5 Minute JournalClub

POST-ASH Issue 6, 2015

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CME Information

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.

CME Information (Continued)

- Assess the safety and efficacy of the proteasome inhibitor oprozomib as a single agent in the treatment of WM.

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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:

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

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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.

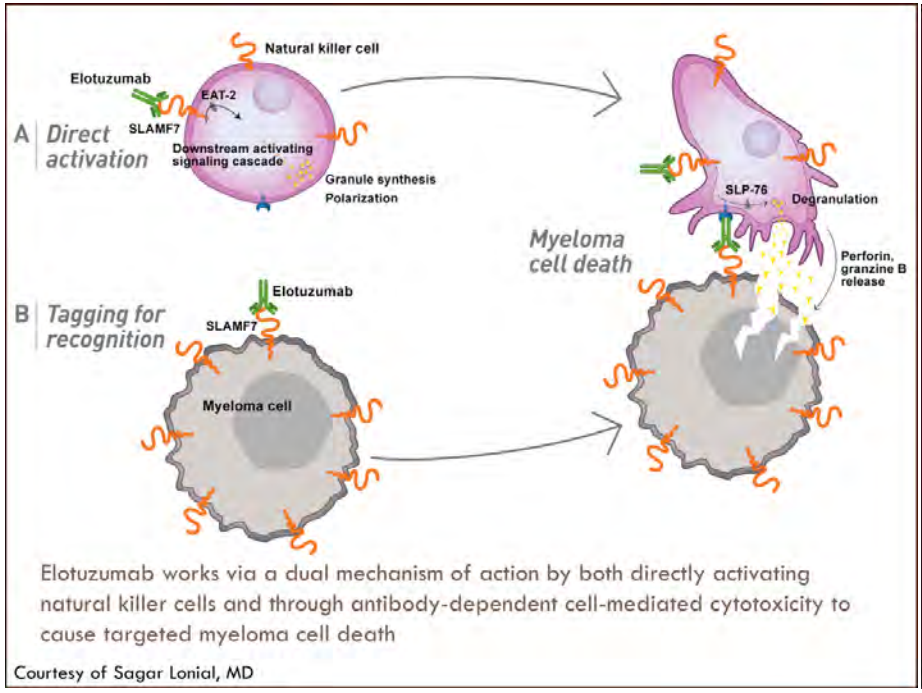
Fast forward to a week ago, when ASCO released online all but the late-breaking abstracts. My first click was to ELOQUENT-2, and to my delight, elo/len/dex resulted in a 30% reduction in the risk of disease progression and also a mortality benefit. While we most definitely need to see the data and hear 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

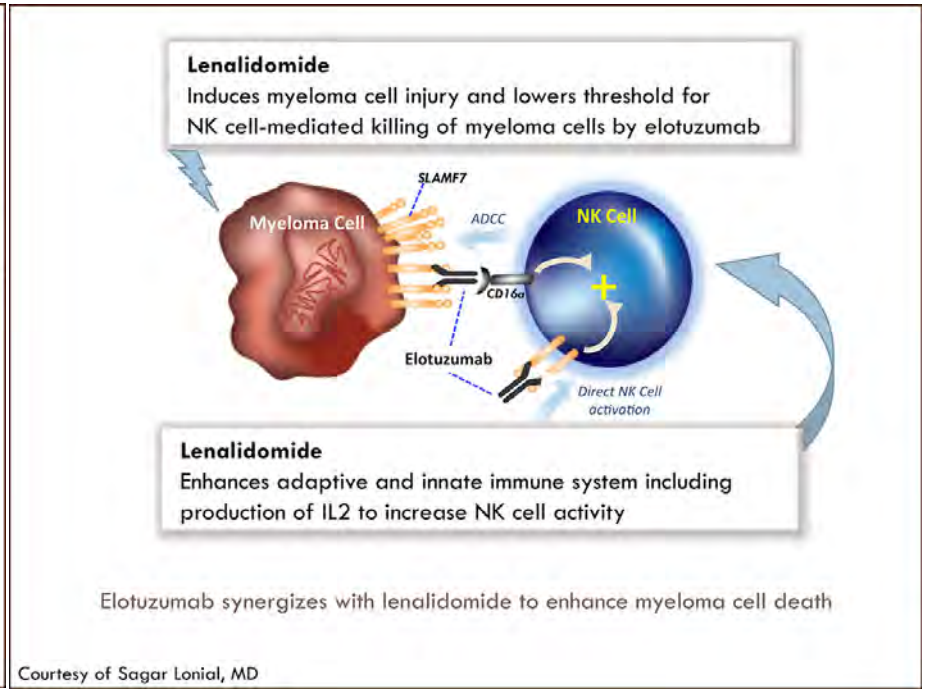
- **Elo / len / dex**

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 tria**l 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.

Neil Love, MD
Research To Practice
Miami, Florida

Final Results for the 1703 Phase 1b/2 Study of Elotuzumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

Richardson PG et al.

Proc ASH 2014;Abstract 302.

Background

- Elotuzumab (Elo) is a humanized IgG1 monoclonal antibody targeted against the signaling lymphocytic activation molecule F7 (SLAMF7, also known as CS1).
  - SLAMF7 is a glycoprotein that is highly expressed on multiple myeloma (MM) and natural killer (NK) cells but not on normal tissues (*Clin Cancer Res* 2008;14:2775).
  - Through direct activation and engagement of NK cells, Elo selectively targets and kills SLAMF7-expressing MM cells.
- In the Phase I part of the 1703 study, Elo in combination with lenalidomide (Len) and low-dose dexamethasone (dex) resulted in an objective response rate (ORR) of 82% among patients with relapsed/refractory MM (RRMM) (*JCO* 2012;30:1953).
- **Study objective:** To report the final Phase I and II efficacy and safety results from the 1703 study for patients with RRMM.

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Phase Ib/II 1703 Trial Design (NCT00742560)

Eligibility

Patients with RRMM
1-3 prior therapies
No prior Len therapy
No peripheral stem cell transplant
≤12 weeks before first dose of Elo
No Grade ≥3 neuropathy

Phase Ib (dose escalation)
Elo at 5, 10, 20 mg/kg
+ Len/dex
(n = 28*)

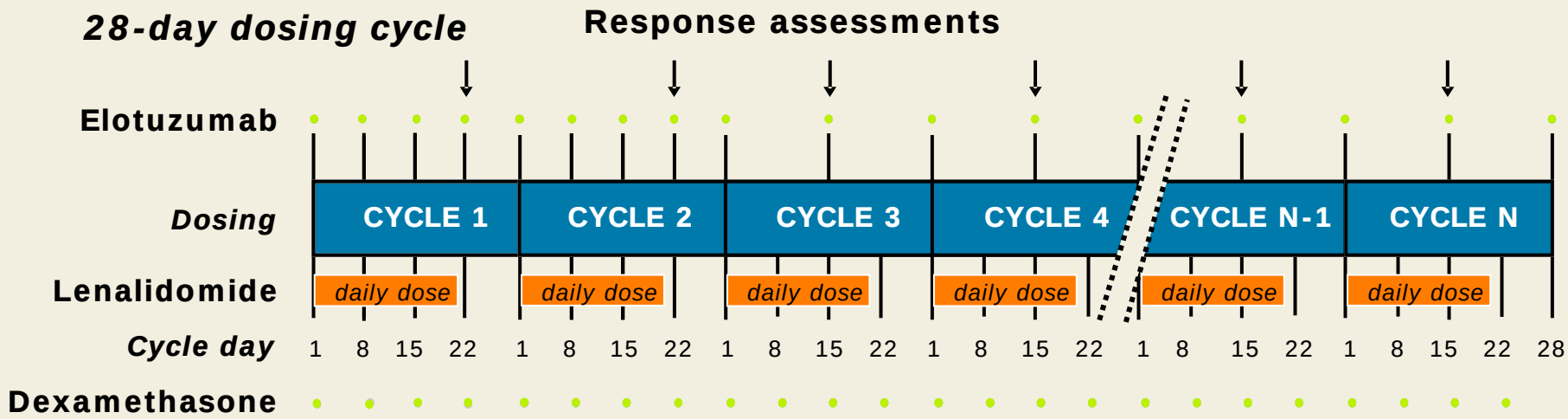
Phase II
Elo at 10 or 20 mg/kg
+ Len/dex
(n = 73)

* The first 5 patients were limited to 6 cycles of tx; the remaining 23 patients received tx until progression or unacceptable toxicity.

- Len dose: 25 mg; dex dose: 40 mg
- **Primary endpoints:**
  - Phase Ib: The maximum tolerated dose (MTD) of Elo
  - Phase II: ORR
- **Secondary endpoints** include progression-free survival (PFS) and safety

Richardson PG et al. *Proc ASH* 2014;Abstract 302; Lonial S et al. *J Clin Oncol* 2012;30(16):1953-9.

Phase II Dosing Schedule



- Patients were randomly assigned to receive Elo at 10 or 20 mg/kg and Len/dex.
- Premedication regimens were administered to reduce the risk of infusion reactions.

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Summary of Results from the Phase Ib Portion of Study 1703

- No dose-limiting toxicities were observed.
- The MTD was not reached.
- As of data cutoff date August 20, 2010
  - The ORR: 23/28 (82%)
  - After a median follow-up of 16.4 months, the median time to progression (TTP) was not reached in the 20-mg/kg cohort
- As of data cutoff date January 16, 2014
  - Median TTP: 33 months for all treatment groups (n = 28)
- These results compare favorably to results in 2 randomized studies of Len/dex with similar patient populations (*NEJM* 2007;357:2133; *NEJM* 2007;357:2123).

Richardson PG et al. *Proc ASH* 2014;Abstract 302; Lonial S et al. *J Clin Oncol* 2012;30(16):1953-9.

Phase II: Response

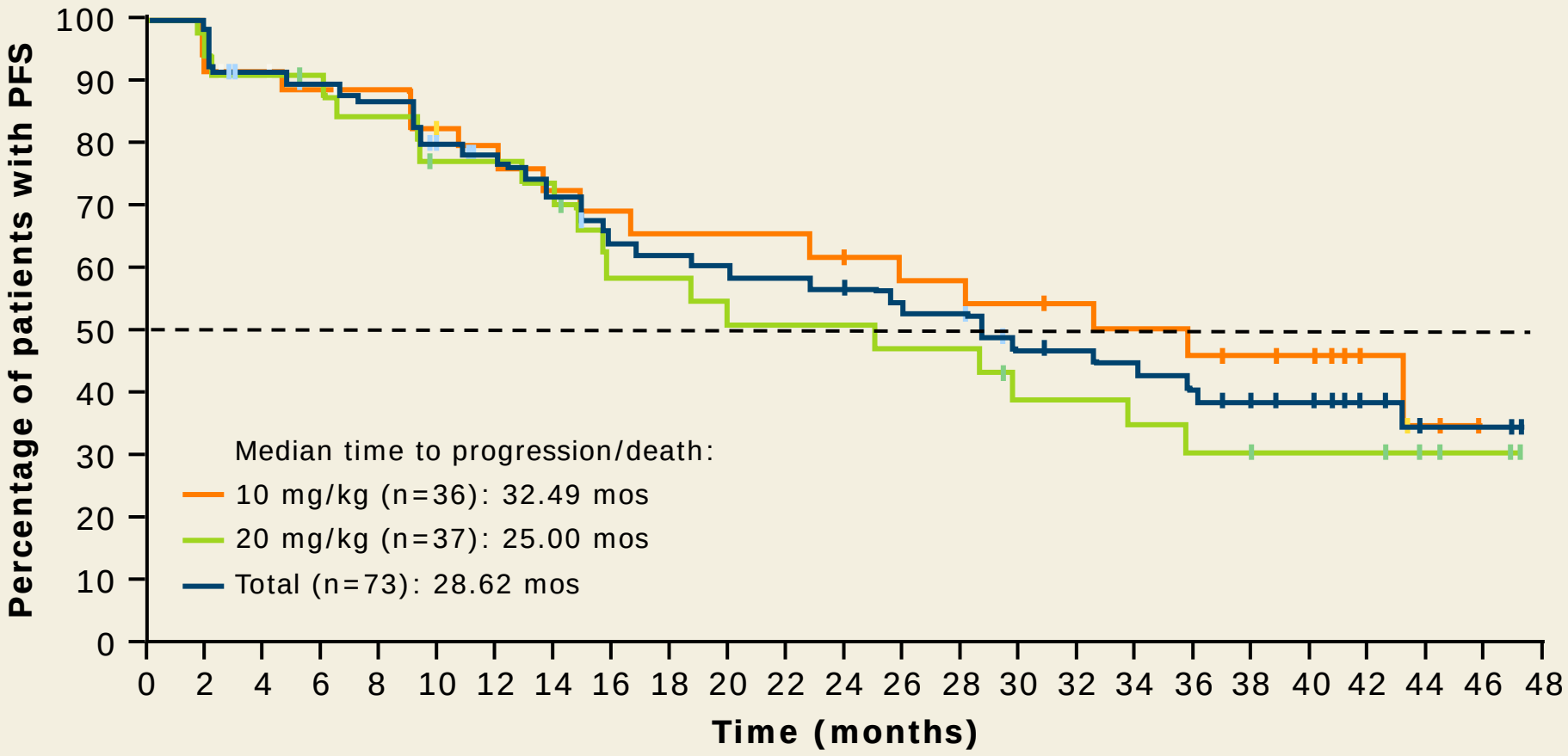
Response rate	Elo (10 mg/kg) (n = 36)	Elo (20 mg/kg) (n = 37)	Total (n = 73)
ORR	33 (92%)	28 (76%)	61 (84%)
sCR	2 (6%)	1 (3%)	3 (4%)
CR	4 (11%)	3 (8%)	7 (10%)
VGPR	17 (47%)	14 (38%)	31 (43%)
PR	10 (28%)	10 (27%)	20 (27%)
Stable disease	3 (8%)	7 (19%)	10 (14%)

