5 Minute JournalClub

POST-ASH Issue 2, 2015

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CME Information

LEARNING OBJECTIVES

- Analyze recent efficacy and safety results from the Phase III ASPIRE trial evaluating carfilzomib in combination with lenalidomide and low-dose dexamethasone in the treatment of relapsed or progressive, symptomatic MM.
- Evaluate the safety and efficacy of weekly carfilzomib combined with cyclophosphamide and dexamethasone for elderly patients with newly diagnosed MM.
- Compare and contrast the benefits and risks of pomalidomide and dexamethasone with cyclophosphamide or bortezomib for patients with lenalidomide-refractory MM.
- Assess the efficacy and safety of the investigational oral proteasome inhibitors ixazomib and oprozomib as maintenance therapy and single-agent treatment, respectively, for relapsed MM.

CME Information (Continued)

LEARNING OBJECTIVES

- Examine the role of age on the efficacy of lenalidomide and low-dose dexamethasone in patients with newly diagnosed MM enrolled in the FIRST trial.
- Appraise minimal residual disease testing modalities in patients with newly diagnosed MM who received carfilzomib in combination with lenalidomide and dexamethasone.

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CME Information (Continued)

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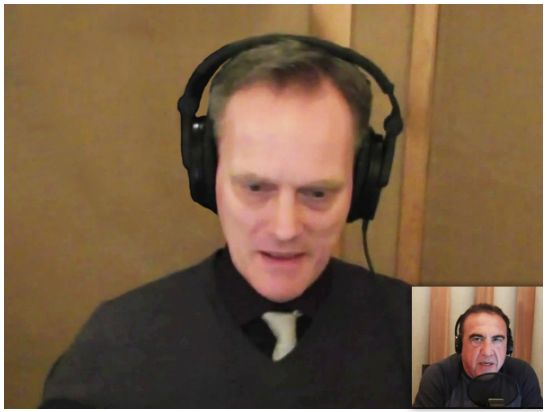
Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary.

5 MinuteJournalClub

POST-ASH Issue 2, 2015



Ola Landgren, MD, PhD

Last fall when I first met clinical investigator Dr Ola Landgren, aside from wanting to greet him with a very Miami-esque "Hola Ola!" I was curious to learn what prompted Memorial Sloan Kettering to lure this prominent researcher away from the cozy confines of the National Cancer Institute (NCI) to be the chief of their multiple myeloma (MM) service.

It didn't take long to see that Dr Landgren is a passionate clinician who, like many others in the field, believes that this disease, which traditionally has been treated in a palliative mode, now seems on the verge of prolonged control for many patients. Since that first encounter, our group has worked with Dr Landgren on a number of occasions, and each time, his astute perspectives and thoughtful commentary have helped bring greater clarity to the rapidly evolving but often opaque clinical research database in this disease. For that reason, we decided to sit down with him again to get his take on the key MM presentations from the recent American Society of Hematology (ASH) meeting in San Francisco. In the first of 2 issues focused on this disease, we review research efforts attempting to maximize the treatment benefit of 2 classes of agents that have

revolutionized the field, proteasome inhibitors and immunomodulatory agents (IMiDs), and in short what we learned is that the marked benefit already observed to this point may increase substantially in the future as a result of a variety of permutations of approved and emerging agents. Here's the summary:

- **Triplet therapy for relapsed/refractory (R/R) disease:**

The ASPIRE trial

Many general oncologists question the concept of "using all your big guns up front," learning long ago in another more common noncurable situation, metastatic breast cancer, that sequential single-agent chemotherapy yielded comparable long-term efficacy outcomes with better tolerability than combination approaches. In MM, although triple regimens like lenalidomide/bortezomib/dexamethasone (RVD) have been widely embraced in the induction setting, most clinicians have used a sequential "breast cancer–like" approach for R/R disease.

In San Francisco — in what Dr Landgren describes as "the number 1 myeloma message from ASH" — and soon after in the *New England Journal*, we saw perhaps the most convincing data available at this time suggesting a different approach. The ASPIRE trial aspired to compare carfilzomib/lenalidomide/low-dose dexamethasone (CRd) to Rd in patients who had previously received 1 to 3 systemic therapies. The study met its primary endpoint of progression-free survival (PFS), demonstrating a bump in efficacy from 17.6 to 26.3 months, and of particular interest, the complete response or better rate tripled (31.8% versus 9.3%). However, the overall survival (OS) analysis results did not cross the prespecified stopping boundary, but a trend for improvement was seen although

few of the patients randomly assigned to Rd subsequently received carfilzomib. Other ongoing and future trials will hopefully further test this concept, but for now — particularly armed with these latest supportive data — many investigators (very much including Dr Landgren) are thinking about 3-drug combinations early in the R/R setting.

Almost as important, this large Phase III study presented an ideal opportunity to again evaluate the critical issue of carfilzomib and the heart, a topic tied into the not infrequent occurrence of early-onset dyspnea. In ASPIRE there was what Dr Landgren views as a minimal increase in the risk of cardiovascular events (Grade 3 or greater heart failure 1.8% versus 3.8%). An unrelated poster also presented in San Francisco specifically evaluated this issue prospectively in 62 patients who received carfilzomib and found 5 instances of cardiac events, 3 of which were considered attributable to the drug, and only 1 of 30 patients with available echocardiogram data pre- and postcarfilzomib treatment experienced an unexplained decrease in ejection fraction. The authors noted a frequent and dramatic rise in N-terminal pro-B-type natriuretic protein, which Dr Landgren believes could have been the result of aggressive hydration, but the study did not examine this possibility. As a result of these and other findings, at this point for most patients Dr Landgren generally recommends only clinical observation and careful hydration, without the need for specific cardiac monitoring.

Pomalidomide (P) triplets in R/R disease

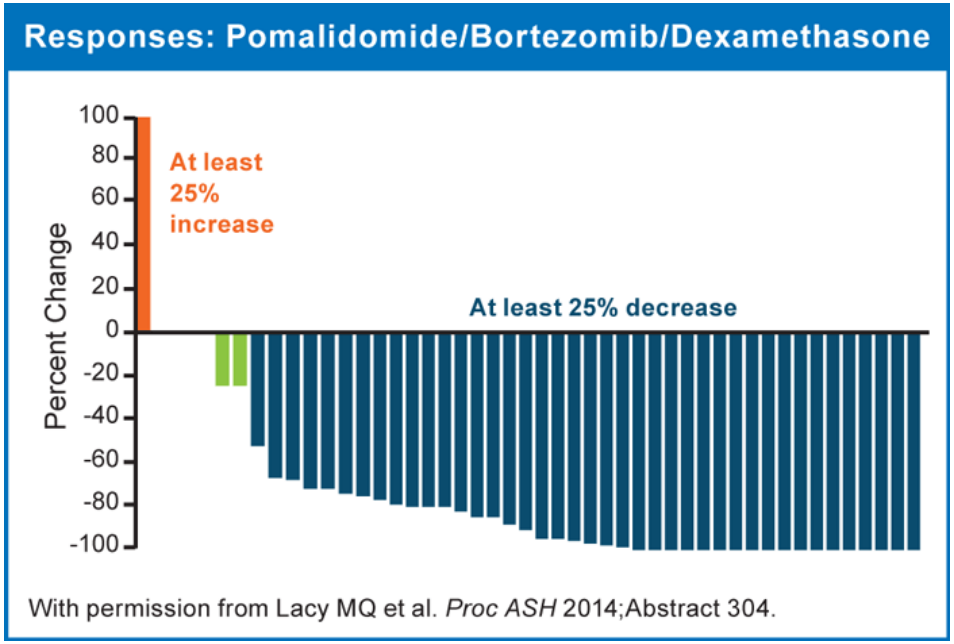
In keeping with the theme of combination versus sequential single agents, a number of studies were also unveiled at ASH examining P in concert with other agents. A randomized Phase II study evaluating Pd with or without

cyclophosphamide in 70 patients demonstrated the superiority of the triplet in terms of response rate (65% versus 39%) and also revealed borderline significant improvements in PFS and OS. Similarly, a single-arm Phase II study (n = 47) evaluating the P version of RVD (PVd) demonstrated an 85% overall response rate with an impressive waterfall plot. Both of these regimens are seen by Dr Landgren as additional evidence — albeit with many fewer patients — that the "ASPIRE" principle of using triplets in the R/R setting is quite sound.

- **Up-front induction regimens**

More on CRd

At ASH, Dr Landgren and his former NCI colleagues updated their important Phase II trial evaluating up-front CRd. Although this specific presentation focused on the optimal assessment of minimal residual disease and showed that next-generation sequencing was more sensitive than flow cytometry, in discussing the study Dr Landgren noted that the median age of patients on the trial was 65 and that no difference was observed in benefit between younger and older individuals. In fact, the oldest trial participant was an 88-year-old man. As such, he sees no reason not to use the most effective induction regimen available, even in older patients.



Phase I-II study of the weekly carfilzomib version of "CyBorD" (weekly CCd) in patients age 65 and over

Dr Antonio Palumbo played a key role in pioneering the initial research on weekly bortezomib, and it should therefore come as no surprise that at ASH he presented findings from a study using a similar approach with carfilzomib. What he showed was that the efficacy and tolerability associated with a once-weekly carfilzomib strategy appear comparable to that of twice-weekly administration. Interestingly, as part of the study, after 9 cycles, patients were maintained on carfilzomib alone and it was noted that with time, responses became deeper. Dr Landgren believes that these results indicate that although effective, the weekly CCd regimen is slightly inferior to other combinations like CRd that include an IMiD, but he does conclude that in countries where lenalidomide is not approved as an up-front therapy, it is a reasonable consideration. Furthermore, he believes that if weekly carfilzomib becomes a reality in general, it would be an important advance for patients.

Additional data from the FIRST trial in older versus younger patients

At the ASH 2013 meeting, the landmark Phase III FIRST study grabbed headlines by revealing a marked improvement in PFS and OS in favor of indefinite Rd compared to 18 months of either Rd or melphalan/prednisone/thalidomide (MPT). One important aspect of the study is that most of the 1,623 participants were older, and although the news wasn't as big at this year's conference, we saw data evaluating outcomes in patients over age 75. Significantly, essentially no difference was observed in efficacy or tolerability

compared to younger patients, and although Dr Landgren recognizes that patients who enter trials are generally more fit and have fewer comorbidities, he sees these results fitting his model of providing the most effective induction antitumor regimen (currently RVD or CRd) to all fit patients regardless of age and myeloma risk status.

- **Oral proteasome inhibitors: The future of maintenance therapy?**

In San Francisco we also saw more data on a critical trend that ties directly into the concept of continuous treatment. Although it could be that oral agents will provide greater efficacy either because of intrinsic antitumor activity or that patients are able to receive more consistent dosing, there can be no denying that even if equivalent, there would be a powerful impact on patient quality of life, particularly in the long-term maintenance setting.

The oral MM agent that is farthest along in development is ixazomib, which is similar to bortezomib, and at ASH we saw more encouraging data from a Phase II up-front study evaluating the agent combined with Rd in the induction setting followed by ixazomib alone as maintenance therapy.

Perhaps even more importantly, however, since ASH we have learned via press release that the pivotal Phase III TOURMALINE-MM1 trial evaluating ixazomib with Rd versus Rd in patients with R/R MM at first interim analysis achieved its primary endpoint of improving PFS. Hopefully these data will be unveiled at the upcoming ASCO meeting, but either way it seems quite plausible that this will help pave the way for widespread availability of this agent in the near future and

hopefully will serve as another important step forward in terms of patient quality of life.

Of course, ixazomib is not alone, as oprozomib, an oral agent similar to carfilzomib, is also being developed. Unlike its close cousin, however, this drug has been plagued a bit by tolerability issues, particularly gastrointestinal toxicities, and at ASH we saw more data from a Phase Ib/II study of 2 dosing schedules that demonstrated good efficacy but again challenges with side effects.

- **Special bonus: Serum versus urine measurement of free light chains (FLC) in light chain MM**

The inconvenience and inaccuracy of 24-hour urine measurement of FLC led to the use of serum evaluation (Freelite® kit), but little is known about how these 2 approaches directly compare. For that reason, as part of the IFM/DFCI 2009 study of RVD induction with immediate versus delayed autologous bone marrow transplant, investigators conducted both these methods of response assessment in the 16.4% of patients (n = 115) enrolled on the trial who secreted only light chains. Based on these results, it appears that serum FLC evaluation was much more accurate, and the authors (and Dr Landgren) conclude that serum FLC should replace urine measurement in these patients.

