 5/14 schedule (n = 11)	Phase II 5/14 schedule (n = 17)
Median age, years (range)	61.5 (50-77)	69.0 (56-79)	62.0 (44-85)
Median prior regimens, n (range)	3 (1-8)	5 (1-10)	3 (1-7)
Prior bortezomib exposure, n (%) Naïve Sensitive Refractory	 3 (38) 1 (13) 2 (25)	 2 (18) 3 (27) 4 (36)	 3 (18) 11 (65) 3 (18)

Siegel DS et al. *Proc ASH* 2014;Abstract 1715 (Abstract only).

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ORR for Patients with WM

Phase Ib patient group (n = 19)*	ORR
2/7 schedule (n = 8)	38%
5/14 schedule (n = 11)	73%
Bortezomib refractory (n = 4)	75%
Phase II patient group (n = 17)	
All patients, 5/14 schedule (n = 17)	59%
Carfilzomib naïve (n = 16)	56%
Bortezomib refractory (n = 3)	67%

* All 19 patients in the Phase Ib portion were carfilzomib naïve.

Siegel DS et al. *Proc ASH* 2014;Abstract 1715 (Abstract only).

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Select Adverse Events (AEs) by OPZ Schedule in Patients with WM

	Phase Ib 2/7 schedule (n = 8)		Phase Ib 5/14 schedule (n = 11)		Phase II 5/14 schedule (n = 17)	
Event	Any grade n (%)	Grade 3-4 n (%)	Any grade n (%)	Grade 3-4 n (%)	Any grade n (%)	Grade 3-4 n (%)
Hematologic AEs						
Anemia	1 (13)	1 (13)	4 (36)	1 (9)	1 (6)	0 (0)
Thrombocytopenia	4 (50)	2 (25)	3 (27)	0 (0)	0 (0)	0 (0)
Neutropenia	3 (38)	2 (25)	3 (27)	1 (9)	0 (0)	0 (0)
Nonhematologic AEs						
Nausea	5 (63)	0 (0)	7 (64)	1 (9)	13 (76)	1 (6)
Diarrhea	2 (25)	0 (0)	6 (55)	2 (18)	10 (59)	1 (6)
Constipation	2 (25)	0 (0)	4 (36)	0 (0)	10 (59)	0 (0)
Fatigue	2 (25)	0 (0)	6 (55)	2 (18)	8 (47)	0 (0)

Siegel DS et al. *Proc ASH* 2014;Abstract 1715 (Abstract only).

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Author Conclusions

- The MTD of OPZ was 300 mg/d in the 2/7 schedule (data not shown) and 240 mg/d in the 5/14 schedule as determined from all patients enrolled with hematologic cancer.
- In patients with WM who received single-agent OPZ, the most common Grade 3 AEs were neutropenia and diarrhea.
  - Grade 4 AEs were infrequent
- Additional measures will be taken to improve gastrointestinal tolerability.
- Single-agent OPZ continues to have promising antitumor activity in patients with WM.
- Enrollment on the 2/7 schedule is continuing; the target for the Phase II portion of the study is 66 patients.
- Extended-release OPZ tablets will be introduced and assessed for safety, activity and pharmacokinetics.

Siegel DS et al. *Proc ASH* 2014;Abstract 1715 (Abstract only).

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