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

- Missing data: 10 mg/kg (none); 20 mg/kg (n = 2)
- Median time to first response: 1 mo (10 mg/kg); 1.7 mo (20 mg/kg), 1 mo (all)
- Median duration of response: 23 mo (10 mg/kg); 18 mo (20 mg/kg), 20.8 mo (all)

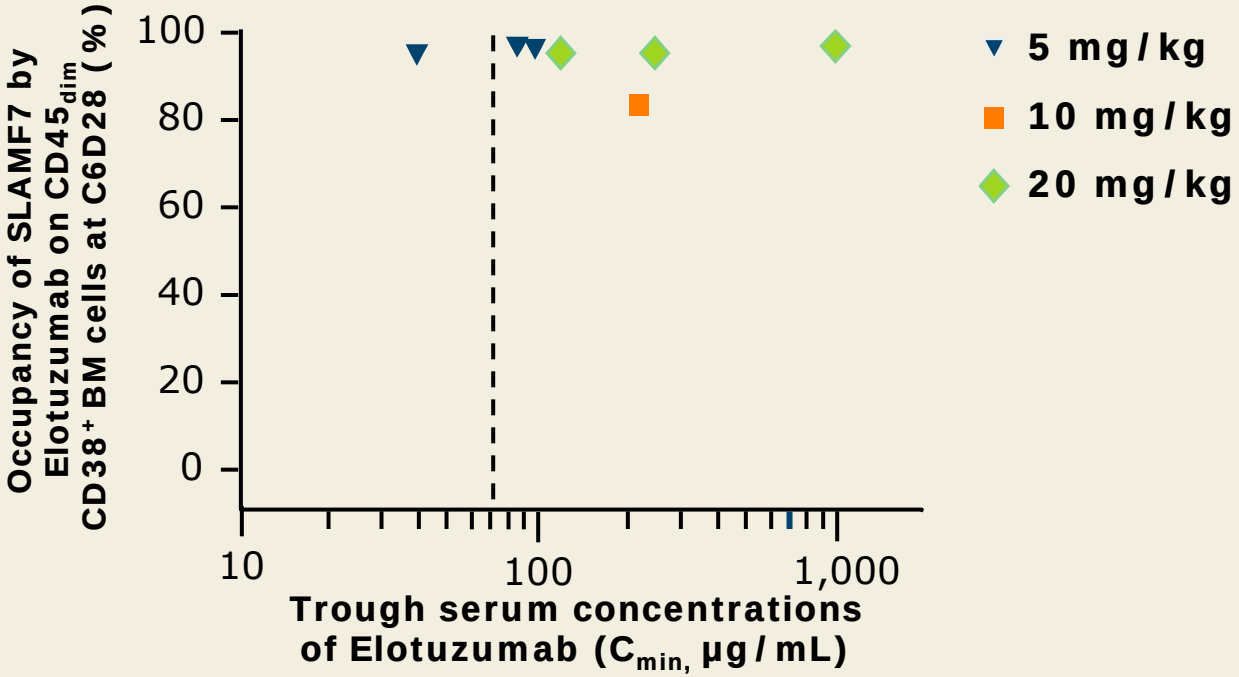
Richardson PG et al. *Proc ASH* 2014;Abstract 302.

PFS



With permission from Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Pharmacokinetics (PK) / Pharmacodynamics (PD)



- Steady state Elo serum concentrations >70 µg/mL maintained at both 10- and 20-mg/kg doses, consistent with optimal antitumor concentration observed in a preclinical model (*JCO* 2012;30:1953; *Blood* 2008;112:1329).
- Saturation of SLAMF7 sites on bone marrow MM cells >80% observed at both 10- and 20-mg/kg doses (*JCO* 2012;30:1953).
- Equivalent tolerability, efficacy and PD between 10- and 20-mg/kg doses observed during the 2 phases of Study 1703.

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Phase II: Select Adverse Events (AEs)

Event	Elo at 10 mg/kg (n = 36)		Elo at 20 mg/kg (n = 37)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	67%	14%	65%	5%
Fatigue	67%	8%	46%	5%
Anemia	47%	17%	32%	14%
Back pain	47%	8%	35%	3%
Pyrexia	39%	3%	46%	3%
Lymphopenia	36%	28%	22%	14%
Thrombocytopenia	36%	19%	19%	16%
Neutropenia	31%	19%	22%	19%
Hyperglycemia	25%	6%	32%	14%

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Phase II: Select Infusion-Related Reactions (IRRs)

Event (n)	Rate ≤2 mL/min		Rate >2 mL/min	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Pyrexia	3	0	0	0
Rash	2	1	0	0
Nausea	1	0	1	0
Abdominal pain	1	0	0	0
Chest discomfort	1	0	0	0
Chills	1	0	0	0

- Other Grade 1 or 2 IRRs at ≤2 mL/min: 1 each of flushing, hot flush, pain.
- For patients who tolerated infusion at 2 mL/min, the flow rate was progressively increased to a maximum of 5 mL/min (infusion time <1 h).
- The overall rate of IRRs was 11%.
- 7 patients had an IRR at <2 mL/min; 1 patient had an IRR at ≥2 mL/min.
- Of the 3,412 infusions given, 1,127 (33%) were at a rate of 5 mL/min.

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Author Conclusions

- In the Phase II portion of the study, Elo in combination with Len/dex demonstrated encouraging efficacy:
  - ORR: 92% in the 10-mg/kg treatment group (84% overall)
  - Median PFS: 32.49 mo in the 10-mg/kg group (29 mo overall)
- The most common treatment-emergent AEs included diarrhea (66%), fatigue (56%), muscle spasms (52%) and constipation (51%).
- The use of premedication regimens successfully mitigated IRRs.
- A faster infusion rate at 5 mL/min with infusion time <1 h was well tolerated.
- Efficacy and safety outcomes observed in the Phase II portion of the study concur with previous Phase Ib study results (*JCO* 2012;30:1953).

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Future Directions

- Phase III controlled trials with 10 mg/kg of Elo in combination with Len/dex in newly diagnosed MM and RRMM are ongoing (ELOQUENT-1 and ELOQUENT-2).
- A Phase II trial to evaluate the safety and tolerability of Elo at 10 mg/kg infused at 5 mL/min and administered in combination with Len/dex to patients with RRMM is under way (NCT02159365).
- An ongoing Phase II trial to evaluate the efficacy of Elo monotherapy for patients with high-risk smoldering MM has completed enrollment (NCT01441973).
- A Phase II trial to evaluate the efficacy of Elo in combination with Len/dex for patients with high-risk smoldering MM is under way (NCT02279394).

Richardson PG et al. *Proc ASH* 2014;Abstract 302.

Investigator Commentary: Final Efficacy and Safety Results from the Phase Ib/II Trial of Elo/Len/Dex in RRMM

In this small study Elo was administered in combination with Len/dex to patients with RRMM. Consistent with what has been shown before in other smaller studies, the combination is meaningful and translates into ORR and PFS outcomes better than those with Len/dex alone. This is another good option for patients who do not achieve results with Len/dex, and I'm happy to see these results. The combination will be tested in a Phase III study, and we are awaiting those results.

The interactions between Len and Elo are not fully understood. Elo targets an antigen, CS1, or SLAMF7, that is expressed on the surface of MM cells, and it also directly activates NK cells. Why it works when combined with Len but not alone is not clear. Initially Elo was tested as a single agent, but it was not effective. Len has immunostimulatory properties, and it seems to stimulate NK cells. One of the reasons why the combination works may be the ability to activate an increased number of NK cells that are targeted against SLAMF7-expressing MM cells, and this has been the proposed mode of action. I don't believe we have preclinical data to prove these proposed models.

Interview with Ola Landgren, MD, PhD, February 9, 2015

A Phase Ib Dose Escalation Trial of SAR650984 (Anti-CD-38 mAb) in Combination with Lenalidomide and Dexamethasone in Relapsed/ Refractory Multiple Myeloma[1]

Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed or Relapsed, Refractory Multiple Myeloma[2]

[1] **Martin TG et al.**
Proc ASH 2014;Abstract 83.

[2] **Plesner T et al.**
Proc ASH 2014;Abstract 84.

A Phase Ib Dose Escalation Trial of SAR650984 (Anti-CD-38 mAb) in Combination with Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Martin TG et al.

Proc ASH 2014;Abstract 83.

Background

- SAR650984 (SAR) is a humanized IgG1 monoclonal antibody that binds selectively to a unique epitope on the human CD38 receptor.
- SAR may induce antitumor effects via antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, direct apoptosis induction without secondary crosslinking and/or allosteric inhibition on CD38 enzymatic activity.
- Preclinical and xenograft data support the clinical use of SAR in combination with lenalidomide (LEN) (*Clin Cancer Res* 2014;20(17):4574; ASH 2014;Abstract 653).
- **Study objective:** To report preliminary efficacy and safety of SAR in combination with LEN and dexamethasone (Dex) for patients with relapsed/refractory (R/R) multiple myeloma (MM).

Martin TG et al. *Proc ASH* 2014;Abstract 83.

Ongoing Phase Ib Trial Design (NCT01749969)

Eligibility (Target: n = 60)

Diagnosis of R/R MM

≥2 prior therapies

Prior bone marrow transplant is allowed

SAR + LEN + Dex

SAR: 3, 5 or 10 mg/kg d1, 15

→ dose escalation (3 + 3 design)

LEN: 25 mg d1-21*

Dex: 40 mg d1, 8, 15, 22

(28-day cycles)

Expansion cohort (n = 18)

Maximum tolerated dose (MTD) or the highest dose tested (10 mg/kg)

* Adjusted to 10 mg if baseline creatinine clearance is ≤60 mL/min

- **Primary endpoint:** Safety
- **Secondary endpoints** include overall response rate (ORR), progression-free survival (PFS) and the assessment of pharmacokinetic parameters

Martin TG et al. *Proc ASH* 2014;Abstract 83.

Patient Characteristics

Characteristic	n = 31*
Median time from initial MM diagnosis to first dose of SAR (range)	4.5 years (1.1-11.7)
Median number of prior treatment regimens (range)	6 (2-12)
Patients who received prior IMiD therapy, including lenalidomide and pomalidomide	>95%
R/R to ≥1 prior IMiD-based therapy	>85%
Received prior bortezomib	>90%
Received prior carfilzomib	48%

* Total number of patients receiving treatment to date, including 24 patients (6 + 18) at the 10-mg/kg dose limit because the MTD was not reached

- Cutoff date: June 7, 2014

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Response

All patients	**n = 31**
ORR	20 (64.5%)
Stringent complete response (sCR)	2 (6.5%)
Very good partial response (VGPR)	8 (25.8%)
Partial response (PR)	10 (32.3%)
With MM R/R to last LEN-containing regimen	**n = 24**
ORR	15 (62.5%)
VGPR	8 (33.3%)
PR	7 (29.2%)
Minimal response	2 (8.3%)

- Median follow-up: 6 months
- Clinical benefit rate:
  - All patients: 71%; R/R to last LEN-containing regimen: 70.8%

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Response (continued)

With MM R/R to both IMiD and PIs*	n = 21
ORR	11 (52.4%)
VGPR	4 (19.1%)
PR	7 (33.3%)
Minimal response (MR)	2 (9.5%)

PIs = proteasome inhibitors

* Clinical benefit rate: 61.9%

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Treatment Outcomes

- Median time to first response among all patients was 4.2 weeks (4.0-10.1).
- Median time to best response was 8.5 weeks (4.0-32.6).
- Patients with improvement of response after a median of 16.1 weeks (8.1-32.6) of therapy (n = 9):
  - PR → sCR (n = 1)
  - VGPR → sCR (n = 1)
  - PR → VGPR (n = 5)
  - MR → PR (n = 2)
- Median time on treatment was 26.4 weeks (2.0-61.0).
- Patients who remained on treatment at the cutoff date: n = 14.
- Median duration of response was 23.1 weeks (0.1-54.7).

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Survival Outcomes

- Overall, 15 (48.4%) patients had PFS events:
  - Death unrelated to treatment (n = 1)
  - Disease progression (n = 14)
- The median PFS was 6.2 months.
- Patients who previously received LEN, bortezomib and at least 1 of the newer agents (carfilzomib and/or pomalidomide and/or elotuzumab): n = 17
  - Median PFS was 4.8 months

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Author Conclusions

- With a median follow-up of 6 months, the treatment with SAR/LEN/Dex for patients with heavily pretreated R/R MM appears effective:
  - ORR of 64.5%
  - Clinical benefit response rate of 71%
  - PFS of 6.2 months
- Responses were seen after the first cycle of therapy and deepened with continued treatment.
- The ORR was 62.5% for patients with MM R/R to their last regimen containing LEN.
- SAR in combination with LEN/Dex was well tolerated, produced impressive durable responses and warrants further evaluation.

Martin TG et al. *Proc ASH* 2014;Abstract 83 (Abstract only).

Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed or Relapsed, Refractory Multiple Myeloma

Plesner T et al.

Proc ASH 2014;Abstract 84.