On the second MM issue of this series, we will review other recent data on new agents in this disease, including the recently approved histone deacetylase inhibitor panobinostat and several exciting monoclonal antibodies, including elotuzumab and daratumumab, but before then we will jump into chronic

lymphocytic leukemia with lots of new information relevant to clinical practice today and, very likely, tomorrow.

Neil Love, MD
Research To Practice
Miami, Florida

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma[1,2]

The Cardiovascular Impact of Carfilzomib in Multiple Myeloma[3]

[1] **Stewart AK et al.**
N Engl J Med 2015;372(2):142-52.

[2] **Stewart AK et al.**
Proc ASH 2014;Abstract 79.

[3] **Rosenthal AC et al.**
Proc ASH 2014;Abstract 4748.

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

Stewart AK et al.
N Engl J Med 2015;372(2):142-52.

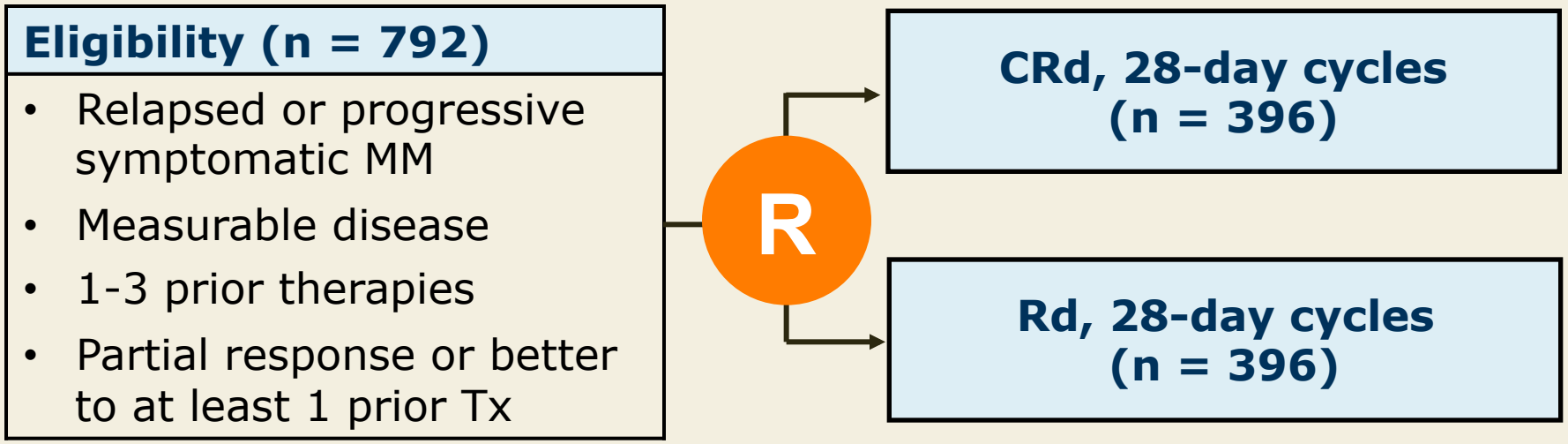
Stewart AK et al.
Proc ASH 2014;Abstract 79.

Background

- Phase III trials confirmed lenalidomide with high-dose dexamethasone (RD) as a reference treatment for relapsed multiple myeloma (MM).
- Lenalidomide with weekly low-dose dexamethasone (Rd) is less toxic than RD and yields similar response rates.
- Carfilzomib is an irreversible proteasome inhibitor approved as a single agent for relapsed and refractory MM.
- Carfilzomib, lenalidomide and weekly dexamethasone (CRd) was well tolerated in Phase I/II trials with encouraging clinical activity in newly diagnosed and relapsed MM (*Blood* 2012;120:1801-9; *Blood* 2013;122:3122-8).
- **Study objective:** To evaluate the safety and efficacy of CRd compared to Rd for patients with relapsed MM.

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Phase III ASPIRE Trial Design



Patients were stratified by β_2-microglobulin, prior bortezomib or prior lenalidomide.

- **Primary endpoint:** Progression-free survival (PFS)
- **Secondary endpoints** included overall survival (OS), overall response rate (ORR), duration of response, safety

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Survival

Outcome	CRd (n = 396)	Rd (n = 396)	Hazard ratio	*p*-value
Median PFS	26.3 mo	17.6 mo	0.69	0.0001
Median OS	NE	NE	0.79	0.04

NE = not estimable

- PFS benefit in the CRd arm was observed across all prespecified sub-groups
- Median OS: Trend in favor of the CRd arm, but results did not cross the prespecified stopping boundary for OS at the interim analysis
- Two-year OS rates: 73.3% (CRd) versus 65.0% (Rd)

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Response

Best response	CRd (n = 396)	Rd (n = 396)	*p*-value
ORR	87.1%	66.7%	<0.001
≥CR	31.8%	9.3%	<0.001
≥VGPR	69.9%	40.4%	<0.001
Clinical benefit rate	90.9%	76.3%	<0.001

CR = complete response; VGPR = very good partial response

- Stringent CR: 14.1% (CRd) versus 4.3% (Rd)
- Median duration of response: 28.6 mo (CRd) versus 21.2 mo (Rd)

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Select Adverse Events (AEs)

Event	CRd (n = 392)		Rd (n = 389)	
	All grades	Grade ≥3	All grades	Grade ≥3
Dyspnea	19.4%	2.8%	14.9%	1.8%
Hypertension	14.3%	4.3%	6.9%	1.8%
Acute renal failure	8.4%	3.3%	7.2%	3.1%
Cardiac failure	6.4%	3.8%	4.1%	1.8%
Ischemic heart disease	5.9%	3.3%	4.6%	2.1%

- Median treatment duration: 88.0 wk (CRd) versus 57.0 wk (Rd)
- Discontinuation due to AEs: 15.3% (CRd) versus 17.7% (Rd)

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Author Conclusions

- CRd led to a significant improvement in PFS compared to Rd for patients with relapsed MM.
- Interim OS analysis showed a trend in favor of the CRd arm.
- The ORR was higher with CRd, and a significantly higher number of patients achieved CR or better with CRd versus Rd.
- In the CRd group, adverse events led to fewer discontinuations, and patients remained on study treatment longer.
  - Cardiac- and renal-event rates were consistent with those in prior studies of single-agent carfilzomib.
- CRd consistently improved health-related quality of life compared to Rd (data not shown).

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Investigator Commentary: The Phase III ASPIRE Study of CRd versus Rd for Relapsed MM

This large Phase III trial is an important study that randomly assigned 792 patients in 20 countries to CRd or Rd. One of the key findings was the depth of responses observed with CRd. A high response rate with deep responses was observed with CRd despite the fact that patients had relapsed disease and had received 1 to 3 prior lines of therapy. The rate of CR or better was 31.8% with CRd, which is unprecedented. Do the depth and duration of response matter? I definitely believe so. The median PFS was 26.3 months with CRd versus 17.6 months with Rd, showing that patients who receive this 3-drug combination can remain progression free for an additional 8 to 9 months. That is an impressive finding. Although in the interim analysis OS did not cross the prespecified stopping boundary, the risk of death was approximately 20% lower with CRd than with Rd.

I'm not a proponent of risk-adapted therapy. I believe that for patients with relapsed MM in addition to those with newly diagnosed disease, we should administer the best therapy based on the data. The best therapy should be administered up front. Reducing the disease burden will translate into the best outcome.

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

The Cardiovascular Impact of Carfilzomib in Multiple Myeloma

Rosenthal AC et al.

Proc ASH 2014;Abstract 4748.

Study Rationale and Design

- In Phase II trials, carfilzomib (Cfz) was associated with dyspnea (34%), hypertension (14%), renal insufficiency (24%), and peripheral edema (24%), with cardiac events reported in 7% of patients.
- **Study objective:** To better understand these toxicities, 62 patients with MM who received Cfz between August 2011 and May 2014 were evaluated.
- **Design**
  - The study recorded Cfz dose, concurrent chemotherapy, hydration, blood pressure, creatinine level on days 1 and 2, troponin and N-terminal pro-B-type natriuretic protein (NT-proBNP), baseline and cycle 4 echocardiograms with ejection fraction, strain and compliance.
  - Notable cardiac events were examined for attribution.

Rosenthal AC et al. *Proc ASH* 2014;Abstract 4748 (Abstract only).

Patient Characteristics

- Median patient age was 65 years, and 60% of the patients were male.
- 20 patients had received no prior therapies, and 42 had relapsed disease (mean: 4 prior therapies).
- 20 patients received induction chemotherapy (Cfz, dexamethasone, thalidomide, cyclophosphamide).
- At relapse, Cfz was administered alone to 21 patients, with cyclophosphamide to 10 patients and with an IMiD to 10 patients.
- Cfz dose was 20 mg/m^2 on days 1 and 2 and ranged from 27 to 45 mg/m^2 on subsequent treatment days.
- Dexamethasone was administered at 20 to 40 mg/week to 77% of the patients.
- Hydration (250 to 500 mL) was delivered in 89% of patients before and 63% after treatment.

Rosenthal AC et al. *Proc ASH* 2014;Abstract 4748 (Abstract only).

Author Conclusions

- Patients with MM frequently have baseline elevated cardiac peptides (59%) and abnormal cardiac strain (15% at new diagnosis and 36% at relapse).
- A frequent and sometimes dramatic rise in NT-proBNP occurs immediately after Cfz-based chemotherapy.
- Acute structural cardiac events were uncommon (3%) in the absence of confounding illness.
  - 5 of 62 (8%) patients had serious cardiac events that were probably attributable to Cfz in 3 cases (5%).
- Prospective controlled studies with longer follow-up and bortezomib-treated controls are necessary to accurately document the cardiovascular effects of Cfz and the role of proteasome inhibition.

Rosenthal AC et al. *Proc ASH* 2014;Abstract 4748 (Abstract only).

Investigator Commentary: Cardiovascular Effects of Carfilzomib

The study used different approaches to evaluate the effect of CFz on the cardiovascular system. The investigators used the blood test for proBNP, which cardiologists use to measure cardiac failure. The study reported that proBNP levels rise after administration of Cfz, and I have observed that in my practice. Cfz is administered with fluid, and that could increase the likelihood of raising the proBNP level. That possibility was not evaluated in this study.

Five of 62 patients in this study experienced a cardiac event, and for 3 of these patients the event was thought to be attributable to Cfz. I believe that this suggests a cardiovascular signal from the drug, which is what other groups have found. However, in the ASPIRE trial analysis of cardiovascular events after the addition of Cfz to Rd, no major difference in cardiovascular adverse outcomes was reported. Dr Stewart reported at ASH that no data from the ASPIRE trial support a significant association between cardiovascular adverse effects and Cfz. It is not clear why a cardiovascular signal was observed in this smaller study. It could be because of a sampling error. It is difficult to determine whether the adverse cardiac outcomes reported in this study are due to Cfz or due to the disease.

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

Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study[1]

Pomalidomide, Bortezomib and Dexamethasone (PVD) for Patients with Relapsed Lenalidomide Refractory Multiple Myeloma (MM)[2]

[1] **Baz R et al.**

Proc ASH 2014;Abstract 303.

[2] **Lacy MQ et al.**

Proc ASH 2014;Abstract 304.

Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study

Baz R et al.