Background

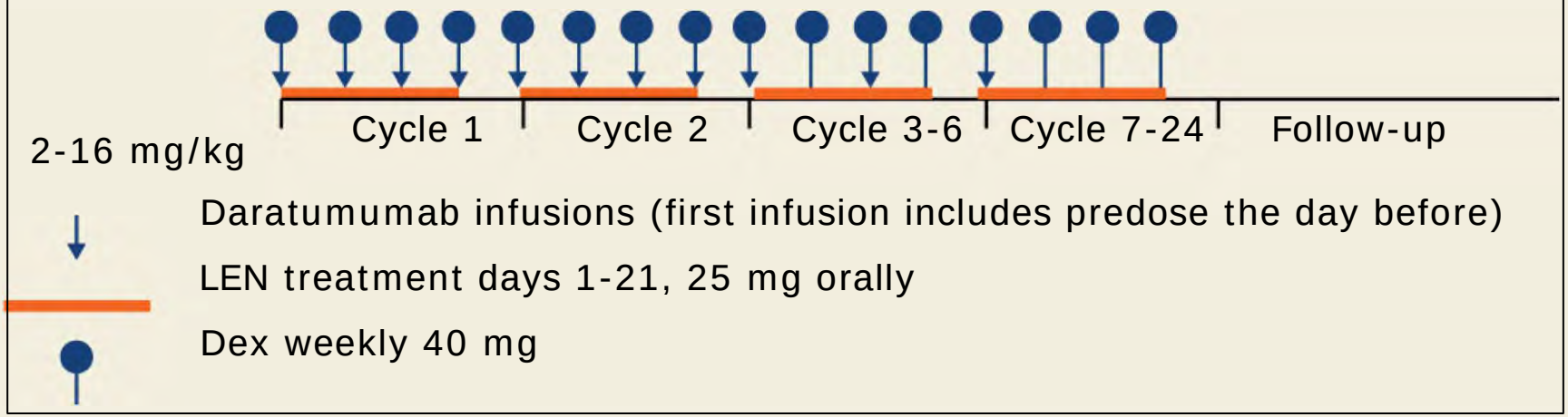
- Daratumumab (DARA) is a human monoclonal antibody that targets CD38-expressing tumor cells.
- In the first-in-human dose-escalation Phase I/II study of DARA (≥4 mg/kg) for patients with heavily pretreated relapsed or relapsed, refractory (RR) multiple myeloma (MM) (*Proc ASCO* 2013;Abstract 8512):
  - Patients who achieved partial response (PR) = 42%
  - Patients who achieved minimal response (MR) = 25%
- Previously, DARA in combination with lenalidomide (LEN) and dexamethasone (Dex) was shown to be well tolerated in patients with heavily pretreated relapsed or RR MM (*Proc ASCO* 2014;Abstract 8533).
- **Study objective:** To report updated efficacy and safety data with DARA in combination with LEN/Dex for patients with relapsed or RR MM.

Plesner T et al. *Proc ASH* 2014;Abstract 84.

Phase I/II Trial Design

Eligibility (n = 45)

Part 1: Relapsed or RR MM after 2-4 lines of therapy (n = 13)
Part 2: Relapsed or RR MM after ≥1 prior line of therapy (n = 32)
Measurable disease by M protein and serum light chain
No LEN-refractory or intolerant MM



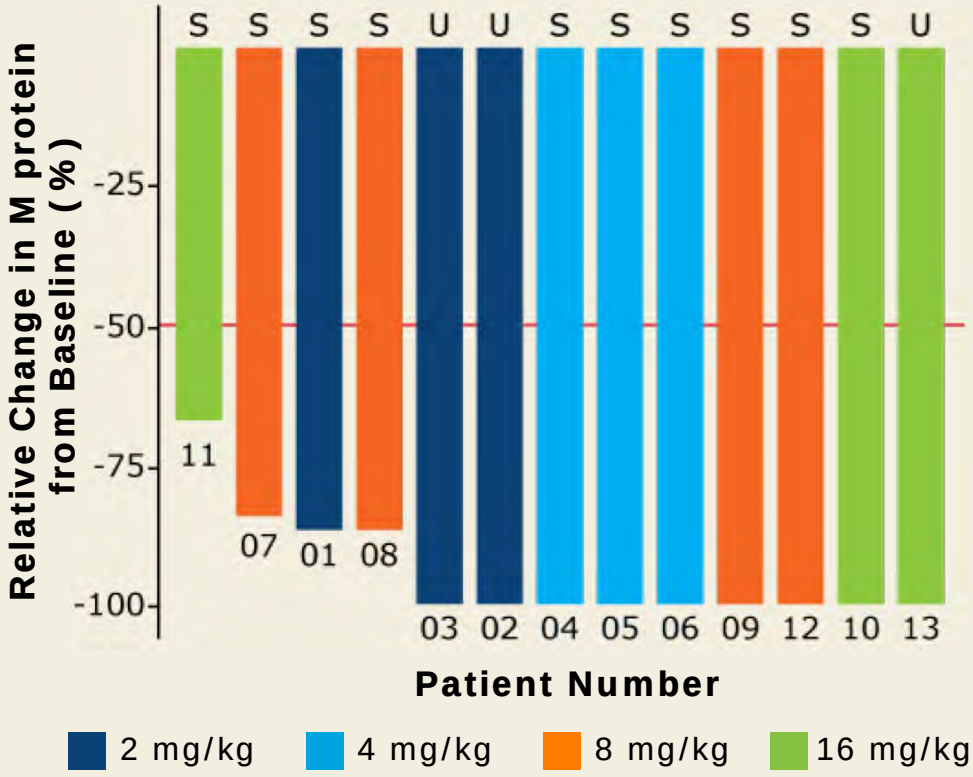
- **Primary endpoint:** Safety

Plesner T et al. *Proc ASH* 2014;Abstract 84.

Maximum Percentage Change in M Protein from Baseline

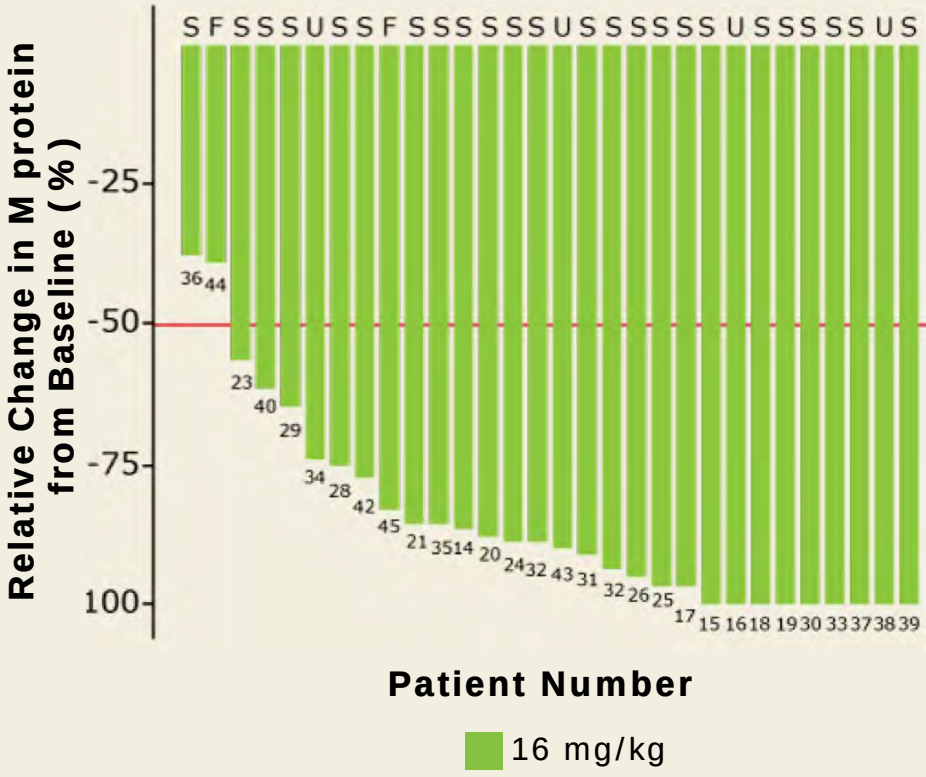
Part 1: Dose Escalation Study

2 – 16 mg/kg dose (n = 13)



Part 2: Expansion Cohort Study

16 mg/kg dose (n = 30)



- Majority of patients had >50% reduction in M protein levels

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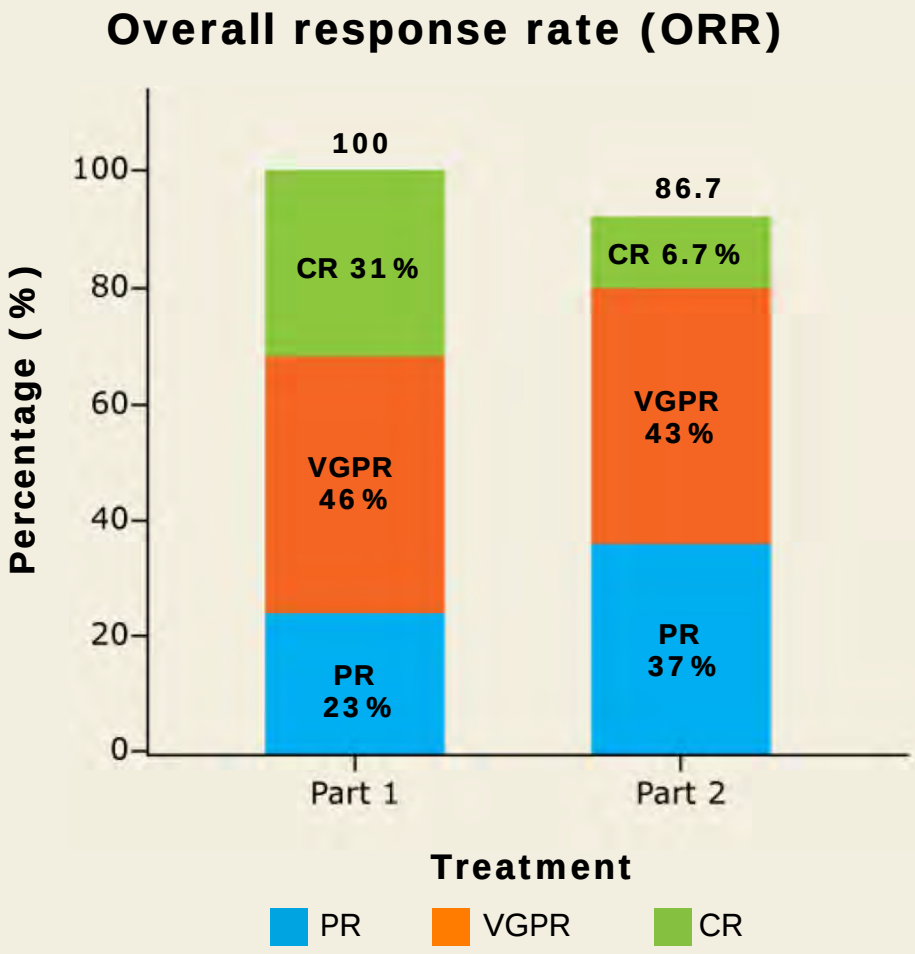
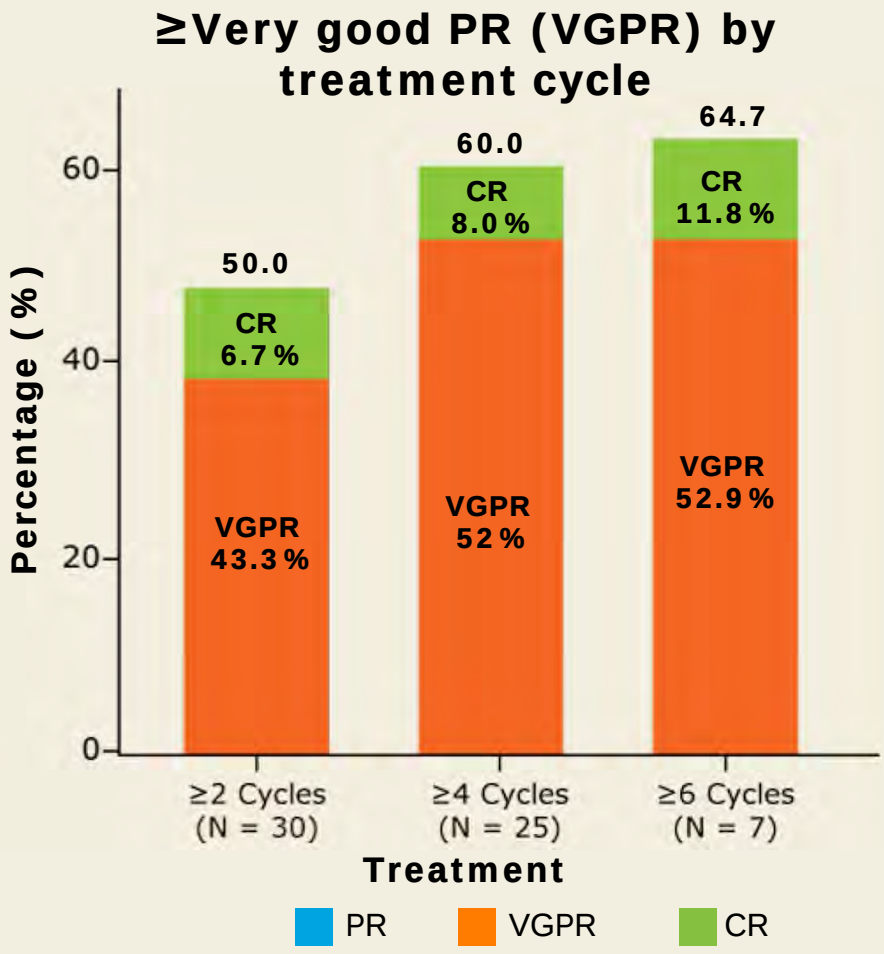
Best Response





- Mean duration of follow-up: 12.9 mo (Part 1) and 5.6 mo (Part 2)

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Response Characteristics

- VGPR or better was achieved by 75% of patients who received treatment for at least 6 months.
- Part 2 (16 mg/kg):
  - Median time to response was 1 month.
  - Median time to complete response was 4.9 months.
- As observed with other monoclonal antibodies, DARA may interfere with the serum immunofixation electrophoresis (IFE) test used to determine response to treatment.
  - The interference assay is yet to be validated.

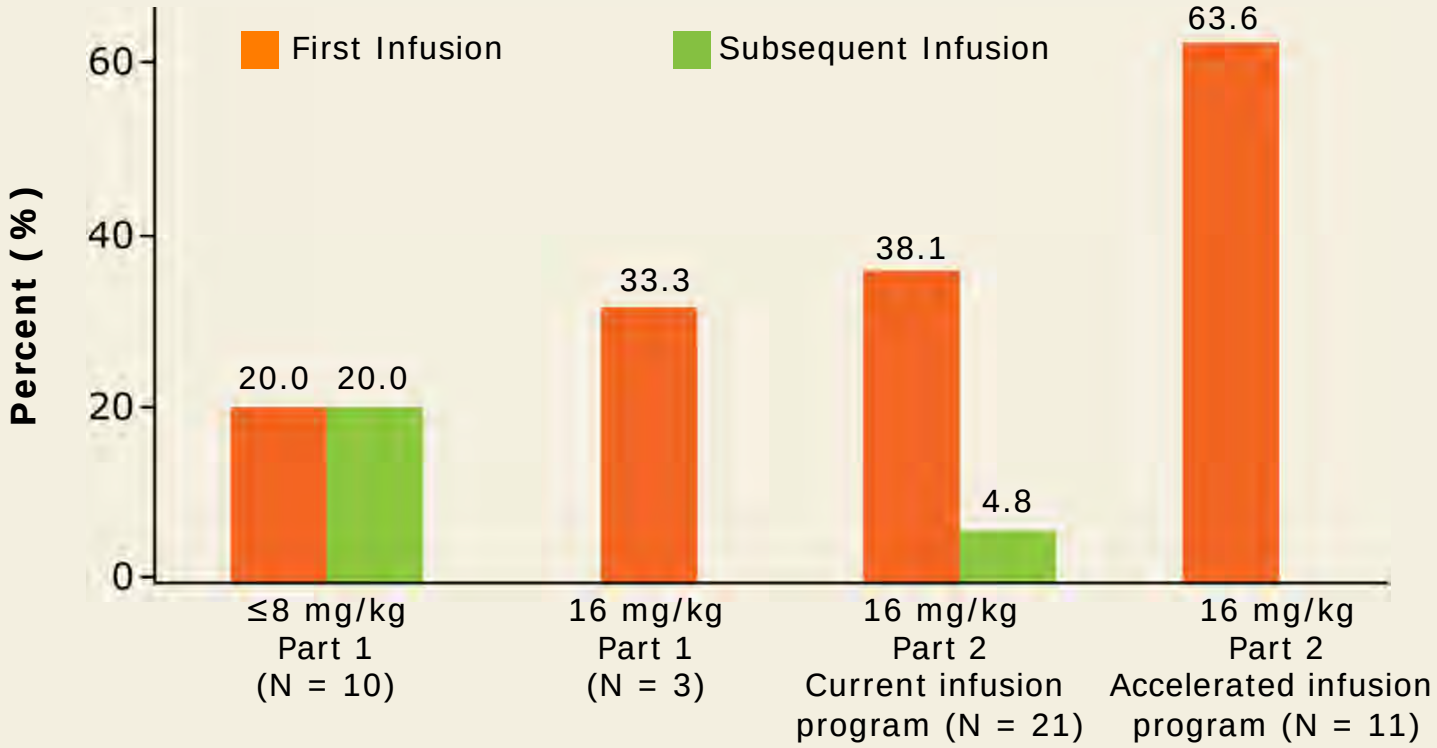
Plesner T et al. *Proc ASH* 2014;Abstract 84.

Safety (N = 45)

- No dose-limiting toxicities were reported.
- In Part 1, patients who discontinued treatment (n = 4)
  - Due to disease progression (n = 3):
    - 1 each in 2-, 8- and 16-mg/kg dose cohorts
  - Due to adverse events (n = 1):
    - Cardiac disorder in the 2-mg/kg cohort, due to recurrence of low-grade QT prolongation unrelated to DARA
  - Serious adverse events (n = 7):
    - All unrelated to DARA
- In Part 2, one patient discontinued treatment due to infusion-related reaction (laryngeal edema)
- Serious adverse events (n = 8) in Part 2:
  - DARA related (n = 4)

Plesner T et al. *Proc ASH* 2014;Abstract 84.

Infusion-Related Reactions (IRRs)



- Majority of IRRs were of Grade 1 and 2
- Patients who reported IRRs: 19 of 45 (42%)
- Most IRRs occurred during first infusion
- 18 of 19 (95%) patients with IRRs recovered and were able to continue with treatment

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Select Adverse Events Occurring in >10% of Patients

Event	Part 1 (n = 13)	Part 2 (n = 32)	Total (n = 45)
Neutropenia	62%	65%	64%
Muscle spasms	62%	38%	44%
Nasopharyngitis	62%	3%	20%
Fatigue	62%	16%	29%
Diarrhea	54%	18%	31%
Constipation	54%	13%	27%
Nausea	38%	19%	24%
Anemia	31%	19%	11%
Dyspnea	23%	6%	11%

DARA-related serious adverse events included pneumonia, neutropenia, diarrhea and laryngeal edema.

Plesner T et al. *Proc ASH* 2014;Abstract 84.

Author Conclusions

- The ORR was 100% in Part 1 and 87% in Part 2 of the study.
  - ≥VGPR in patients who received treatment for at least 6 months: 75%
- Data from Part 1 are mature and demonstrate impressive complete response rates.
- Early results from Part 2 are consistent with Part 1 results:
  - Median follow-up <6 months with depth of response expected to further improve
- Accelerated infusion was tolerable but associated with a higher incidence of Grade 1 and 2 adverse events:
  - Accelerated infusion requires further investigation
- DARA/LEN/Dex demonstrated a favorable safety profile and manageable toxicities in relapsed and RR MM.
- Phase III trials of DARA/LEN/Dex are ongoing:
  - MMY3003-POLLUX trial for patients with relapsed or refractory MM
  - MMY3008-MAIA trial in the MM front-line setting

Plesner T et al. *Proc ASH* 2014;Abstract 84.

Investigator Commentary: Efficacy and Safety Results from the Phase Ib Trial of SAR/LEN/Dex and the Phase I/II Trial of DARA/LEN/Dex for Patients with Relapsed and/or Refractory MM

In the ongoing Phase Ib trial of SAR/LEN/Dex for patients with relapsed or refractory MM after a median follow-up of 6 months, the investigators demonstrated an ORR of about 65% for all patients. The study showed that the addition of SAR, a CD38 monoclonal antibody, improves on the outcomes we have observed with LEN and low-dose Dex only.

In the Phase I/II trial of DARA/LEN/Dex, 75% of patients achieved VGPR or better, whereas with LEN/Dex alone only about 15% of patients usually achieve a complete response. The addition of DARA to LEN/Dex is tolerable and produces good response rates. However, I would argue that the administration of a proteasome inhibitor in this setting could result in about 75% of patients achieving a complete response. This begs the question of what would happen if an anti-CD38 monoclonal antibody were also added. Of course, several aspects of that approach have to be considered, including the cost of therapy, as it would be expensive, and the requirement for intravenous infusions, which would affect the patient's quality of life.

Interview with Ola Landgren, MD, PhD, February 9, 2015

continued

Investigator Commentary: Efficacy and Safety Results from the Phase Ib Trial of SAR/LEN/Dex and the Phase I/II Trial of DARA/LEN/Dex for Patients with Relapsed and/or Refractory MM (continued)

I believe that for patients with newly diagnosed disease, it may be worthwhile to use a strategy capable of producing deep responses in order to maintain long-term benefit from treatment.

In my opinion, the findings from these 2 studies are similar and support the idea that the addition of a monoclonal antibody to backbone therapy will probably become the standard therapy in this setting.

Interview with Ola Landgren, MD, PhD, February 9, 2015

Ibrutinib, Single Agent or in Combination with Dexamethasone, in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Preliminary Phase 2 Results

Vij R et al.

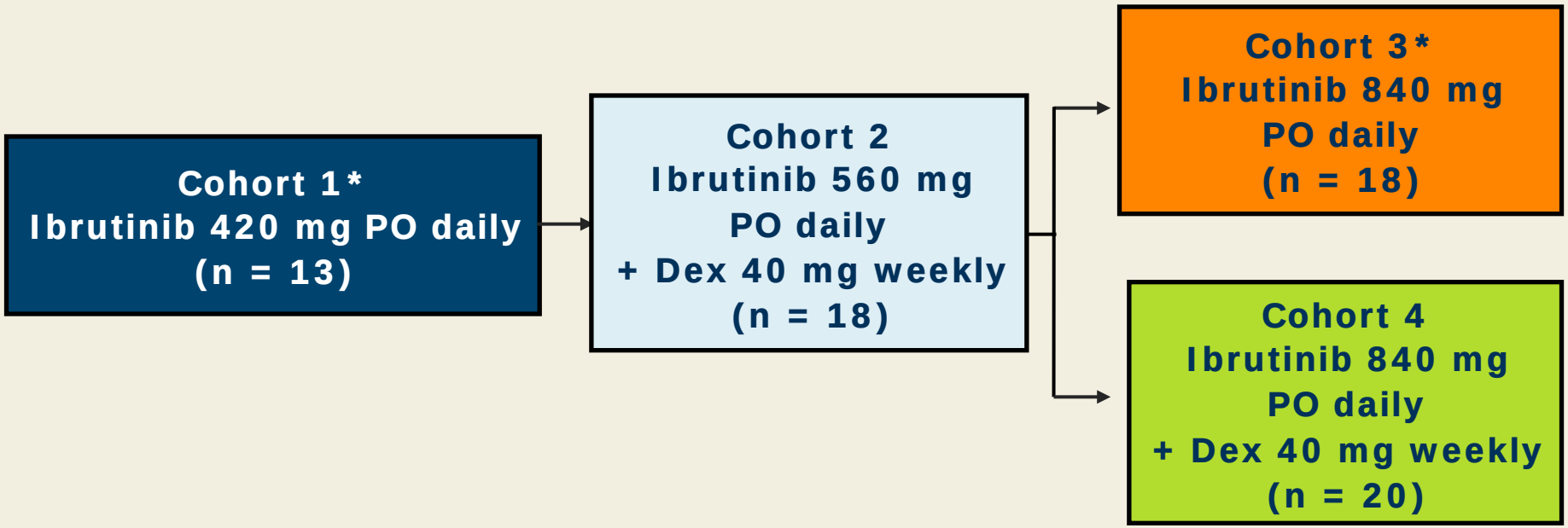
Proc ASH 2014;Abstract 31.

Background

- Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton tyrosine kinase (BTK), an essential enzyme in the B-cell receptor signaling pathway.
- Preclinical studies show that BTK inhibition with ibrutinib led to direct inhibition of both osteoclast bone resorption and the release of osteoclast-derived tumor growth factors (*Blood* 2012;120:1877).
- Robust BTK expression has been shown in the majority of MM plasma cells (*Am J Hematol* 2013;88:463).
- Taken together, these data suggest that ibrutinib may have a role in the treatment of MM.
- **Study objective:** To investigate the efficacy and safety of ibrutinib as a single agent or in combination with dexamethasone (Dex) in relapsed or relapsed/refractory (R/R) MM.

Vij R et al. *Proc ASH* 2014;Abstract 31.

Phase II PCYC-1111 Trial Design



* For cohorts 1 and 3, the addition of Dex at 40 mg q1wk was permitted at disease progression per investigator discretion.

- **Primary endpoint:** Clinical benefit rate (CBR) defined as minimal response (MR) or better.
- **Secondary endpoints** include duration of clinical benefit, objective response rate, duration of objective response, safety and pharmacokinetic analyses.

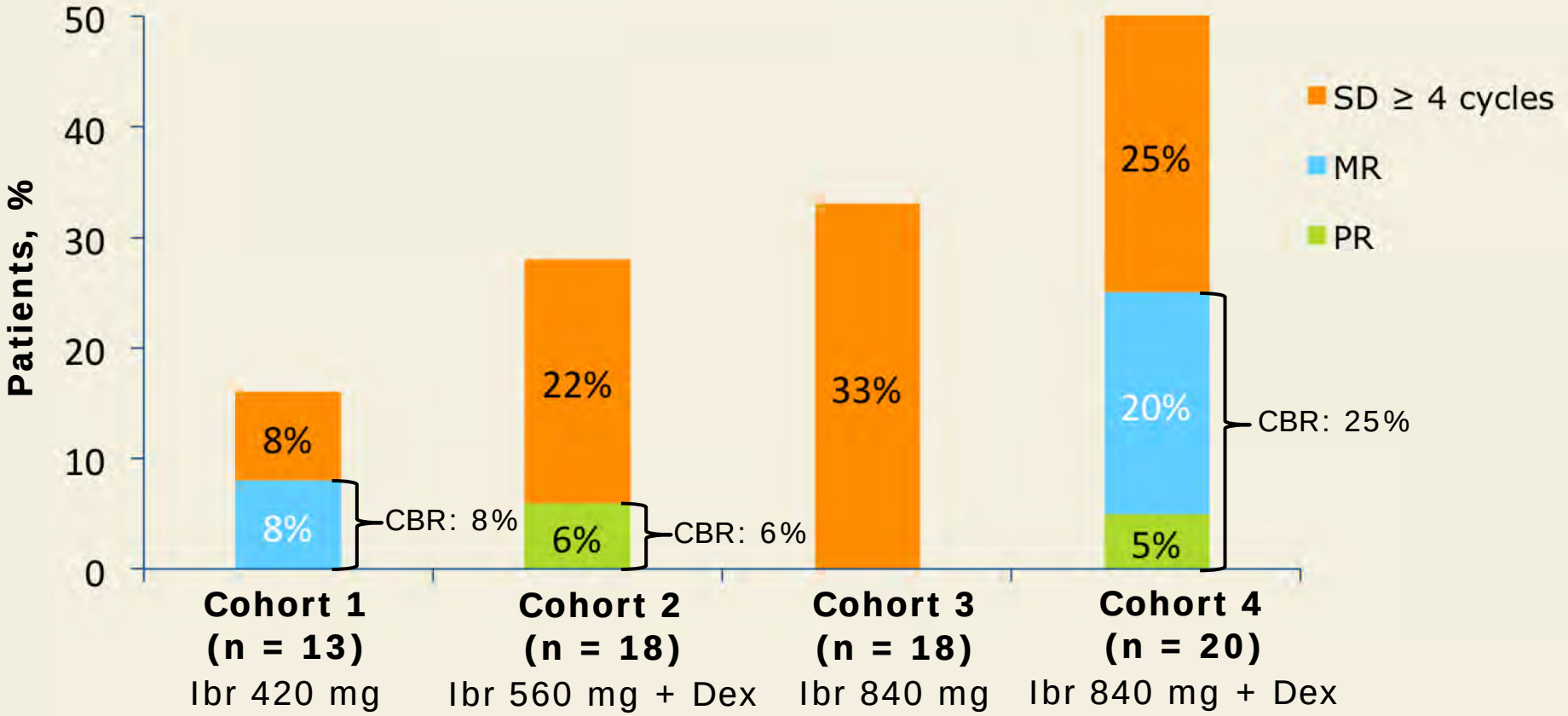
Vij R et al. *Proc ASH* 2014;Abstract 31.