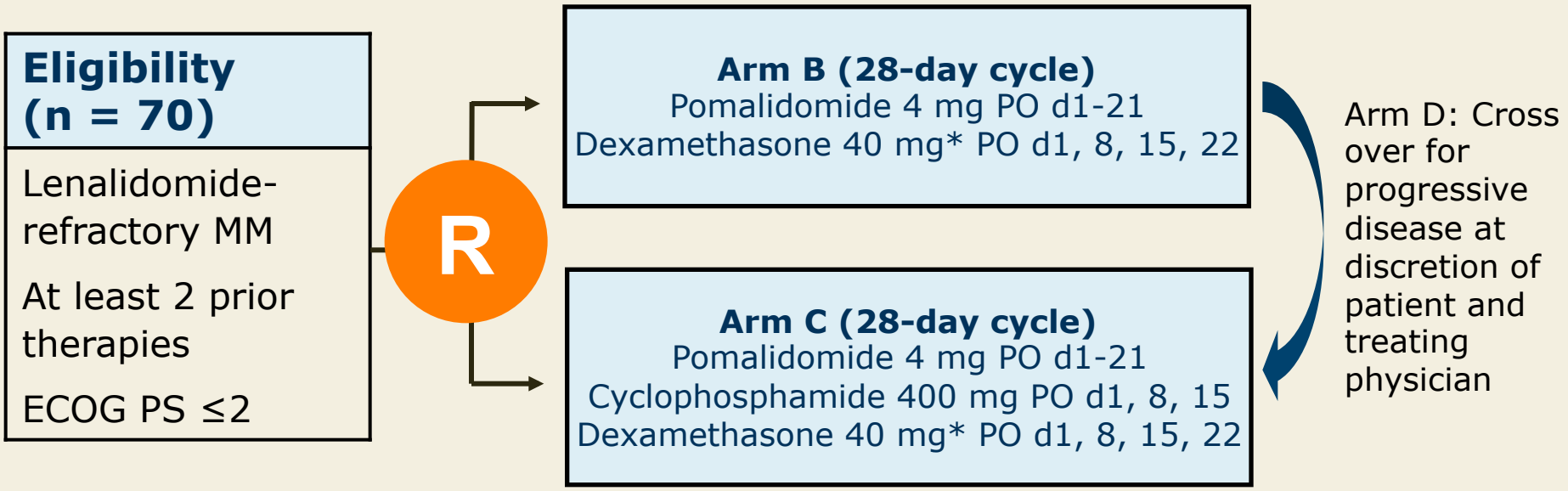
Proc ASH 2014;Abstract 303.

Background

- The combination of pomalidomide and dexamethasone results in an overall response rate of 33%, median progression-free survival (PFS) of 4.2 months and median overall survival of 16.5 months for patients with multiple myeloma (MM) who received prior lenalidomide and bortezomib (*Blood* 2014;123(12):1826).
- Alkylating agents (melphalan, cyclophosphamide) represent a standard therapy for patients with MM, the latter being associated with less myelosuppression.
- The previously reported recommended Phase II dose of cyclophosphamide with standard-dose pomalidomide and dexamethasone was 400 mg orally on days 1, 8 and 15 of a 28-day cycle (Arm A, *Proc ASH* 2012;Abstract 4062).
- **Study objective:** To compare pomalidomide and dexamethasone to pomalidomide, dexamethasone and cyclophosphamide for patients with lenalidomide-refractory MM.

Baz R et al. *Proc ASH* 2014;Abstract 303.

Phase II Trial Design

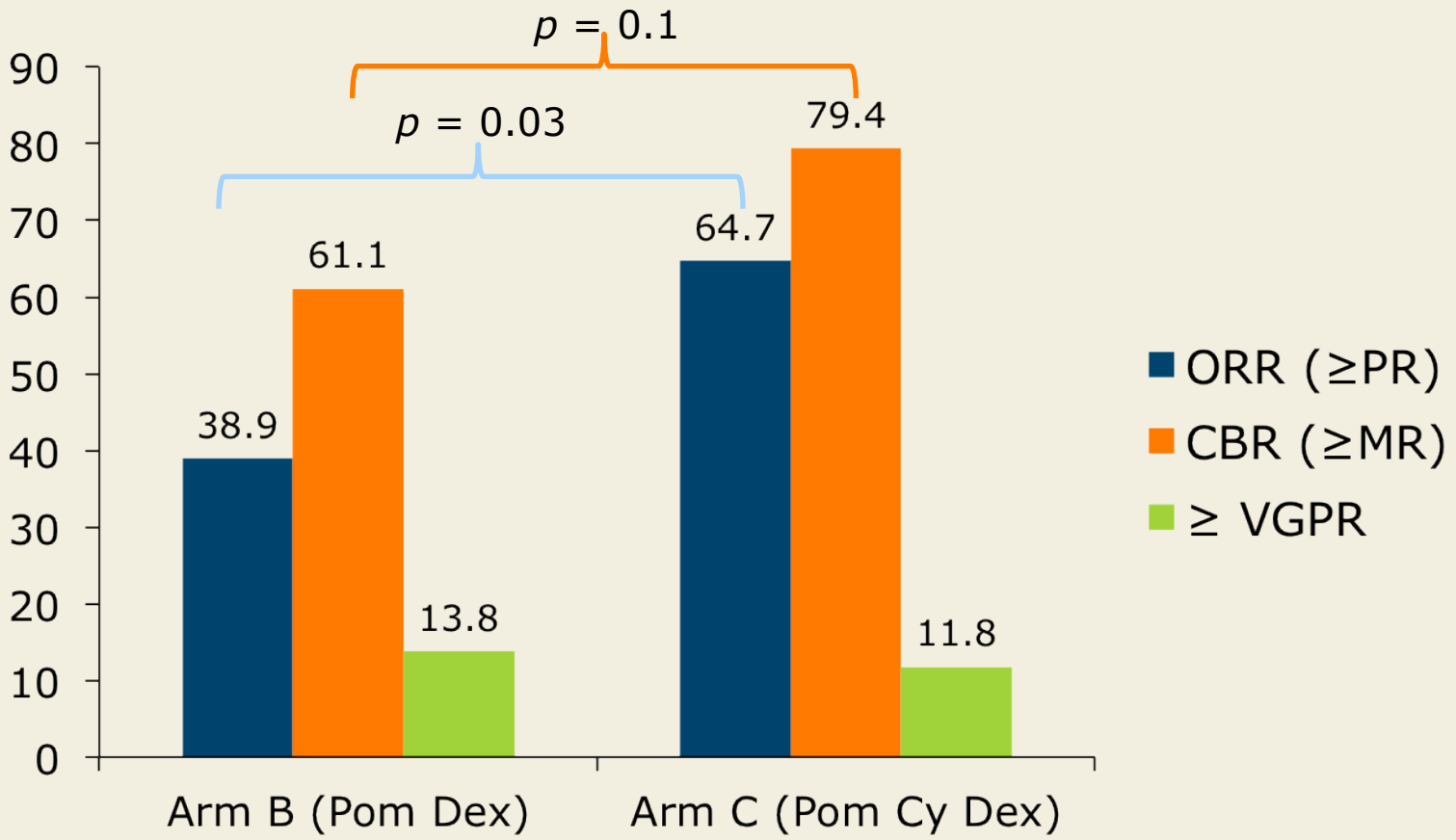


* Dexamethasone 20 mg was administered if the patient was older than 75 years or unable to tolerate 40 mg of dexamethasone.

- Aspirin 81-325 mg daily was administered as prophylactic antithrombotic treatment unless contraindicated. If aspirin was contraindicated, patients received low-molecular-weight heparin or therapeutic anticoagulation with warfarin.

Baz R et al. *Proc ASH* 2014;Abstract 303.

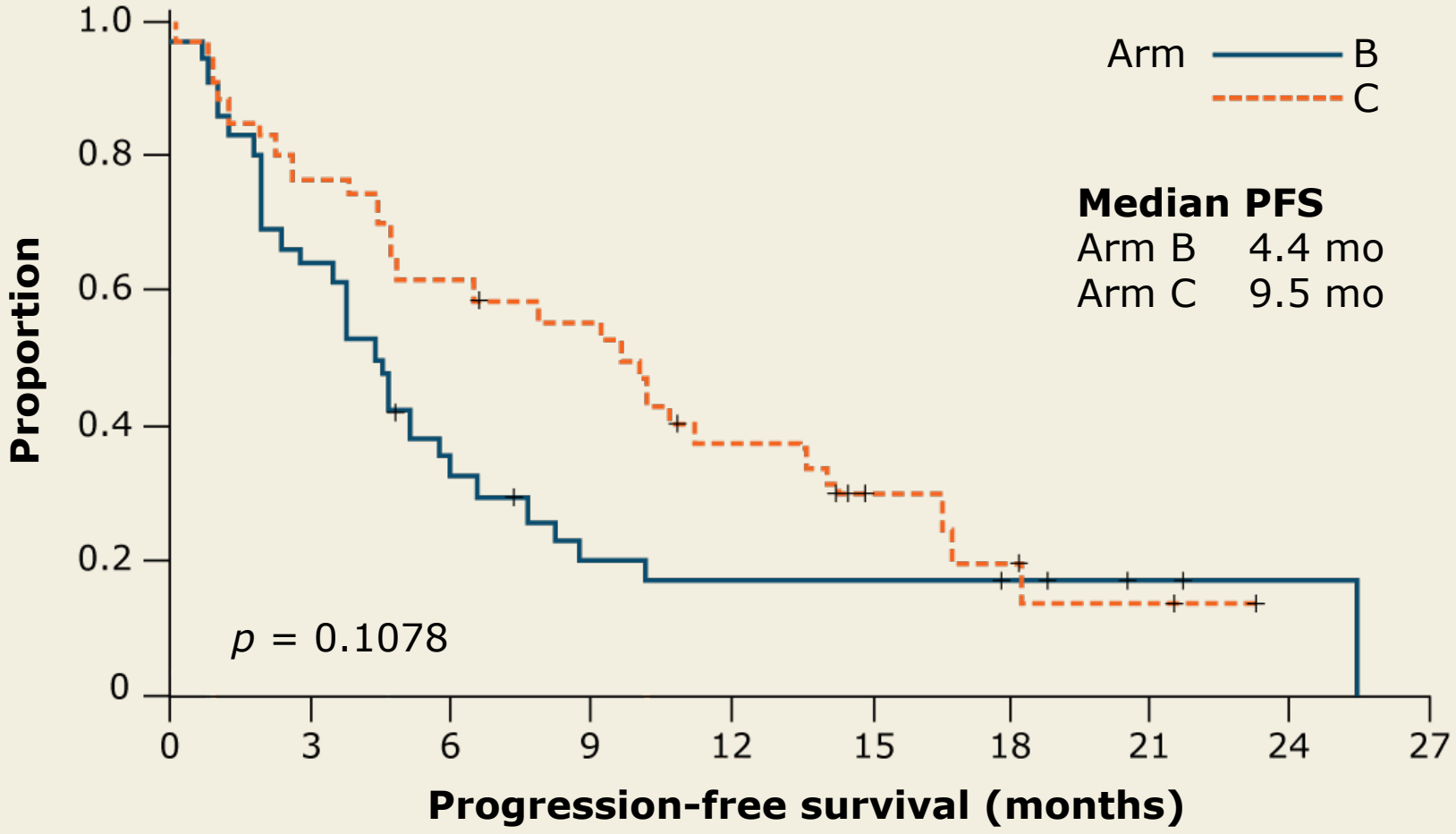
IMWG Response Rate



IMWG = International Myeloma Working Group; ORR = overall response rate; PR = partial response; CBR = clinical benefit rate; MR = minimal response; VGPR = very good partial response