Key Eligibility Criteria

- Measurable symptomatic relapsed or R/R MM
  - Refractory MM is defined as nonresponsive disease with failure to achieve MR while on treatment, or progressive disease within 60 days of last treatment
- Two or more previous lines of therapy
  - Including an immunomodulatory agent
- ECOG performance status ≤1
- No inadequate bone marrow function
- No creatinine level >2.5 mg/dL
- No currently active clinically significant cardiovascular disease
- No Grade ≥2 peripheral neuropathy

Vij R et al. *Proc ASH* 2014;Abstract 31.

Overall Response



- Rate of disease stabilization or better increased with dose
- CBR rate was 25% for those treated in cohort 4

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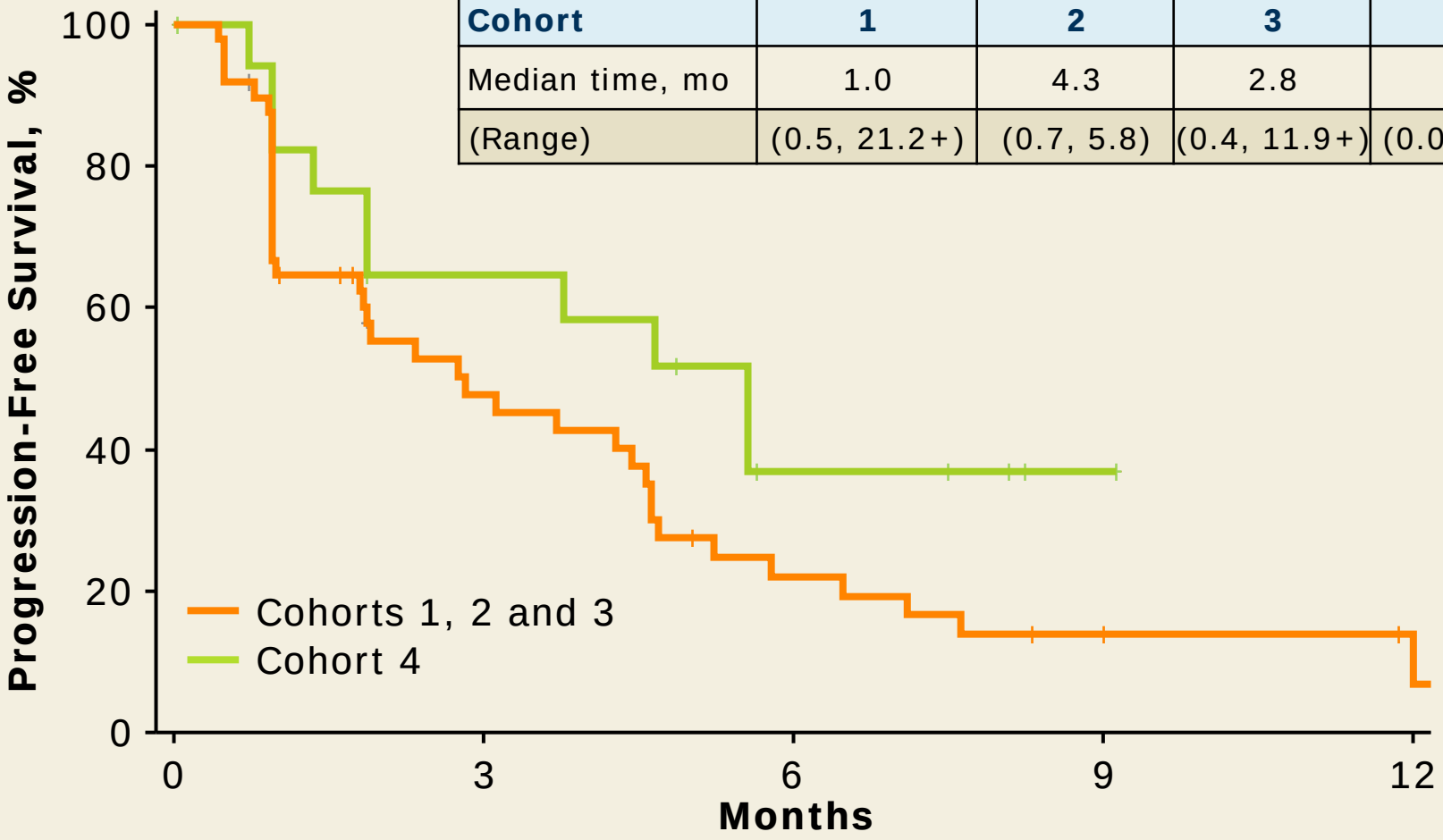
Progression-Free Survival

Cohort	1	2	3	4
Median time, mo	1.0	4.3	2.8	5.6
(Range)	(0.5, 21.2+)	(0.7, 5.8)	(0.4, 11.9+)	(0.0, 9.1+)



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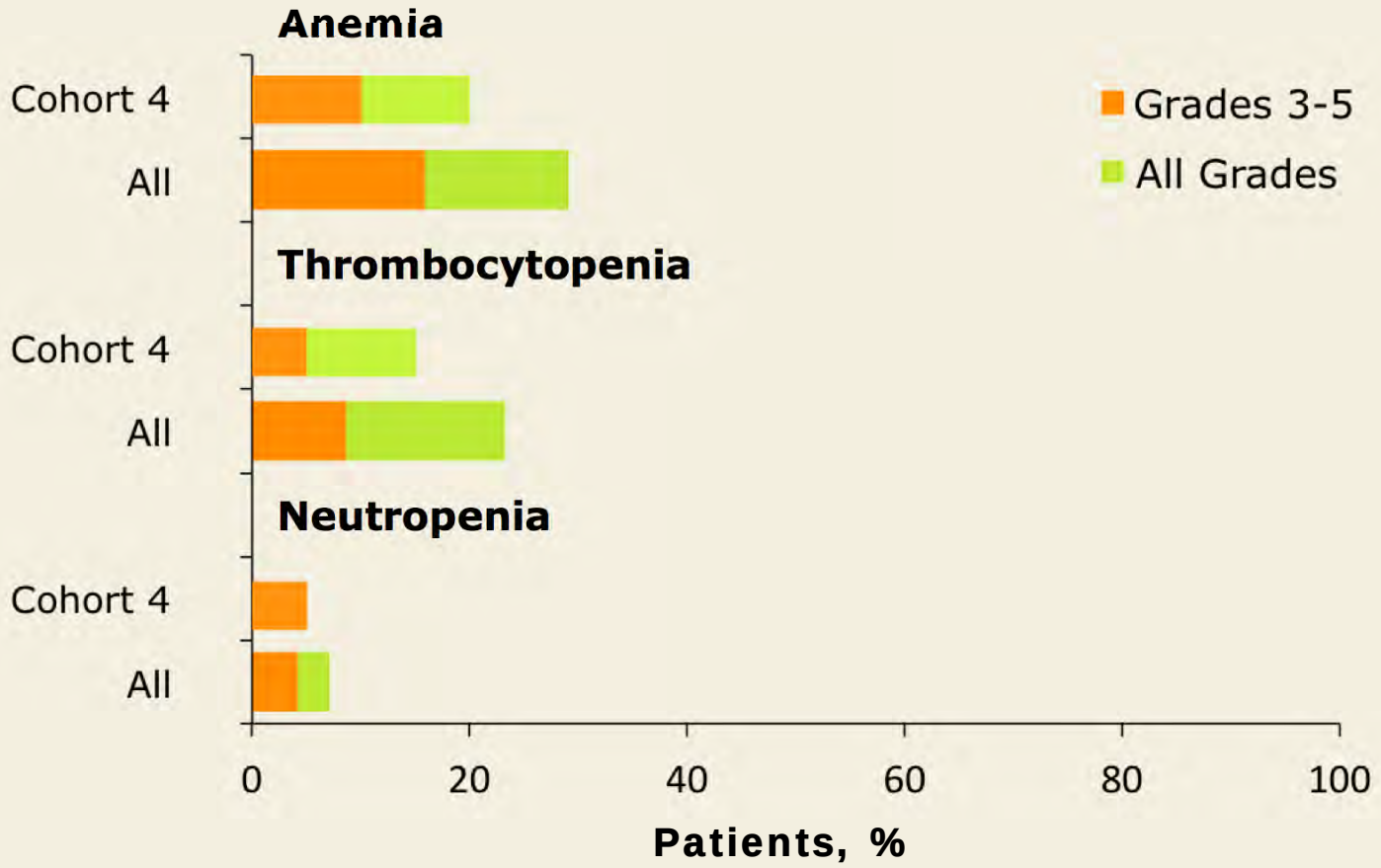
Hematologic Adverse Events



- Grade ≥3 febrile neutropenia occurred in 2.9% of patients
- 1 patient discontinued treatment due to hematologic adverse events

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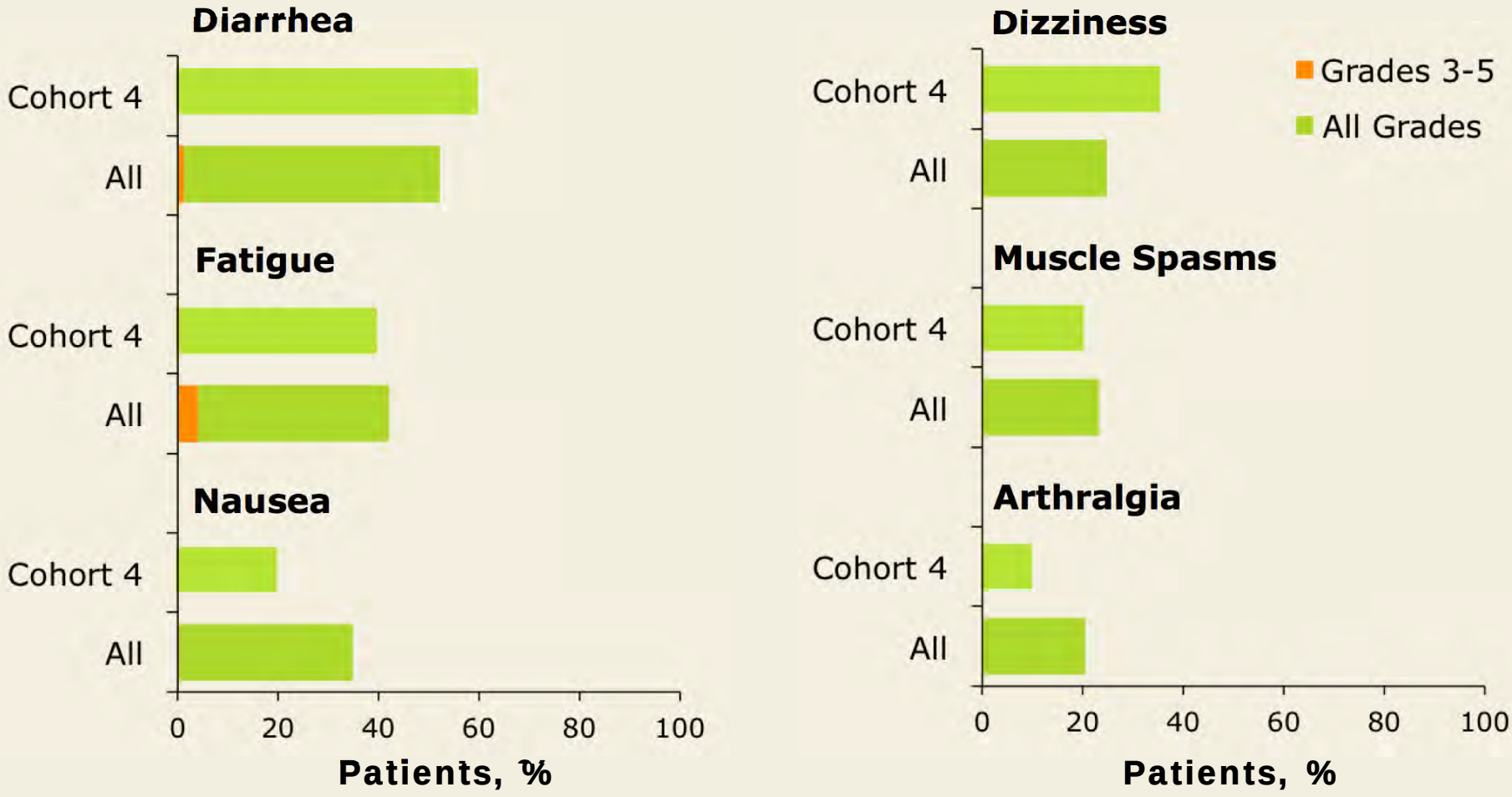
Nonhematologic Adverse Events Occurring in >20% of Patients



- 6 patients discontinued therapy due to nonhematologic adverse events

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Author Conclusions

- The safety profile of ibrutinib was tolerable, with similar adverse event rates across dosing cohorts and consistent with those reported in other histologies.
- Ibrutinib with or without weekly Dex demonstrated activity in heavily pretreated relapsed or R/R MM.
- The highest activity was observed in patients in cohort 4:
  - CBR = 25%
  - Sustained stable disease was observed in an additional 25% of patients (data not shown)
  - Median PFS = 5.6 months
- The enrollment of 23 additional patients to cohort 4 is complete, and evaluation of these patients is ongoing.

Vij R et al. *Proc ASH* 2014;Abstract 31.

Future Directions

- Further study of ibrutinib in combination with other backbone agents is warranted:
  - A Phase Ib/II trial of ibrutinib and carfilzomib is ongoing and has completed enrollment of the dose-escalation phase (NCT01962792)
- Exploratory analysis of ibrutinib in patients with MM will include the determination of:
  - Ibrutinib exposure in comparison to other B-cell cancer types
  - The impact of Dex on ibrutinib exposure
  - The evaluation of potential predictive/prognostic biomarkers, such as markers of bone metabolism, microenvironmental cytokines and chemokines and hematopoietic markers

Vij R et al. *Proc ASH* 2014;Abstract 31.

Investigator Commentary: Efficacy and Safety Results from the Phase II PCYC-1111 Trial for Patients with Relapsed or R/R MM

These preliminary results from a study of ibrutinib as a single agent or in combination with Dex for patients with relapsed or R/R MM are not impressive. In lymphoma, B-cell receptor signaling is active, and this pathway is one of the drivers of many lymphomas. That is the setting in which ibrutinib is known to be effective. In our laboratory, studies in MM have shown that B-cell receptor signaling is not active in the vast majority of patients. With this knowledge, I was not surprised when I saw these results from the PCYC-1111 trial.

The investigators reported modest responses, with some patients achieving stable disease and some minimal responses, which is the lowest degree of response used for clinical trials. Though disappointing, these results align with what we've observed in our laboratory. Sometimes results obtained in the laboratory are inconsistent with those from clinical trials because drugs may possess additional mechanisms to those already known. I would not have been surprised if ibrutinib proved to be effective in the absence of laboratory evidence. Therefore, these results are important and the study was definitely worth doing.

Interview with Ola Landgren, MD, PhD, February 9, 2015

Long Term Follow-up on the Treatment of High Risk Smoldering Myeloma with Lenalidomide plus Low Dose Dex (Rd) (Phase III Spanish Trial): Persistent Benefit in Overall Survival[1]

Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Final Results from the NCI Phase 2 Pilot Study[2]

[1] **Mateos MV et al.**
Proc ASH 2014;Abstract 3465.

[2] **Landgren O et al.**
Proc ASH 2014;Abstract 4746.

Long Term Follow-up on the Treatment of High Risk Smoldering Myeloma with Lenalidomide plus Low Dose Dex (Rd) (Phase III Spanish Trial): Persistent Benefit in Overall Survival

Mateos MV et al.

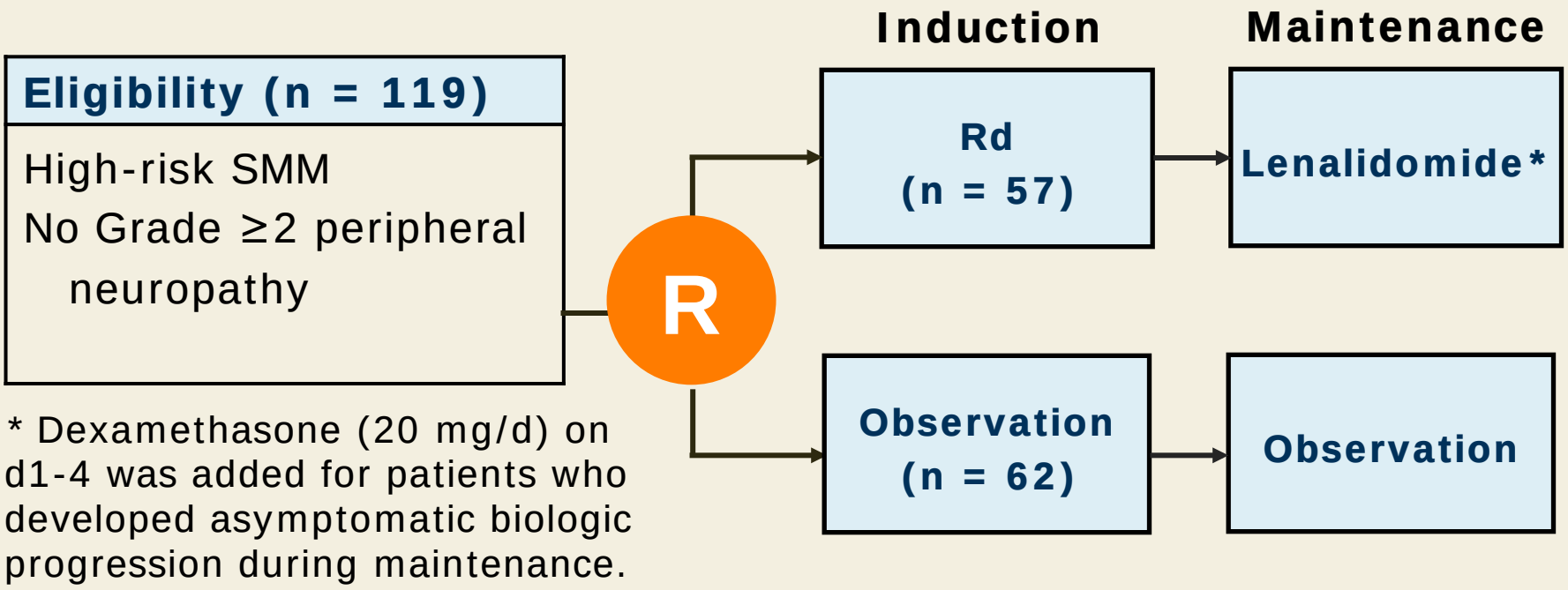
Proc ASH 2014;Abstract 3465.

Background

- The current standard approach for smoldering multiple myeloma (SMM) is watchful waiting until disease progression.
- Several small randomized studies have explored the value of early treatment with either conventional agents (melphalan/prednisone) or thalidomide or bisphosphonates, but these studies showed no significant benefit.
  - Notably, these trials did not focus on high-risk SMM.
- The Phase III trial by the Spanish Myeloma Group comparing lenalidomide/low-dose dexamethasone (Rd) to observation in high-risk SMM (*NEJM* 2013;369:438) demonstrated that:
  - After a median follow-up of 40 months, Rd was superior in time to progression (TTP) to active disease and overall survival (OS).
- **Study objective:** To report updated efficacy and safety results from the Phase III trial of Rd for patients with high-risk SMM after a median follow-up of 5 years.

Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

Phase III QUIREDEX Trial Design



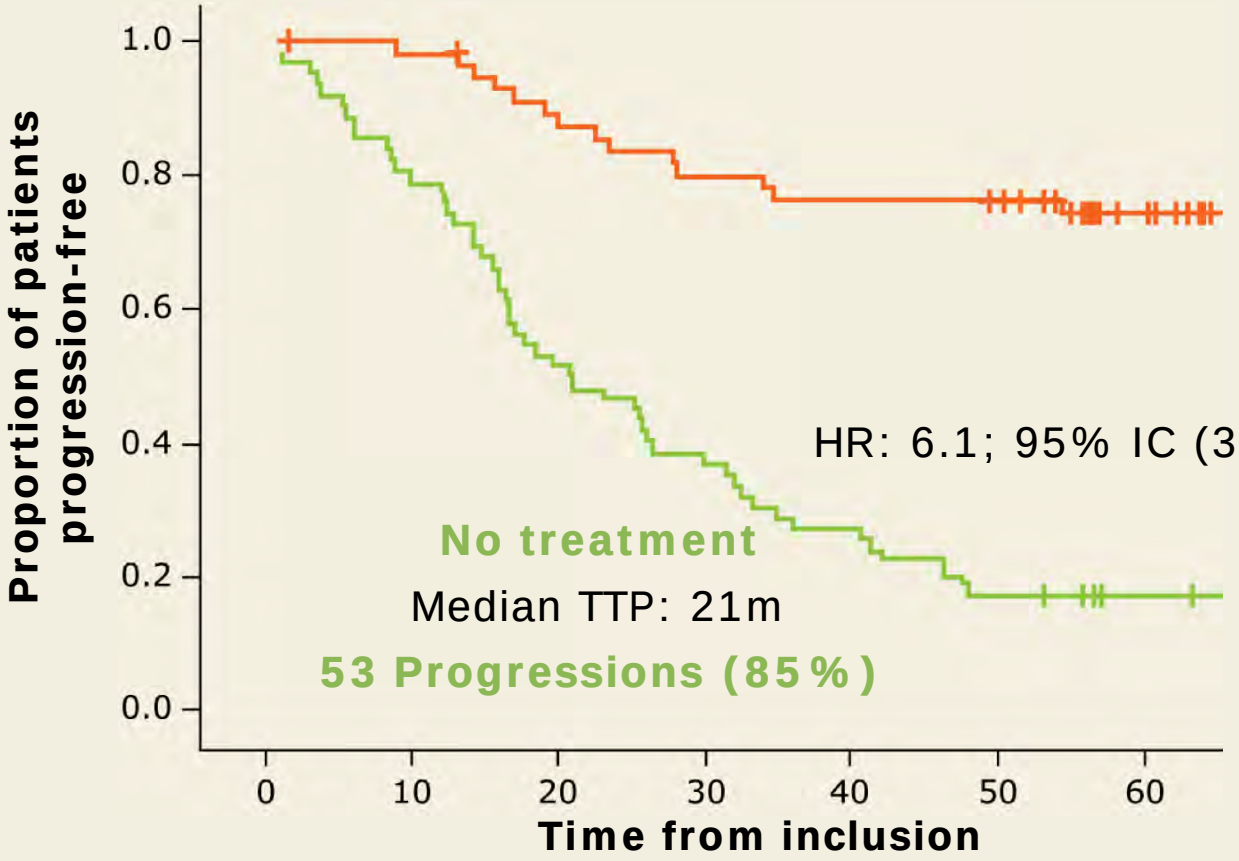
* Dexamethasone (20 mg/d) on d1-4 was added for patients who developed asymptomatic biologic progression during maintenance.

- Induction: Lenalidomide 25 mg/d on d1-21 and dexamethasone 20 mg/d on d1-4 and d12-15 every 4 weeks for 9 cycles
- Maintenance: Lenalidomide 10 mg/d on d1-21 for up to 2 years (initially until disease progression before protocol amendment in Aug 2011)
- **Primary endpoint:** TTP to symptomatic disease

Mateos MV et al. *Proc ASH* 2014;Abstract 3465; Mateos MV et al. *N Engl J Med* 2013;369(5):438-47.

TTP to Active Disease (N = 118)

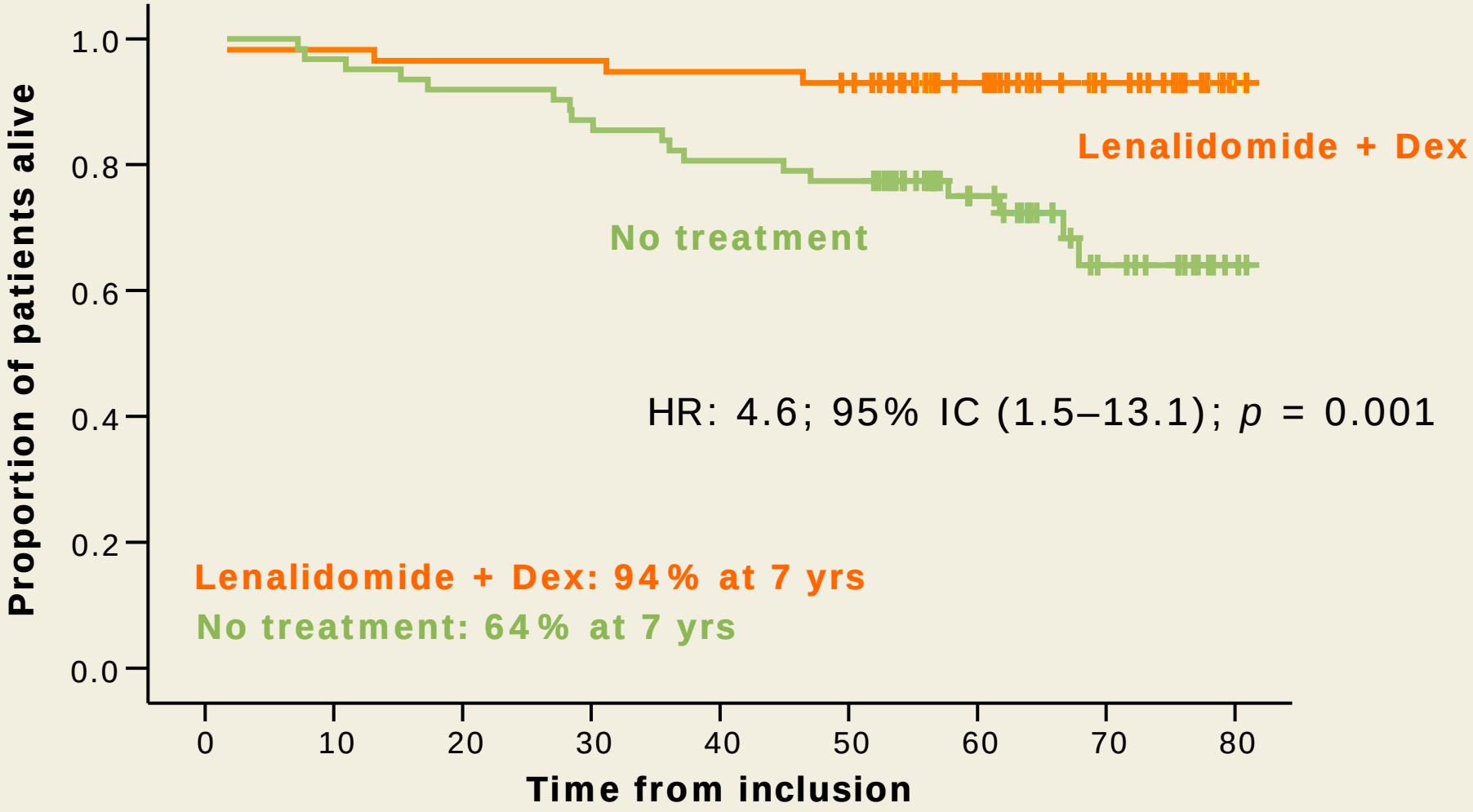
Median follow-up: 64 months (range 49–81)