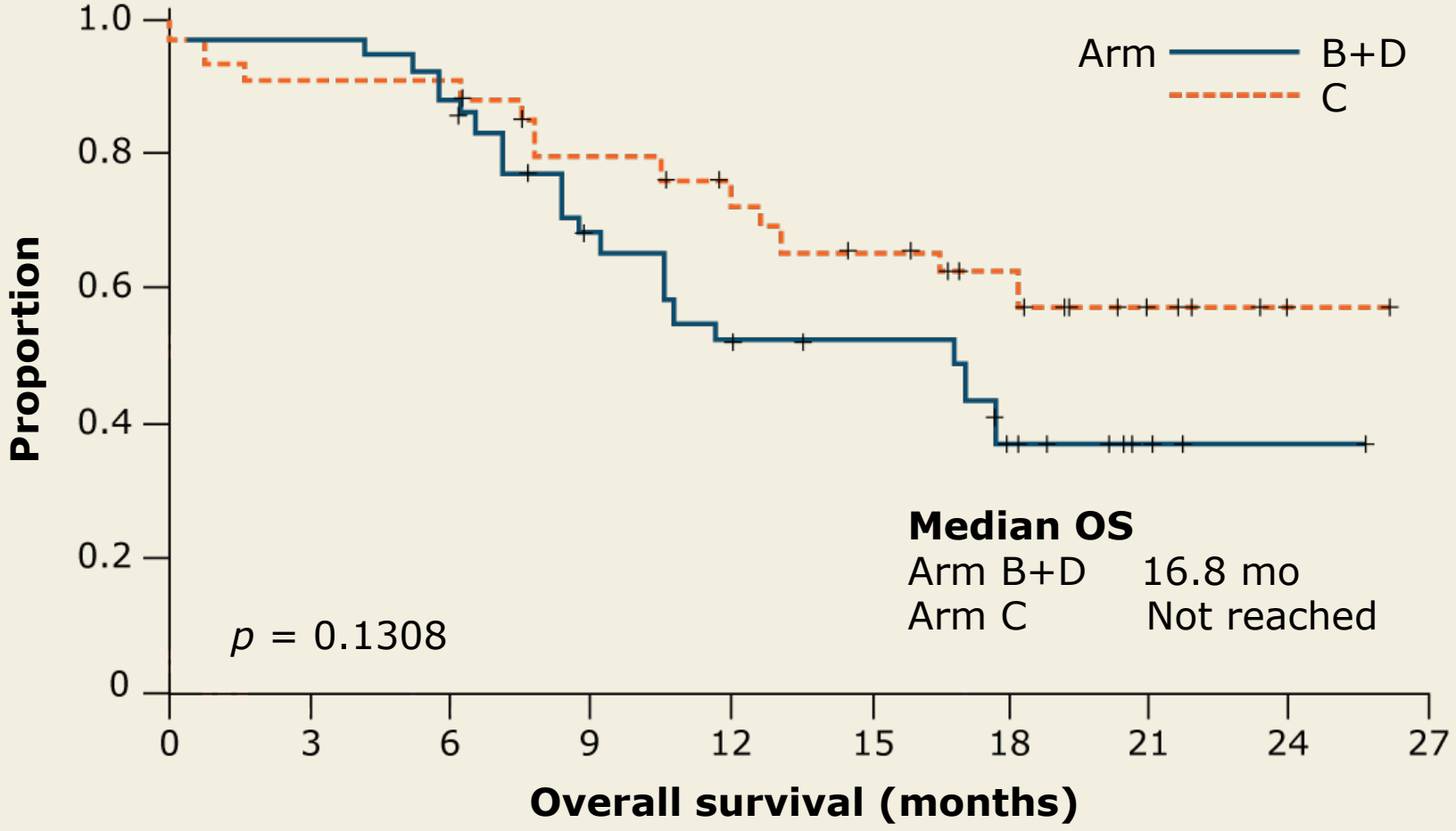
With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.

PFS



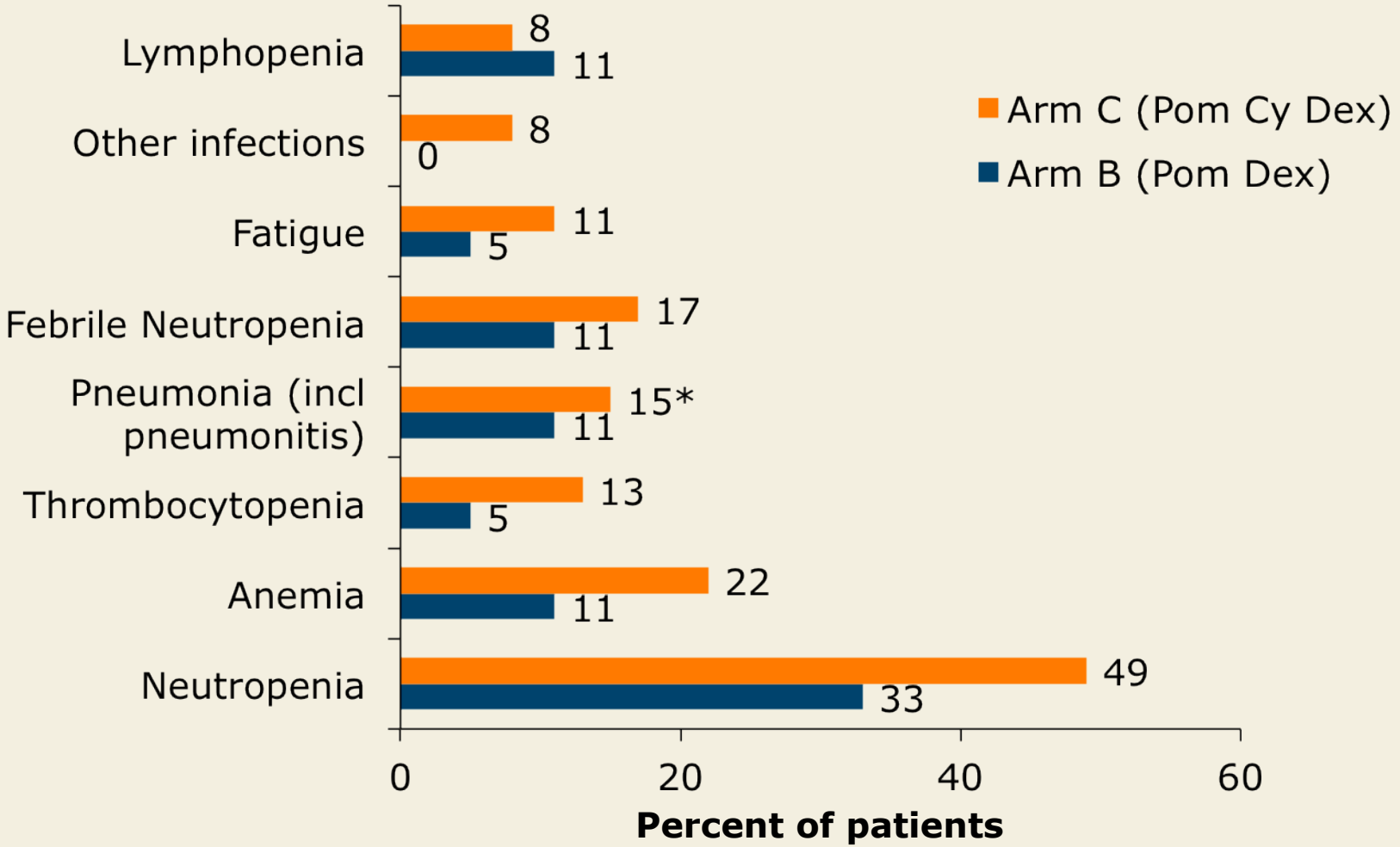
With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.

Overall Survival (OS)



With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.

Select Grade 3/4 Adverse Events



* Includes 1 patient with grade 5 pneumonia.

With permission from Baz R et al. *Proc ASH* 2014;Abstract 303.

Author Conclusions

- In comparison to pomalidomide and dexamethasone the combination of pomalidomide, cyclophosphamide and dexamethasone resulted in:
  - Superior response rate (ORR: 65% versus 39%)
  - Improvements in PFS and OS of borderline significance
- The combination of pomalidomide, cyclophosphamide and dexamethasone was well tolerated, with a possible increase in hematologic adverse events, which were manageable.
- This regimen compares favorably with other pomalidomide-based regimens in terms of efficacy, toxicities and cost.
- The addition of cyclophosphamide for patients experiencing disease progression on pomalidomide and dexamethasone results in minimal clinical benefits (data not shown).

Baz R et al. *Proc ASH* 2014;Abstract 303.

Pomalidomide, Bortezomib and Dexamethasone (PVD) for Patients with Relapsed Lenalidomide Refractory Multiple Myeloma (MM)

Lacy MQ et al.

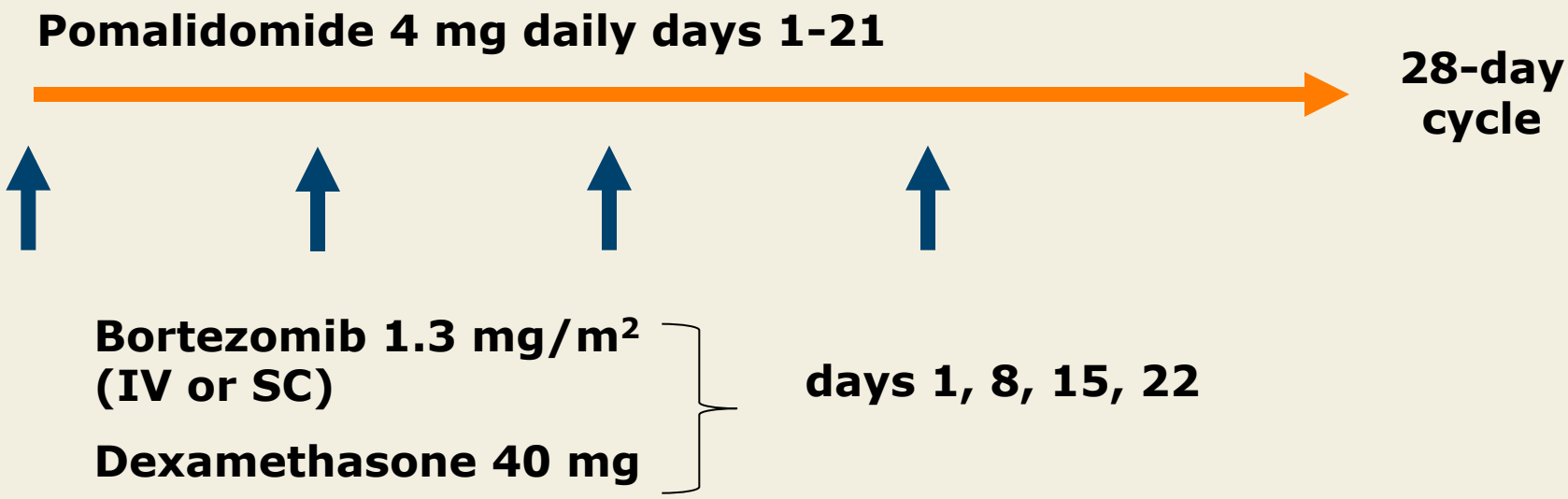
Proc ASH 2014;Abstract 304.

Background

- Pomalidomide and dexamethasone has been extensively studied in patients with lenalidomide-refractory MM.
- The combination of IMiDs and proteasome inhibitors has potential for deeper and more durable responses.
- The Phase I MM-005 study evaluating *twice weekly* bortezomib with pomalidomide and dexamethasone reported promising results (*Proc ASH* 2013;Abstract 1969):
  - ORR = 75% and VGPR or better = 30%
- **Study objective:** To evaluate the safety and efficacy of the maximum tolerated dose combination of pomalidomide, *once weekly* bortezomib and dexamethasone (PVD) for patients with relapsed, lenalidomide-refractory MM.

Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Phase II Trial Design

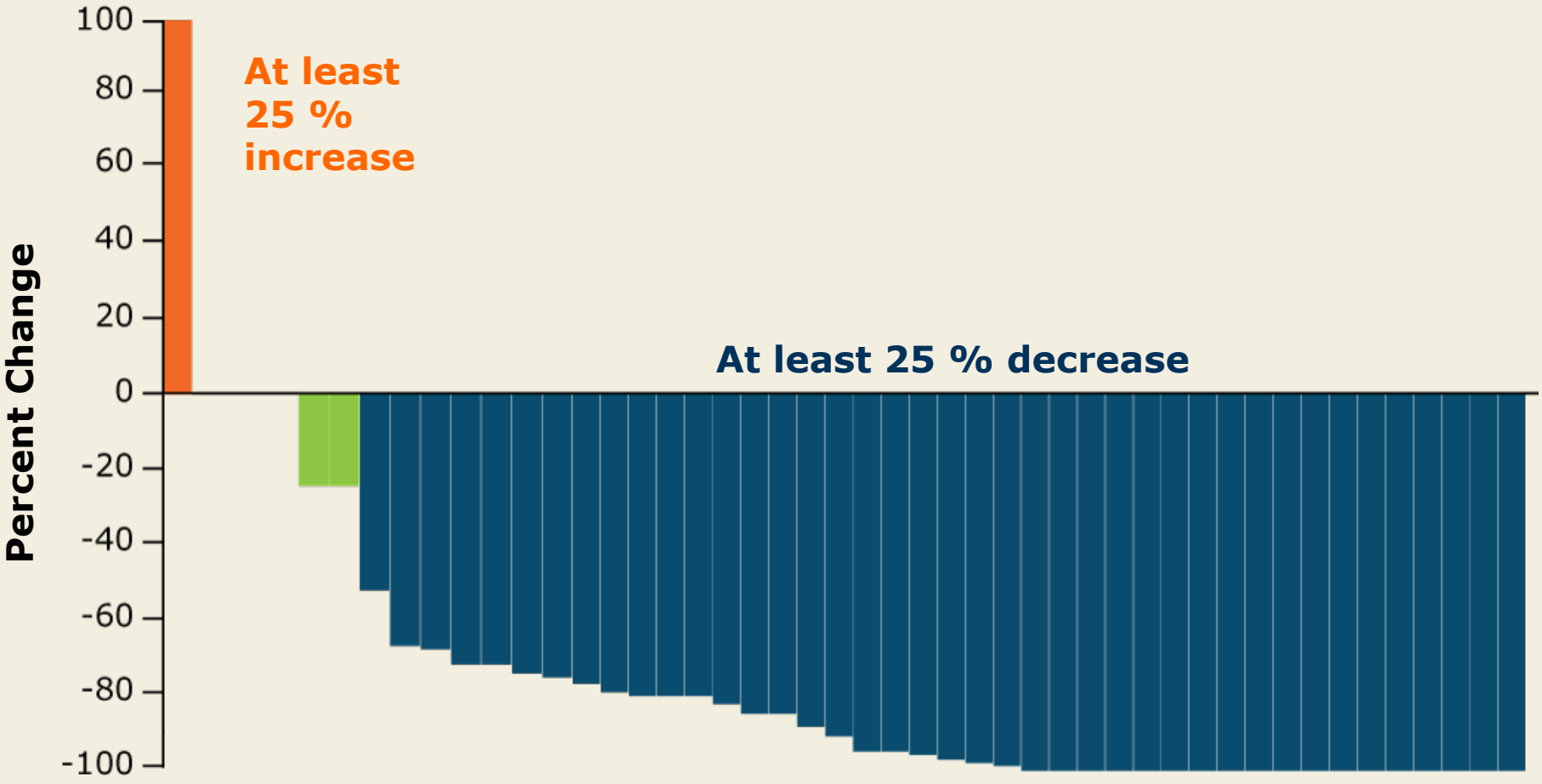


After 8 cycles, dexamethasone and bortezomib were stopped and pomalidomide continued until disease progression.

Thromboprophylaxis was administered to all patients as either aspirin or full-dose anticoagulation.

Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

IMWG Response



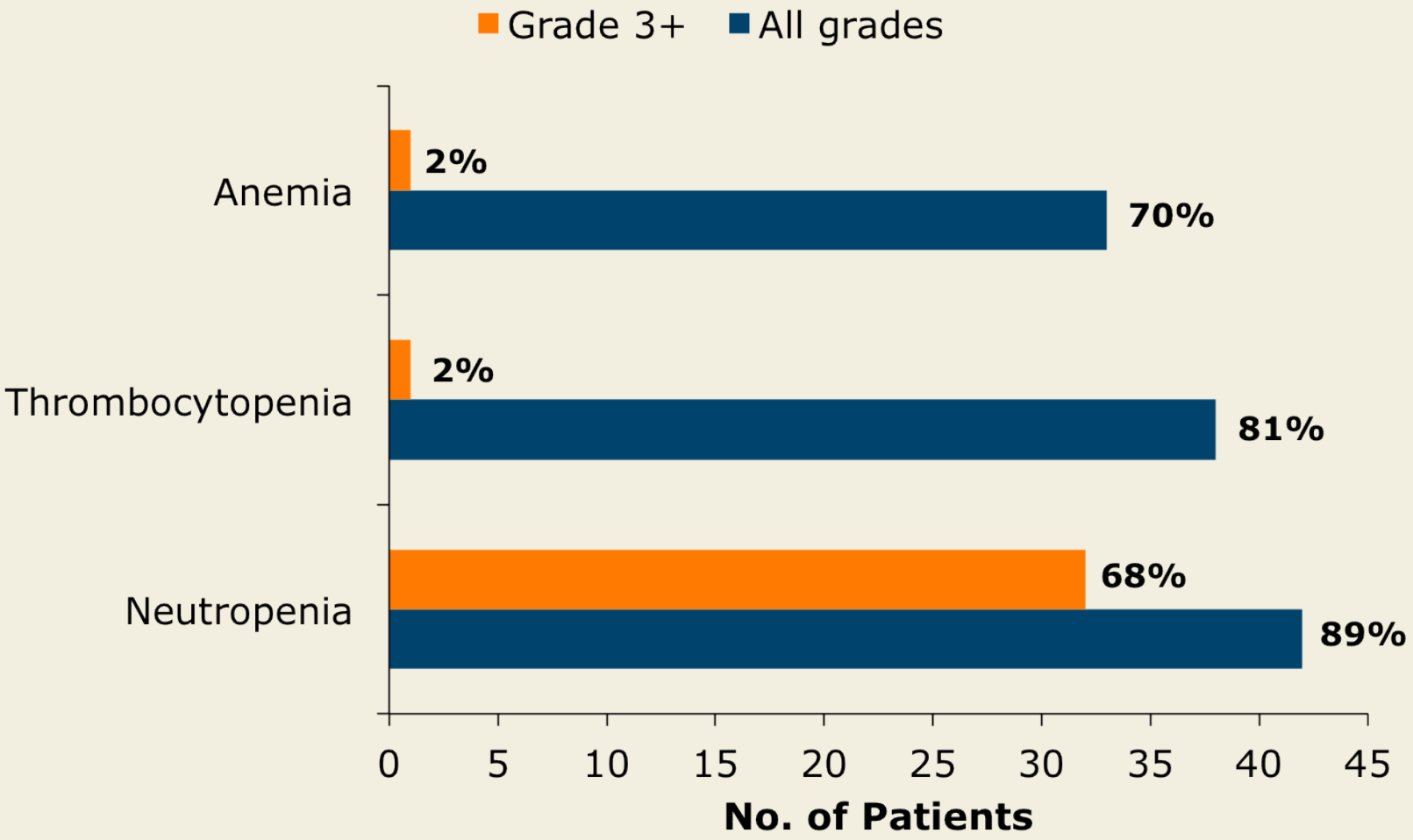
With permission from Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Efficacy

	N = 47
Overall response rate	85%
Stringent complete response (n)	3
Complete response (n)	6
VGPR (n)	12
Partial response (n)	19
Median PFS	10.7 mo
Median duration of response	13.7 mo
Six-month event-free survival	100%
Twelve-month event-free survival	94%

Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Hematologic Adverse Events



With permission from Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Author Conclusions

- PVD is a highly effective combination in patients with MM refractory to lenalidomide:
  - Confirmed responses in 85% of patients
- Weekly administration of bortezomib and dexamethasone enhanced the tolerability and convenience of this regimen.
- Toxicities were manageable, mostly consisting of mild cytopenias.
- PVD is a highly attractive option for patients with relapsed and refractory MM.

Lacy MQ et al. *Proc ASH* 2014;Abstract 304.

Investigator Commentary: Triplet Pomalidomide-Based Therapies for Patients with Relapsed/Refractory MM

Carfilzomib-based 3-drug combinations, such as the one studied in the ASPIRE trial (*N Engl J Med* 2015;372:142), have set a high bar that will be hard to beat. Each of these current trials was a Phase II study evaluating a pomalidomide-based triplet regimen for patients with relapsed/refractory MM. As is typical for this type of study, the sample sizes were relatively small. The study by Baz and colleagues evaluated pomalidomide/dexamethasone versus pomalidomide/cyclophosphamide/dexamethasone. The authors concluded that the 3-drug combination translated into better response and PFS rates. Similar results were reported with the study of PVD.

So compared to a 2-drug combination, these 3-drug combinations of an IMiD/dexamethasone with either a proteasome inhibitor or cyclophosphamide produce deeper, longer-lasting responses. The depth of response was less with the combination containing cyclophosphamide, however. These combinations provide some more options for 3-drug therapy for patients who do not have access or have contraindications to carfilzomib.

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

Minimal Residual Disease (MRD) Testing in Newly Diagnosed Multiple Myeloma (MM) Patients: A Prospective Head-to-Head Assessment of Cell-Based, Molecular, and Molecular-Imaging Modalities

Korde N et al.

Proc ASH 2014;Abstract 2105.

Background

- Recent studies show that patients with newly diagnosed MM (NDMM) who achieve MRD negativity have better progression-free (PFS) and overall survival outcomes (*Blood* 2014;123:3073; *JCO* 2013;31:2540).
- Measurement of MRD in these studies was carried out by either multicolor flow cytometry (MFC) or next-generation sequencing (NGS).
- Heterogeneity in MRD testing techniques may hinder interpretation of results.
- **Study objective:** To prospectively conduct comprehensive assessment of MRD testing modalities in a patient cohort uniformly treated with carfilzomib/ lenalidomide/dexamethasone (CRd) followed by lenalidomide maintenance.

Korde N et al. *Proc ASH* 2014;Abstract 2105.

Study Methods

- 45 patients with NDMM who received 8 cycles of CRd followed by 2 years of maintenance lenalidomide (ASH 2013;Abstract 538) were evaluated.
- At baseline, NGS was used to amplify IgH, IgK and joining gene segments (VDJ rearrangement analysis) from DNA obtained from CD138+ bone marrow (BM) lysate or cell-free BM aspirate.
- MM clonotype was defined as a VDJ rearrangement identified by NGS at a frequency of ≥5%.
- MRD assessment was repeated by NGS, MFC and positron emission tomography (PET) when patients achieved complete response (CR) or completed 8 cycles of therapy.
- NGS was performed in peripheral blood (plasma) at baseline and after 2 cycles of treatment in a subset of patients.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

MRD Assessments

- MRD assessments by NGS:
  - At least 1 clonal rearrangement was detected in BM CD138+ cell samples in 31/34 patients (91%).
  - Overall, clonal rearrangement was detected in 37/45 (82%) BM aspirates at baseline.
  - 18/32 patients (56%) who had achieved CR or completed 8 cycles of therapy had MRD as assessed in cell-free BM aspirates.
- Among 31 patients assessed by NGS and MFC, 23 samples were concordant (9 positive, 14 negative).
  - Among 8 discordant cases, all were positive by NGS and negative by MFC ($p = 0.0078$).
- Assessment by PET scan for patients who achieved CR or completed 8 cycles of therapy:
  - 19/43 (44%) had positive/partial PET scans.
  - 24/43 (56%) had negative/declined PET scans.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

MRD and PFS Estimates

Clinical parameter	By NGS		By MFC		By PET	
	MRD-neg	MRD-pos	Flow-neg	Flow-pos	Neg/dec PET	Pos/partial PET
12-month PFS	100%	94%	100%	79%	100%	89%
18-month PFS	100%	84%	100%	63%	92%	89%
p-value	0.025		0.0022		0.54	

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

MM Clonotype

- NGS was performed in peripheral blood samples collected at baseline from 14 patients.
- 13/14 patients had at least 1 MM clonotype detected in their baseline BM that was also detected in their plasma samples.
- The number of myeloma-specific molecules per million diploid genomes in the plasma was 3-log-fold lower than in the BM:
  - Median 252 vs 730,950 MM-specific clonal molecules per million diploid genomes
- After 2 cycles of treatment, 12/13 patients were still positive by serum electrophoresis and/or immunofixation.
  - Only 1 patient had detectable myeloma clonotypes in the plasma.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

Author Conclusions

- Detection of myeloma-specific clonotypes by NGS of the immunoglobulin VDJ segments in the BM is feasible for the majority of patients with NDMM.
- MRD detection by NGS compares favorably to detection by MFC because all patients with residual disease by MFC were MRD-positive by NGS.
  - An additional 8 patients who were MRD-negative by MFC were MRD-positive by NGS.
- MRD negativity by MFC or NGS are both associated with significantly better PFS.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

Author Conclusions (continued)

- Tumor load in the peripheral blood plasma is >2,000-fold lower than in the BM. Therefore, using standard volumes of plasma the levels of myeloma-specific clonotypes were too low to be quantified after 2 cycles of therapy.
  - This was true despite the presence of positive serum electrophoresis and/or immunofixation.
- Additional studies to understand the dynamics of the myeloma clonotype level in peripheral blood plasma are necessary in order to determine the optimal MRD testing regimen.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

Investigator Commentary: MRD Assessments in NDMM

MRD testing has come to stay in MM. We now have effective therapies that are not intense, and using the established response criteria it's apparent that in the NDMM setting the vast majority of patients reach the highest level of responses.