- **Median follow-up = 64 months (range, 49-81)**

With permission from Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

OS from Study Entry (N = 118)



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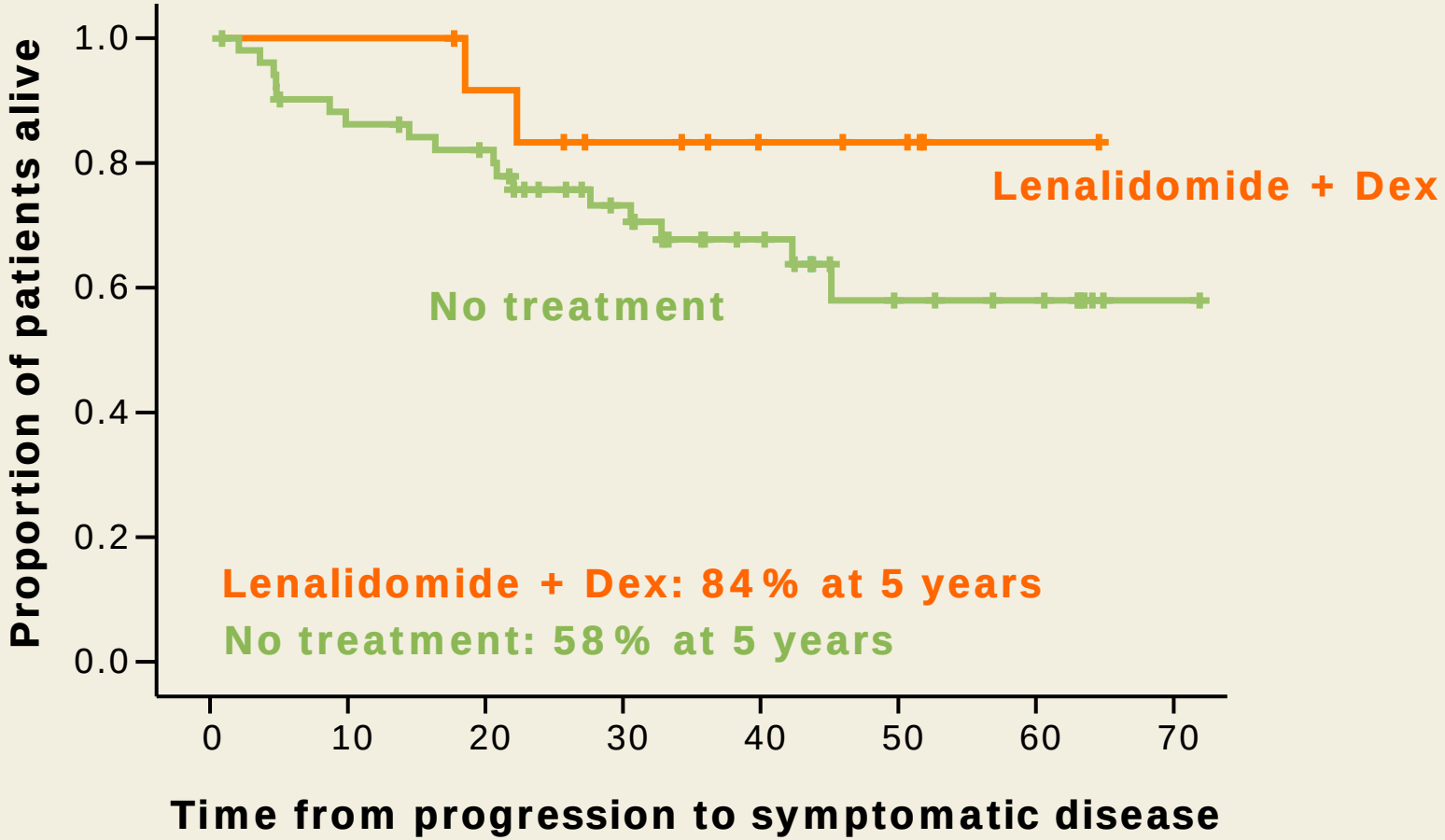
OS from Progression to Symptomatic Disease (N = 65)



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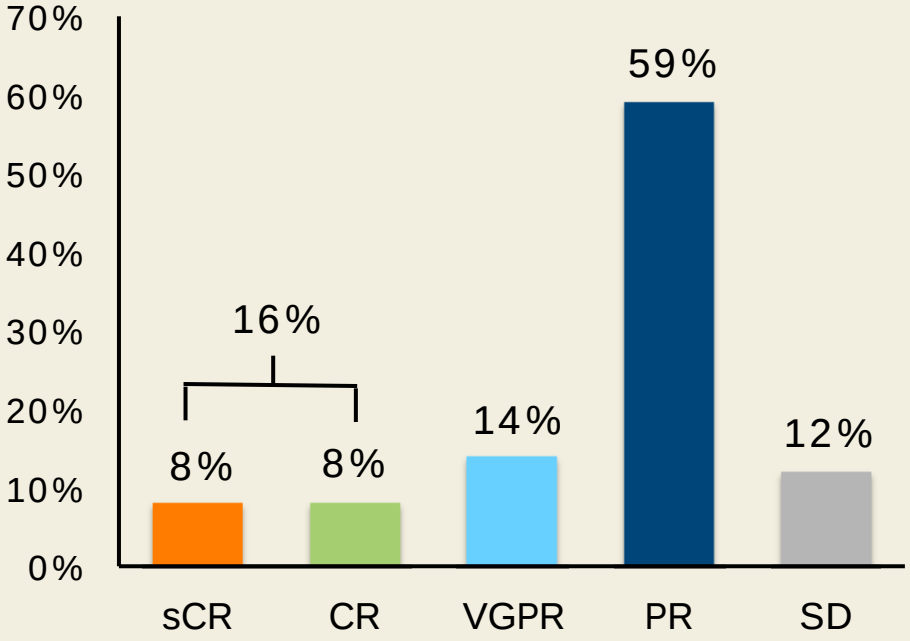
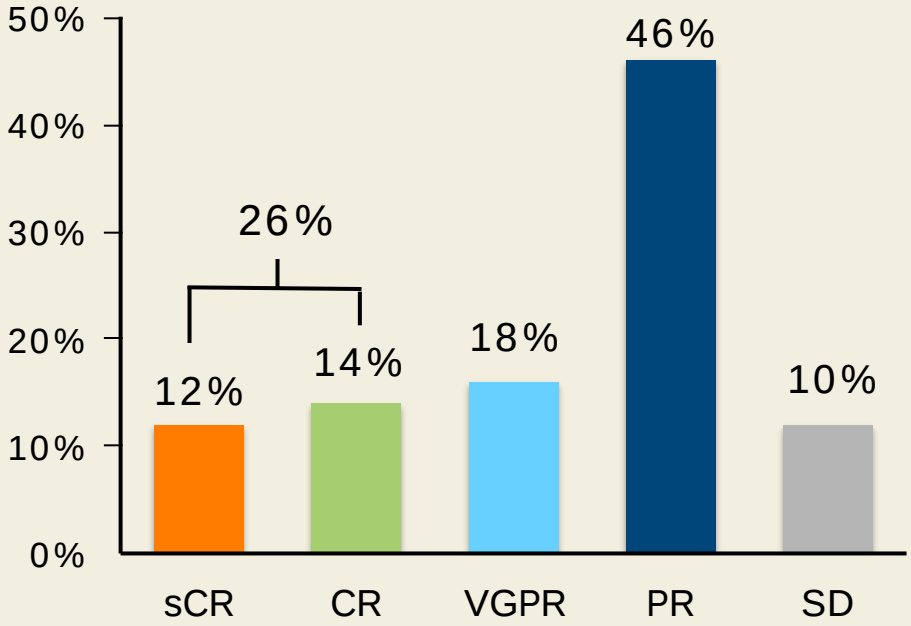
Response Rates

After 9 induction cycles (n = 51)



After a median of 15 maintenance cycles (n = 50)



- **In the ITT population (n = 57):** ORR = 80%; stringent complete response (sCR) = 7%; complete response (CR) = 7%; very good partial response (VGPR) = 11%; partial response (PR) = 65%; stable disease (SD) = 21%

With permission from Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

Select Adverse Events

Event	Induction		Maintenance	
	Grade 1	Grade 2	Grade 1	Grade 2
Infection	35%	11%	21%	11%
Rash	23%	11%	NR	NR
Anemia	20%	7%	11%	3%
Diarrhea	17%	7%	NR	NR
Tremor	13%	4%	2%	NR
Thrombocytopenia	11%	2%	0%	9%
Asthenia	11%	9%	NR	2%
Neutropenia	6%	14%	3%	9%
Paresthesia	2%	4%	NR	2%

- Number of second primary malignancies: 4 (lenalidomide arm) vs 1 (observation arm)

Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

Author Conclusions

- After long-term follow-up, early treatment of high-risk SMM with Rd continued to show benefits:
  - Significant reduction in the risk of progression to active disease
  - Significant reduction in the risk of death
- The long postrelapse survival observed among patients who received early treatment with Rd and subsequently experienced progression to symptomatic disease indicates that this strategy does not induce the development of more resistant cancer cell clones.

Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

Investigator Commentary: Updated Efficacy and Safety Results from the Phase III QUIREDEX Trial of Rd in High-Risk SMM

The initial results from this study were published in 2013 (Mateos MV et al. *NEJM* 2013;369(5):438). After an initial follow-up of 40 months, progression-free survival (PFS) and OS were significantly improved in the treatment arm compared to the observation group. In the updated analysis the median follow-up was 64 months. The investigators showed that progression to symptomatic disease occurred in 25% of the patients who received Rd versus 85% of those on the observation arm. These results are significantly different. Also, no evidence indicated that patients who received Rd had an inferior response to treatment.

Second primary cancer occurred in 4 patients on the Rd arm and 1 in the observation group. Of note, 4 patients versus 1 does not provide information on how many patients were at risk. If patients do not survive, there will be fewer potential events. In essence, these numbers are similar. The bottom line is that with long-term follow-up, Rd as an early treatment for patients with high-risk SMM continues to show significant improvement in both PFS and OS. Importantly, there is no evidence that Rd induces more resistant disease clones later.

Interview with Ola Landgren, MD, PhD, February 9, 2015

Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Final Results from the NCI Phase 2 Pilot Study

Landgren O et al.

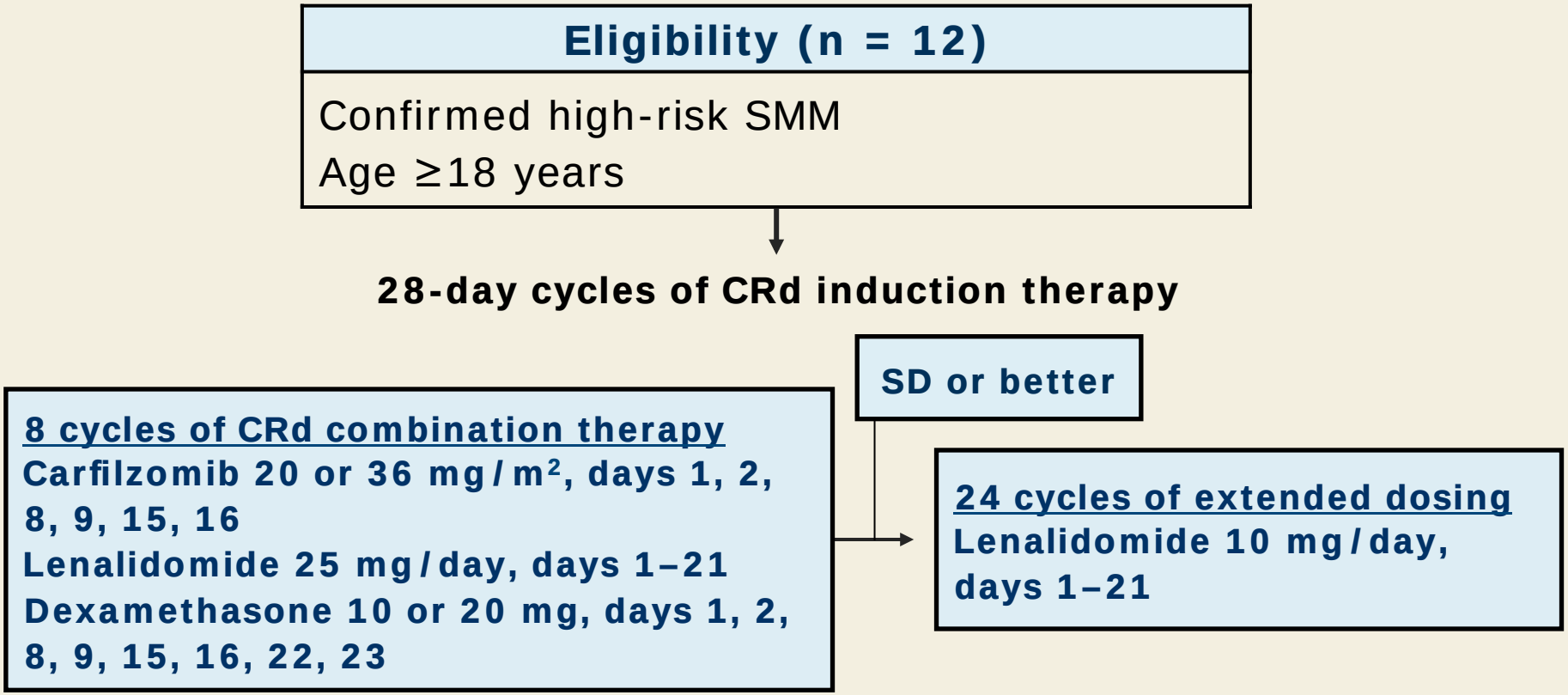
Proc ASH 2014;Abstract 4746.

Background

- The standard approach for smoldering multiple myeloma (SMM) has been to clinically follow the patient and initiate therapy when the disease becomes symptomatic.
- Recently a subgroup of patients with SMM at high risk for disease progression was identified (*Blood* 2007;110:2586; *Blood* 2008;111:785):
  - This subgroup has a 5-year risk of progression of about 75% and a median time to progression of 2 years.
- The addition of the selective proteasome inhibitor carfilzomib to lenalidomide and dexamethasone is highly effective in newly diagnosed MM (*Blood* 2012;120:1801).
- **Study objective:** To report the final results of a Phase II study evaluating whether early treatment with carfilzomib/lenalidomide/dexamethasone (CRd) will result in deeper and more durable responses among patients with high-risk SMM.

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Phase II Pilot Trial Design



SD = stable disease

- **Primary endpoint:** ≥Very good partial response (VGPR) after 8 cycles of CRd
- **Secondary endpoints** include progression-free survival and safety

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Best Response and Mean Monoclonal Protein Levels by Cycle

- Evaluable patients: Cycles 1-6 (n = 12); cycles 7-8 (n = 11)
- Patients who completed 8 cycles of CRd (n = 11):
  - All patients (100%) achieved near complete response (nCR) or better after 8 cycles of CRd
- The study met its prespecified endpoint of ≥5 of 12 patients achieving VGPR or better after 8 cycles of therapy
- Extended dosing (maintenance) with lenalidomide improved the depth of response in 4 of 11 (36%) patients
  - The level of response achieved during induction therapy with CRd was maintained in the remaining 7 patients
    - Stringent complete response (sCR): n = 6
    - Complete response (CR): n = 1
- The mean monoclonal protein level decreased significantly from baseline to completion of cycle 1 and continued to decrease with the increasing number of completed cycles

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Minimal Residual Disease (MRD) Status

- After 8 cycles or achievement of a CR, 10 (83%) and 11 (92%) patients tested negative for MRD by next-generation sequencing (NGS) and flow cytometry criteria, respectively.
- After 1 year of extended dosing with lenalidomide, 3 patients underwent additional MRD analysis: 2 remained negative for MRD by flow cytometry; 1 tested positive by flow cytometry despite remaining negative by NGS.

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Select Adverse Events

N = 12	All events	Grade 3 or 4
Lymphopenia	100%	42%
Leukopenia	92%	8%
Thrombocytopenia	92%	25%
Electrolyte disturbances	92%	17%
Elevated liver function tests	92%	17%
Rash/pruritus	75%	25%
Anemia	67%	17%
Diarrhea	67%	17%
Neutropenia	42%	17%
Increased serum creatinine	17%	17%

- No deaths occurred during therapy

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Author Conclusions

- Early treatment with CRd followed by extended dosing with lenalidomide was associated with rapid, deep and durable responses among patients with high-risk SMM.
  - Patients who achieved ≥VGPR after 2 cycles of CRd: 50%
  - Patients who achieved ≥nCR after 8 cycles of CRd: 100%
  - No patient experienced disease progression on study
- MRD negativity was observed in at least 10/12 (83%) patients using both flow cytometry and NGS criteria.
  - This high rate of MRD-negativity may translate into improved patient outcomes as time-to-event data continue to mature.
- Overall, the CRd regimen was safe and tolerable with manageable toxicities.
- These data support the need for larger studies for patients with high-risk SMM.

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

Investigator Commentary: Final Efficacy and Safety Results of the Phase II Trial of CRd for Patients with High-Risk SMM

The Phase III QUIREDEX trial intellectually sets the stage for 3-drug combinations in high-risk SMM, and the pilot Phase II trial of CRd for 12 patients addresses that issue. All 11 patients (100%) who completed 8 cycles of therapy achieved nCR or better after receiving 8 cycles of CRd. Of the 12 treated patients, 11 were MRD-negative by multicolor flow cytometry and 10 patients were MRD-negative by NGS. One of the 2 patients who were MRD positive by NGS was the patient who was positive by flow cytometry, but an additional patient was also positive by NGS.

Although we have to be cautious comparing across studies, results with the 2- versus 3-drug combinations in the population of patients with high-risk SMM are fascinating if one compares the 100% achievement of nCR or better with CRd head to head with the results obtained in the Spanish QUIREDEX study, in which 16% of patients who received Rd achieved a CR or sCR after 9 cycles of therapy.

Interview with Ola Landgren, MD, PhD, February 9, 2015

continued

Investigator Commentary: Final Efficacy and Safety Results of the Phase II Trial of CRd for Patients with High-Risk SMM (continued)

If data from these 2 trials are then compared to data from the Phase III ASPIRE trial (Stewart AK et al. *NEJM* 2015;372(2):142), showing the depth of response for patients with relapsed MM and how the results differ for 2- versus 3-drug regimens using the same drug combinations (Rd versus CRd) and showing PFS and OS benefits, the comparison becomes even more fascinating. If the same rule applied to the setting of high-risk SMM, that would be a huge readout, but this is a small study and we do not yet have the long-term follow-up results. At this time I don't treat high-risk SMM outside of a protocol setting. I try to open several new trials and offer patients careful monitoring. If such data continue to emerge, we may start offering therapy outside the trial setting.

Interview with Ola Landgren, MD, PhD, February 9, 2015

A European Collaborative Study of 230 Patients to Assess the Role of Cyclophosphamide, Bortezomib and Dexamethasone in Upfront Treatment of Patients with Systemic AL Amyloidosis

Palladini G et al.

Proc ASH 2014;Abstract 305.

Background

- Early small studies have reported unprecedented response rates for patients with systemic light chain (AL) amyloidosis treated with the combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD) (*Blood* 2012;119(19):4391).
  - Response rate: 94%
  - Complete hematologic response: 71%
- Based on these results, CyBorD has become one of the most commonly prescribed front-line regimens in AL amyloidosis outside of clinical trials.
- Subsequently, it was shown that CyBorD is unable to overcome the poor prognosis of patients with advanced cardiac disease (*Blood* 2013;121(17):3420-7).
- **Study objective:** To assess the role of CyBorD as up-front treatment for patients with AL amyloidosis.

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Study Methods

- Prospectively maintained databases of the London National Amyloidosis Centre and the Pavia Amyloidosis Research and Treatment Center were searched for newly diagnosed patients who received CyBorD between 2006 and 2013.
- Number of patients identified (n = 230)
  - Median estimated glomerular filtration rate: 82 mL/min
  - Median bone marrow plasma cell infiltrate: 12%
  - Difference between involved and noninvolved free light chain (dFLC): 248 mg/L
- Cyclophosphamide: 300 mg/m^2 on d1, 8, 15
- Bortezomib: 1.0 mg/m^2 q1wk to 1.3 mg/m^2 twice weekly
- Dexamethasone: Mostly 10, 20 or 40 mg per week
  - 69 patients (30%) received ≥160 mg/week
- Median number of cycles: 4 (range, 1-8)

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Patient Characteristics

Characteristic	N = 230
Median age (range)	60 years (38-85)
Involved organs: Heart	169 (73%)
Kidney	149 (65%)
Soft tissues	35 (15%)
Liver	25 (11%)
Peripheral nervous system	6 (3%)
Cardiac disease: Stage I	41 (18%)
Stage II	77 (33%)
Stage III	112 (49%)
N-terminal pronatriuretic peptide type B >8,500 ng/L	51 (22%)

- 201 patients with measurable disease

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Response in Intent-to-Treat (ITT) Population

Response rate (All ITT)	**n = 201***
Hematologic response	62%
Complete response (CR)	42 (21%)
Very good partial response (VGPR)	45 (22%)
Cardiac Stage I	
Hematologic response	77%
≥VGPR	56%
Cardiac Stage IIIB	
Hematologic response	42%
≥VGPR	23%

* Evaluable patients (40 deaths before response evaluation)

- Response was affected by cardiac stage.

Palladini G et al. *Proc ASH* 2014;Abstract 305.

Response by NT-proBNP and Second-Line Therapy

- Patients with N-terminal pronatriuretic peptide type B (NT-proBNP) >8,500 ng/L who achieved a response: 37%
  - Patients alive at 12 months: 28%
    - Responders in this group: 85%
      - Achieved CR/VGPR: 69%
- The most common second-line treatments:
  - Autologous stem cell transplant (ASCT) (n = 17)
    - Response rate: 65%
      - CR: 47%
  - Lenalidomide/dexamethasone (n = 20)
    - Response rate: 65%
      - CR: 10%

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Cardiac and Renal Response

- Patients with renal responses: 27%
- Cardiac response decreased with increasing cardiac stage:
  - In patients with Stage II disease: 29%
  - In patients with Stage IIIA disease: 17%
  - In patients with Stage IIIB disease: 4%

Palladini G et al. *Proc ASH* 2014;Abstract 305.

Survival Outcomes

- Median survival for all patients: 72 months
- After a median follow-up of 25 months:
  - Deaths: 94 (41%)
  - Estimated 5-year survival:
    - For patients with Stage I disease: 100%
    - For patients with Stage II disease: 52%
    - For patients with Stage III disease: 27%

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Treatment Outcomes

- Cardiac staging was the main factor affecting survival.
- There were no deaths among patients with Stage I disease without cardiac involvement.
- Survival was similar between patients with Stage II and Stage IIIA disease
  - Indicating that this regimen can rescue and improve survival of some patients with advanced disease
- However, the survival of patients with advanced cardiac Stage IIIB disease was still poor
  - Median survival: 7 months

Palladini G et al. *Proc ASH* 2014;Abstract 305.

Treatment Outcomes (continued)

- Response improved survival only in patients with Stage II or Stage IIIA disease, with best survival outcomes in those who achieved VGPR or CR.
- There was an improvement of survival in patients who achieved PR.
- Patients with Stage IIIB disease who survived until the landmark analysis at 3 months survived longer if they responded to treatment.

Palladini G et al. *Proc ASH* 2014;Abstract 305.

Author Conclusions

- This is the largest study of CyBorD treatment in AL amyloidosis.
- This study confirms that CyBorD is remarkably effective in patients at low risk, with 56% CR/VGPR and no deaths observed in patients with Stage I disease.
- Unfortunately, outcomes in patients with advanced cardiac disease were poor.
  - However, 28% of these patients who achieved a CR or VGPR had improved survival, showing the importance of striving for a good response even in this poor-risk group.
- The very high clonal response and excellent outcome in early-stage AL with CyBorD therapy confirm its place as a regimen of choice for this group and raise the need for a randomized trial assessing the role of up-front ASCT in this era of novel agent-based therapy in AL amyloidosis.

Palladini G et al. *Proc ASH* 2014;Abstract 305 (Abstract only).

Investigator Commentary: A European Collaborative Study to Determine the Role of Up-Front CyBorD in AL Amyloidosis

This is an important study of 230 patients with AL amyloidosis who received up-front CyBorD therapy. Most oncologists treat AL amyloidosis with CyBorD based on information from a series of smaller studies. Hence, this large study was initiated and showed that 56% of patients with cardiac Stage I disease achieved VGPR or better. For patients with advanced cardiac disease, the outcome was worse, but 28% of these patients achieved CR or VGPR. For these patients, survival was improved. One could evaluate these results from different perspectives and say that it's better to administer CyBorD to patients with low-risk disease than to those at high risk. On the other hand, for high-risk disease, whatever therapy is used will result in a worse outcome. Also, one could probably interpret the results to say that this therapy works for both high-risk and low-risk disease, but, as expected, it's even better for patients with low-risk disease.

Such deep responses with this regimen, similar to those seen in newly diagnosed and relapsed multiple myeloma, raise the question of what the role is for up-front ASCT in AL amyloidosis. The high clonal response and excellent outcome with CyBorD in early-stage AL amyloidosis necessitate a randomized study of up-front versus delayed ASCT in this setting.

Interview with Ola Landgren, MD, PhD, February 9, 2015

Lenalidomide Is Safe and Active in Waldenstrom Macroglobulinemia (WM)[1]

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

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

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

Lenalidomide Is Safe and Active in Waldenstrom Macroglobulinemia (WM)

Leleu X et al.

Proc ASH 2014;Abstract 4478.

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.

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).

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).

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).

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).

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.

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.

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).

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).

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).

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).