Studies conducted for patients who have achieved a CR by standard criteria have been able to show, by sensitive techniques such as MFC and NGS, that detectable disease is left behind in these patients. It is important to know that for patients in the CR category, detectable disease is associated with a PFS and overall survival difference. This affects patient outcome. This study suggests that NGS is a more sensitive method of detecting MRD than MFC because some patients with negative results by MFC received positive results by NGS. Peripheral blood is unfortunately not reliable for defining MRD because of the low concentrations of tumor DNA in comparison to that in the bone marrow.

We are almost at a turning point. In my practice I am starting to implement MRD testing for our patients because we are now able to administer effective therapies that take many patients into CR, and we need to see if disease is left behind. That will affect how we care for patients beyond that point.

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

Weekly Carfilzomib, Cyclophosphamide and Dexamethasone (wCCd) in Newly Diagnosed Multiple Myeloma Patients: A Phase I-II Study

Palumbo A et al.

Proc ASH 2014;Abstract 175.

Background

- Carfilzomib is a second-generation proteasome inhibitor with significant activity and a favorable toxicity profile, including limited neurotoxicity and neutropenia in patients with multiple myeloma (MM).
- The agent is administered as a twice-weekly infusion. However, administration could become more feasible and patient friendly if a weekly infusion schedule were adopted.
- **Study objective:** To determine the maximum tolerated dose (MTD) of once-weekly carfilzomib combined with cyclophosphamide and dexamethasone (wCCd) and to assess the efficacy and safety of this combination in elderly patients with newly diagnosed MM.

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Rationale for Investigating a Once-Weekly Schedule of Carfilzomib

	Bortezomib twice weekly	Bortezomib once weekly	*p*-value
Complete response	35%	30%	0.27
3-year progression-free survival	47%	50%	1.00
3-year overall survival	89%	88%	0.54
Hematologic adverse events (AEs)	45%	44%	0.83
Nonhematologic AEs	51%	35%	0.003
Peripheral neuropathy	28%	8%	<0.001
Gastrointestinal AEs	11%	6%	0.08
Median dose intensity	59%	84%	<0.001
Dose reduction	41%	17%	<0.001
Discontinuation	15%	5%	<0.001

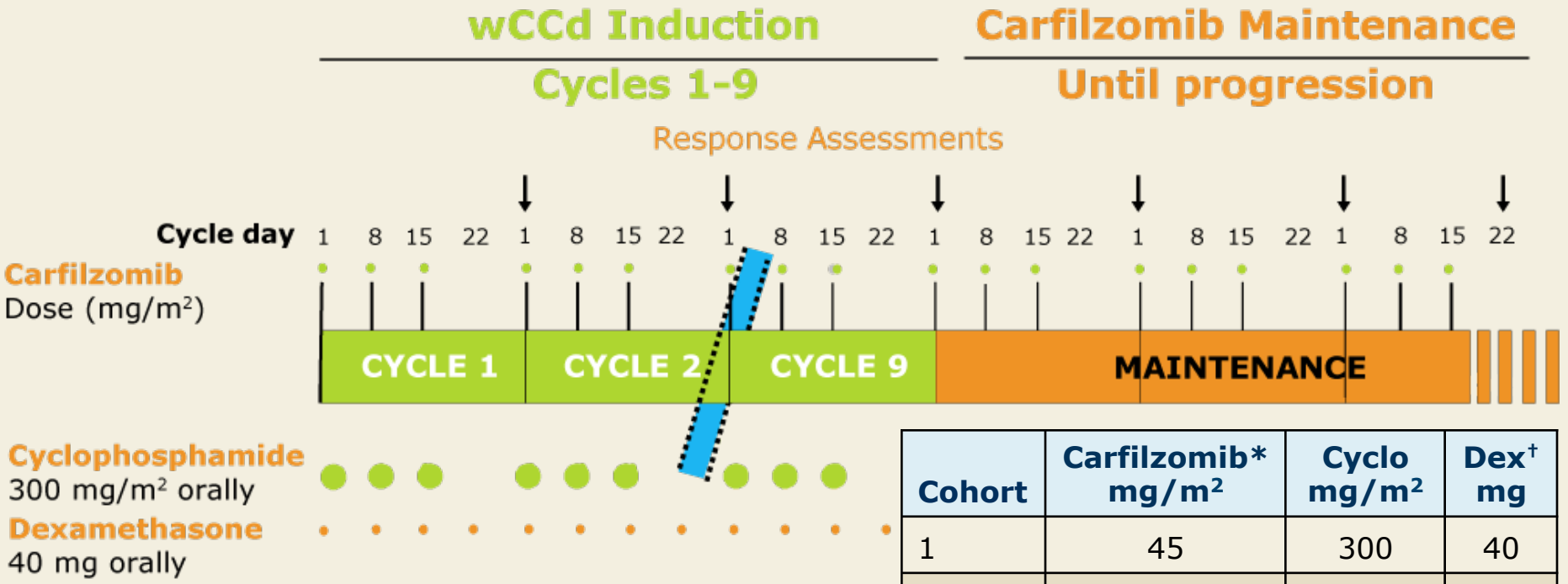
Palumbo A et al. *Proc ASH* 2014;Abstract 175; Bringhen S et al. *Blood* 2010;116(23):4745-53.

Patient Eligibility

- Symptomatic newly diagnosed MM
- ≥65 years of age or ineligible for autologous stem cell transplant
- Measurable disease (≥0.5 g/dL of M-protein or urine light-chain excretion of >200 mg/24 hours)
- ECOG PS 0-2
- Adequate hepatic function (ALT ≤3.5 times the upper limit of normal and serum direct bilirubin ≤2 mg/dL)
- Creatinine clearance ≥15 mL/min
- No prior systemic therapy for MM
- No relapsed or refractory disease
- No history of severe heart disease
- No uncontrolled hypertension or congestive heart failure

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Phase I/II Trial Design



Cohort	Carfilzomib* mg/m²	Cyclo mg/m²	Dex† mg
1	45	300	40
2	56	300	40
3	70	300	40

* All patients received 20 mg/m² carfilzomib on D1 of cycle 1; subsequent doses were escalated to the indicated levels; † Or 20 mg of dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Preliminary Response Data

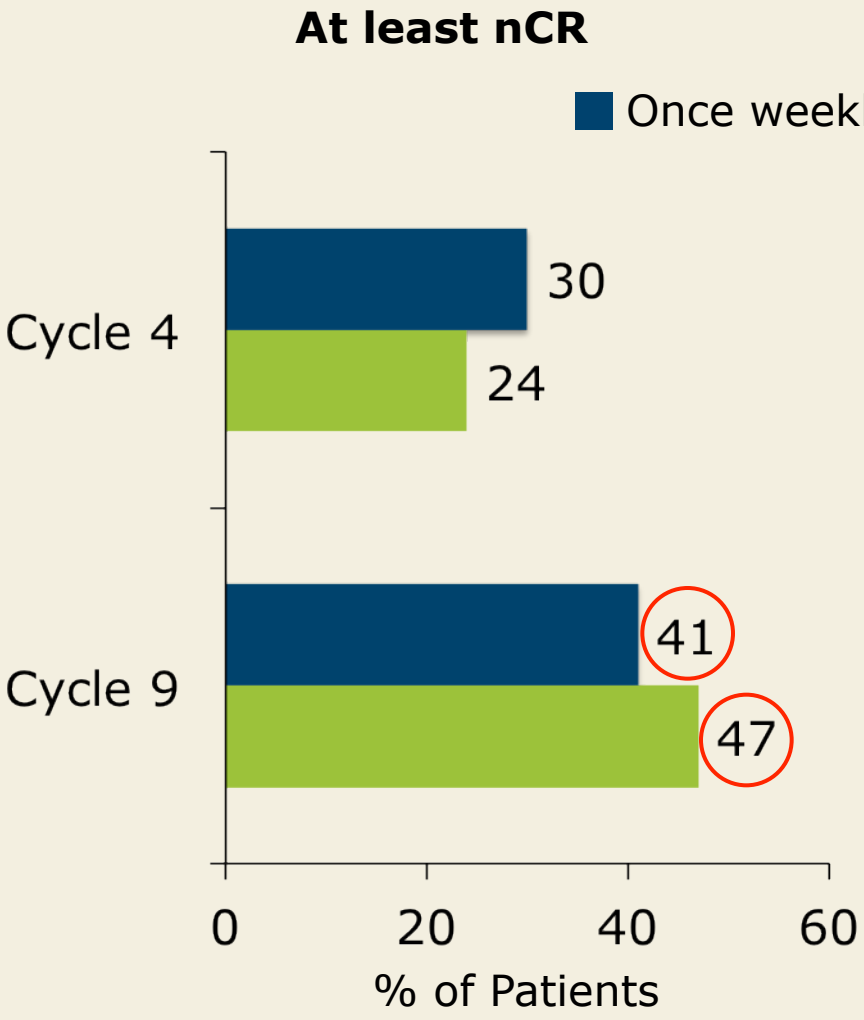
	Phase I (n = 12)	MTD – 70 mg/m^2 (n = 19)	Total (n = 28)
Median cycles received, n (range)	9 (1-9)	4 (1-9)	8 (1-9)
Overall response rate (≥PR)	92%	79%	86%
≥VGPR	75%	58%	64%
sCR + CR + nCR	33%	21%	25%

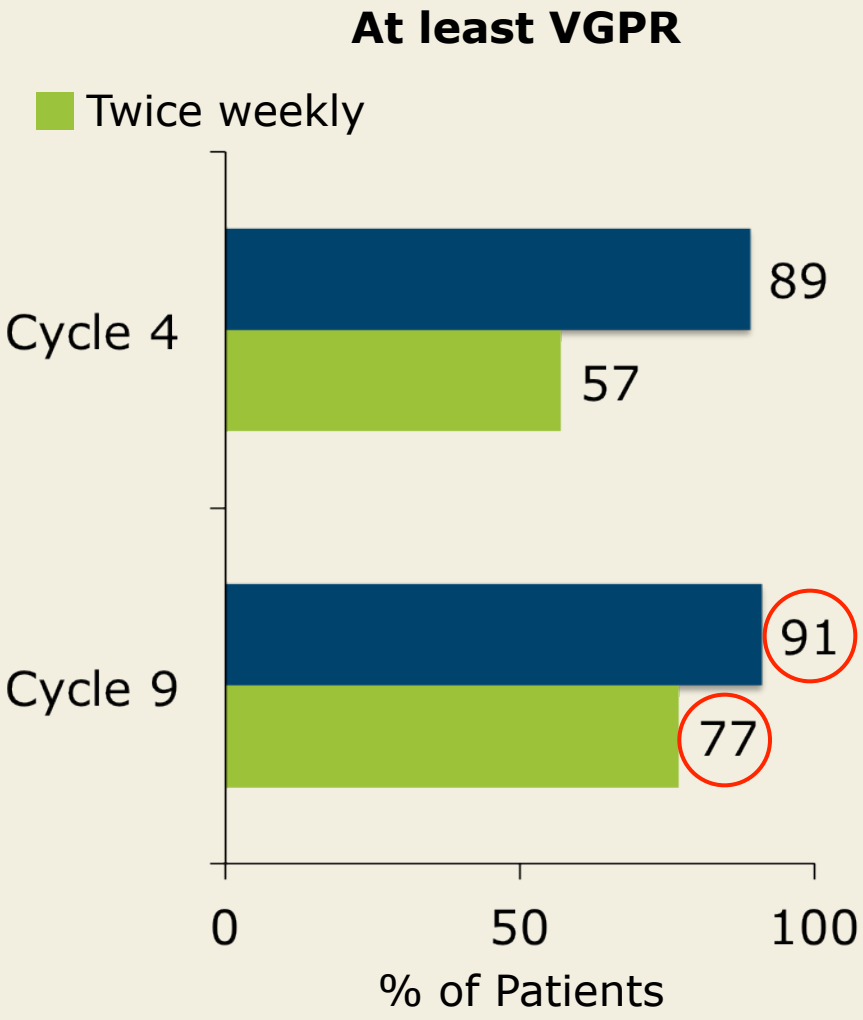
- 28 of 30 patients were evaluable for response (2 patients not evaluable for response due to early discontinuation [pulmonary edema] and first cycle ongoing)
- Median time to first response (≥PR) was 1 month
- Median duration of response not reached

PR = partial response; VGPR = very good partial response; sCR = stringent complete response; nCR = near complete response

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Response Rate by Treatment Duration





Palumbo A et al. *Proc ASH* 2014;Abstract 175.

AE Summary

	Phase I (n = 12)	MTD (n = 21)	Total (n = 30)
Any serious AE (SAE)	8%	19%	17%
Any treatment-related SAE	8%	19%	13%
Dose reduction due to AE	25%	0%	10%
On-study death	0%	5%	3%

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Key Objectives Summary

	CCd once weekly	CCd twice weekly
≥nCR*	41%	47%
PR*	99%	91%
Grade 3 or 4 hematologic AE	23%	27%
Grade 3 or 4 nonhematologic AE	30%	29%
Median delivered carfilzomib dose*	3,534 mg	2,904 mg
Dose reduction	10%	21%
Discontinuation	13%	14%

* After 9 cycles of CCd

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Author Conclusions

- This is the first prospective study evaluating once-weekly carfilzomib for patients with treatment-naïve MM.
- wCCd therapy appears to be safe and effective in patients with newly diagnosed MM.
- Responses became deeper with subsequent cycles, and toxicities were manageable.
- The response rate observed with weekly carfilzomib, compares favorably to that seen in similar studies of standard twice-weekly carfilzomib infusion.
- These are early results, and longer follow-up is required to confirm these observations.

Palumbo A et al. *Proc ASH* 2014;Abstract 175.

Investigator Commentary: A Phase I/II Study of wCCd in Newly Diagnosed MM

This relatively small Phase I/II study evaluated carfilzomib with cyclophosphamide and dexamethasone, which is a variant of CyBorD. CyBorD has been found among various groups to be a combination that works. People have started implementing it, but we do not have many data to back that combination up.

This study used the combination of bortezomib/cyclophosphamide and dexamethasone as the framework, but they replaced bortezomib with carfilzomib. The investigators used the once-a-week dosing for carfilzomib, which was day 1, 8 and 15 at a MTD of 70 mg/m^2. The results were clearly interesting and indicate that you can deliver carfilzomib therapy once a week.

This combination was not quite as efficacious as the combination of carfilzomib, lenalidomide and dexamethasone, but cyclophosphamide is a much cheaper drug and the use of lenalidomide as up-front treatment is not yet approved in certain parts of the world, such as Europe. So I do believe that this combination could be of major interest in many instances. It could also be used in situations in which lenalidomide is contraindicated.

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

continued

Investigator Commentary: A Phase I/II Study of wCCd in Newly Diagnosed MM (continued)

Another feature of this study that's a bit unique is that after they delivered the 9 cycles of wCCd, they administered carfilzomib as maintenance therapy. That has not really been done in many other studies. It's interesting to use this agent as a maintenance therapy.

At this point we are still using the twice-a-week dosing of carfilzomib because that's what is approved by the FDA and that's where all the strong data currently are. But I do think that, based on preliminary data that are coming out as we speak, it seems that the once-a-week schedule at a little higher dose could be equal to a lower dose twice a week. It's likely that we will soon switch over to once a week. This would be a major improvement for patients because coming into the clinic twice a week has an effect on their lifestyle.

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

Effect of Age on Efficacy and Safety Outcomes in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Receiving Lenalidomide and Low-Dose Dexamethasone (Rd): The FIRST Trial

Hulin C et al.

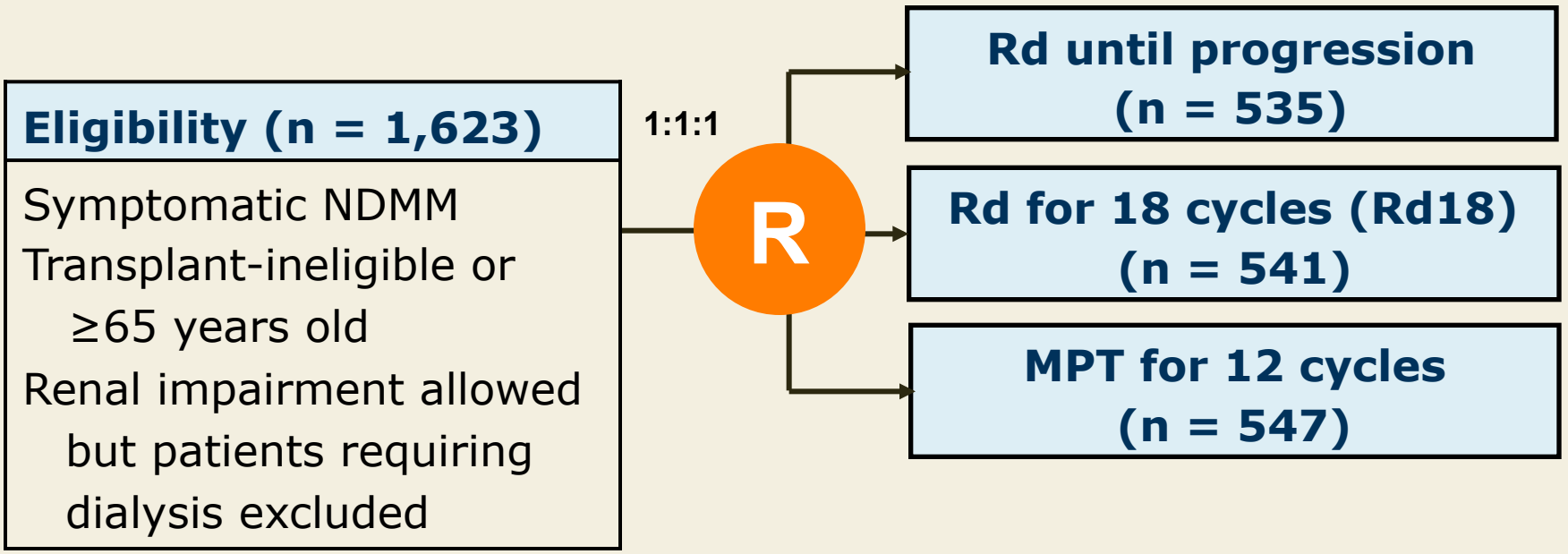
Proc ASH 2014;Abstract 81.

Background

- In patients with untreated multiple myeloma, the combination of lenalidomide (R) with low-dose dexamethasone (d) is associated with better short-term overall survival (OS) and lower toxicity versus R in combination with high-dose dexamethasone (*Lancet Oncol* 2010;11(1):29).
- Results from the pivotal Phase III FIRST trial demonstrated that continuous Rd improved progression-free survival (PFS) (HR = 0.72; $p < 0.001$) compared to melphalan/prednisone/thalidomide (MPT) for patients with newly diagnosed multiple myeloma (NDMM) (*NEJM* 2014;371:906).
  - OS at 4 years: Continuous Rd 59% versus MPT 51%
- **Study objective:** To evaluate the effect of age on the efficacy and safety of Rd in patients with NDMM on the FIRST trial.

Hulin C et al. *Proc ASH* 2014;Abstract 81.

Phase III FIRST Trial Design



- Patients were stratified by age (≤75 vs >75 years), country and ISS stage.
- Starting doses were reduced for patients aged >75 years: dexamethasone 20 vs 40 mg, melphalan 0.20 vs 0.25 mg/kg and thalidomide 100 vs 200 mg.
- **Primary endpoint:** PFS

Benboubker L et al. *N Engl J Med* 2014;371(10):906-17; Hulin C et al. *Proc ASH* 2014;Abstract 81.

Intention-to-Treat Population: Median PFS

Age ≤75 years			Age >75 years			All patients		
Cont Rd (n = 349)	**Rd18** (n = 348)	**MPT** (n = 359)	**Cont Rd** (n = 186)	**Rd18** (n = 193)	**MPT** (n = 188)	**Cont Rd** (n = 535)	**Rd18** (n = 541)	**MPT** (n = 547)
27.4 mo	21.3 mo	21.8 mo	21.2 mo	19.4 mo	19.2 mo	25.5 mo	20.7 mo	21.2 mo
Continuous Rd versus Rd18 (HR; *p*-value)								
0.68; $p < 0.01$			0.75; $p = 0.03$			0.70; $p < 0.01$		
Continuous Rd versus MPT (HR; *p*-value)								
0.68; $p < 0.01$			0.81; $p = 0.11$			0.72; $p < 0.01$		

Cont Rd = continuous Rd

Median follow-up = 37 months

Hulin C et al. *Proc ASH* 2014;Abstract 81 (Abstract only).

Intention-to-Treat Population: 4-Year OS

Age ≤75 years			Age >75 years			All patients		
Cont Rd (n = 349)	**Rd18** (n = 348)	**MPT** (n = 359)	**Cont Rd** (n = 186)	**Rd18** (n = 193)	**MPT** (n = 188)	**Cont Rd** (n = 535)	**Rd18** (n = 541)	**MPT** (n = 547)
66%	61%	58%	47%	47%	39%	59%	56%	51%
Continuous Rd versus Rd18 (HR; *p*-value)								
0.88; $p = 0.36$			0.94; $p = 0.70$			0.90; $p = 0.31$		
Continuous Rd versus MPT (HR; *p*-value)								
0.77; $p = 0.06$			0.80; $p = 0.16$			0.78; $p = 0.02$		

Hulin C et al. *Proc ASH* 2014;Abstract 81 (Abstract only).

Intention-to-Treat Population: Response Rate (RR)

	Age ≤75 years			Age >75 years		
	Cont Rd (n = 349)	**Rd18** (n = 348)	**MPT** (n = 359)	**Cont Rd** (n = 186)	**Rd18** (n = 193)	**MPT** (n = 188)
RR*	77%	77%	66%	71%	66%	55%
DoR*	40 mo	23 mo	22 mo	31 mo	20 mo	24 mo

	All patients		
	Cont Rd (n = 535)	**Rd18** (n = 541)	**MPT** (n = 547)
RR*	75%	73%	62%
DoR*	35 mo	22 mo	22 mo

* Partial response or better

DoR = Duration of response

Hulin C et al. *Proc ASH* 2014;Abstract 81 (Abstract only).

Grade 3-4 Adverse Events (AEs) in ≥10% of Patients

AEs	Age ≤75 years			Age >75 years		
	Cont Rd (n = 347)	**Rd18** (n = 348)	**MPT** (n = 357)	**Cont Rd** (n = 185)	**Rd18** (n = 192)	**MPT** (n = 184)
Neutropenia	28%	25%	47%	28%	29%	40%
Thrombocytopenia	8%	9%	13%	9%	7%	7%
Anemia	18%	12%	20%	19%	23%	17%
Leukopenia	5%	6%	11%	4%	5%	8%
Infections	29%	21%	16%	29%	23%	20%
DVT and/or PE	10%	6%	8%	7%	8%	4%
Peripheral sensory neuropathy	1%	1%	10%	1%	0%	8%
Discontinuation due to AEs	28%	18%	28%	32%	25%	30%

DVT = deep vein thrombosis; PE = pulmonary embolism

Hulin C et al. *Proc ASH* 2014;Abstract 81 (Abstract only).

Author Conclusions

- In patients with NDMM, continuous Rd was effective regardless of age (≤75 vs >75 years):
  - It increased PFS and interim OS
  - It was generally well tolerated compared to MPT
- The duration of response was improved with continuous Rd versus MPT and Rd18, irrespective of age but with a more profound benefit observed among younger patients.
- Continuous Rd represents a new clinical option and standard for these patients in the first-line setting.

Hulin C et al. *Proc ASH* 2014;Abstract 81 (Abstract only).

Investigator Commentary: FIRST Trial — Effect of Age on Efficacy and Safety Outcomes in Patients with NDMM

The FIRST trial compared continuous Rd to Rd for 18 cycles or MPT for transplant-ineligible patients with NDMM. MPT is still the standard approach in Europe. The original study demonstrated that continuous Rd was associated with better PFS and OS in comparison to MPT (Benboubker et al. *NEJM* 2014;371(10):906). The current study analyzed treatment outcomes on the FIRST trial based on age: Patients were stratified by whether they were 75 or younger, or older than 75 years. The data demonstrated that PFS and OS were similar at the time of analysis, with continuous Rd being effective independent of age. This is what I would have expected, but it is important to have the data to confirm this expectation.

This is a large, randomized study that answers a relevant question. The average age of onset for multiple myeloma is 70 years, and many patients with the disease are older than 75.

We now have access to effective drugs that are not intense. We should stop discriminating by age in the selection of therapy. Patients older than 75 should have access to effective therapies.

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

Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients with Previously Untreated Multiple Myeloma (MM): Phase 2 Study Results[1]

Clinical Profile of Single-Agent Oprozomib in Patients with Multiple Myeloma: Updated Results from a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study[2]

[1] **Kumar SK et al.**
Proc ASH 2014;Abstract 82.

[2] **Vij R et al.**
Proc ASH 2014;Abstract 34.

Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients with Previously Untreated Multiple Myeloma (MM): Phase 2 Study Results

Kumar SK et al.

Proc ASH 2014;Abstract 82.

Background

- Triplet regimens combining a proteasome inhibitor, an immunomodulatory agent and a steroid have been shown to be active and well tolerated in patients with previously untreated MM.
- Ixazomib is an investigational proteasome inhibitor that has shown single-agent activity in relapsed/refractory MM, with a manageable safety profile, including limited peripheral neuropathy (PN) (*Blood* 2014;124:1047).
- Results of weekly ixazomib with lenalidomide (len) and dexamethasone (dex) in a Phase I/II trial for untreated MM were previously reported (*Lancet Oncol* 2014;15:1503):
  - Treatment comprised the triplet induction regimen followed by single-agent ixazomib maintenance therapy.
- **Study objective:** To report the long-term safety and efficacy of ixazomib maintenance therapy in patients who received triplet induction therapy in the Phase I/II trial.

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

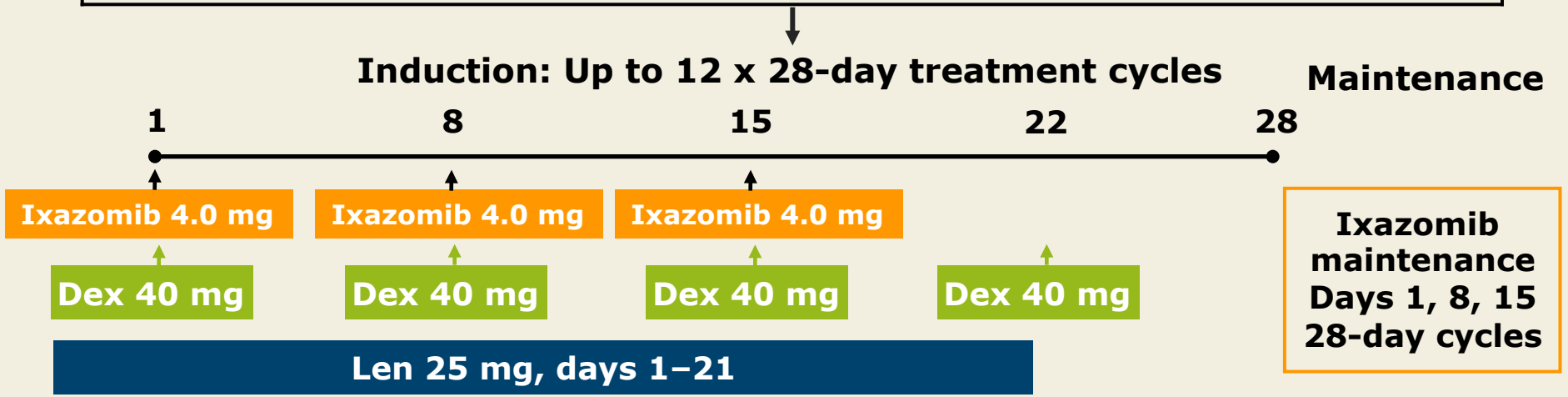
Phase I/II Trial Design (NCT01217957)

Eligibility (n = 65): Phase I (n = 15), Phase II (n = 50)

Patients with previously untreated MM

ECOG PS 0-2

No DVT/PE; No Grade ≥2 PN



DVT = deep vein thrombosis; PE = pulmonary embolism

- Mandatory thromboembolism prophylaxis with aspirin 81-325 mg/d or low-molecular-weight heparin while receiving len/dex
- **Primary endpoint:** Complete response (CR) + very good partial response (VGPR)

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

Best Response: All Patients

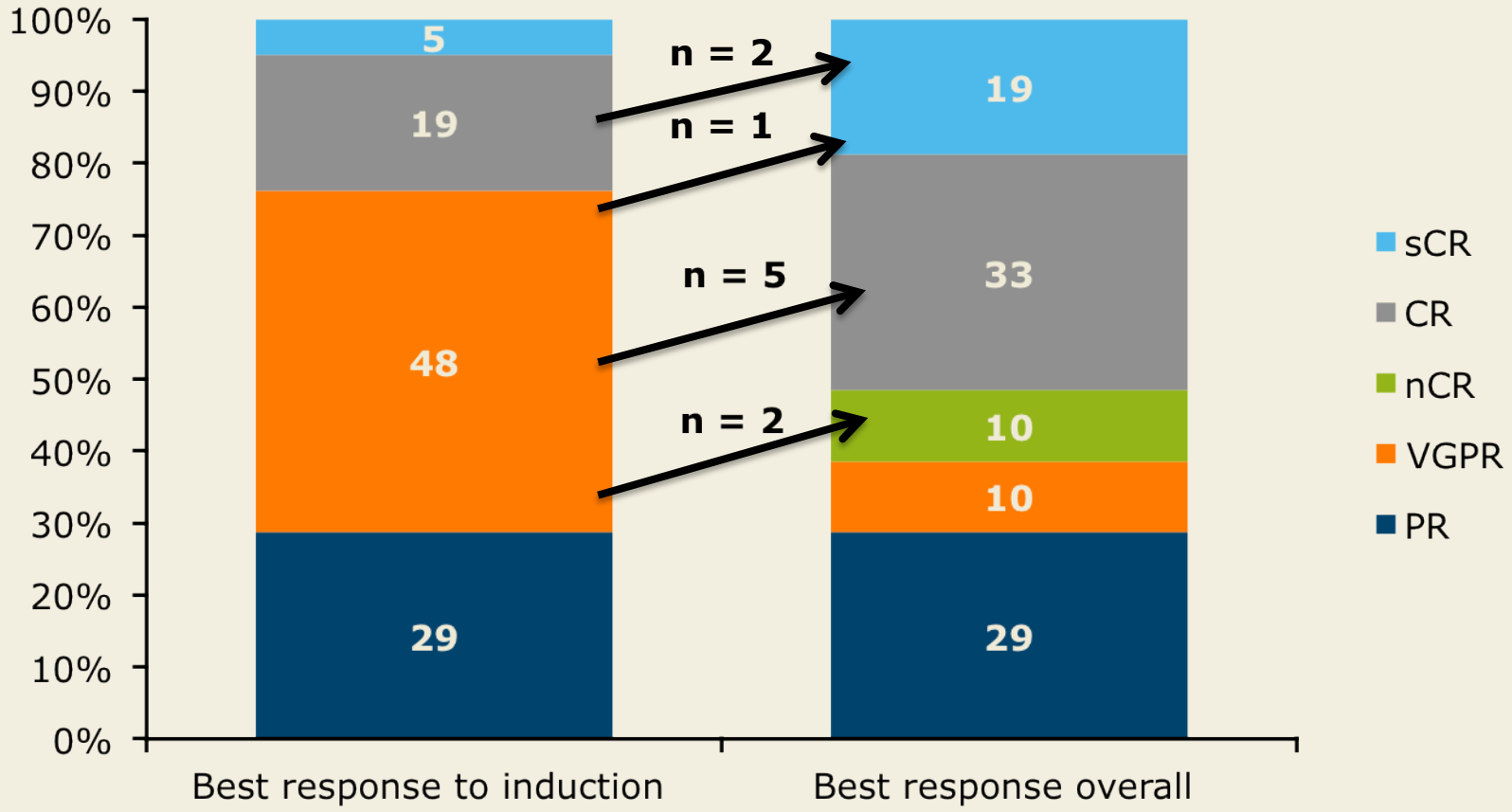
All patients (n = 49)*	Induction	Overall
CR + VGPR + partial response (PR)	44 (90%)	44 (90%)
CR	11 (22%)	17 (35%)
Stringent CR (sCR)	5 (10%)	8 (16%)
VGPR	18 (37%)	12 (24%)
Near CR (nCR)	2 (4%)	4 (8%)
PR	15 (31%)	15 (31%)
Minimal response (MR)	3 (6%)	3 (6%)
Stable disease (SD)	2 (4%)	2 (4%)

* 14 patients discontinued induction therapy to undergo ASCT. Best response to induction therapy included

- sCR = 4 (29%)
- VGPR = 4 (29%)
- PR = 6 (43%)

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

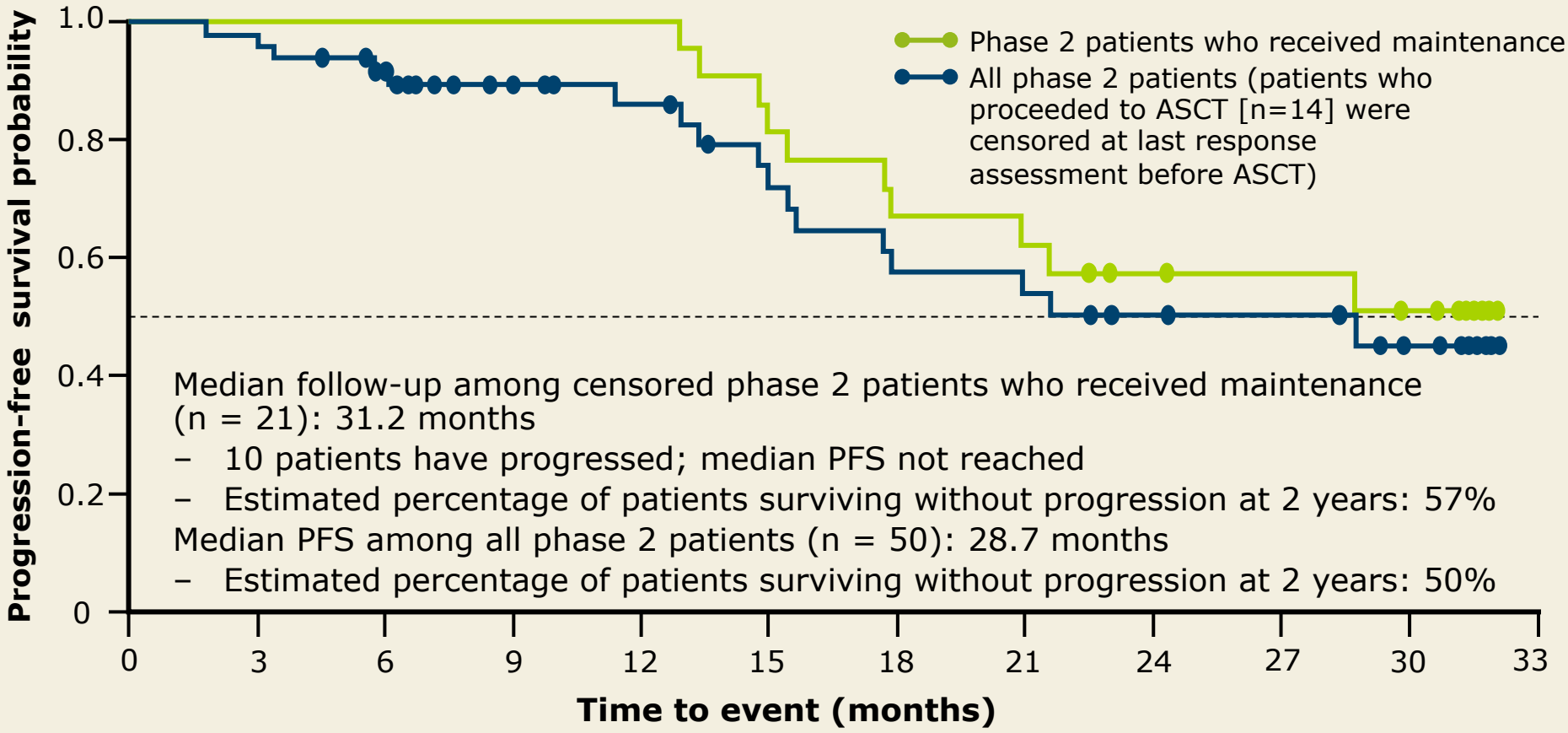
Best Response: Patients in the Phase II Portion Receiving Maintenance Therapy (N = 21)



- Patients with improved response during maintenance: 10 (48%)
  - VGPR to nCR (n = 2); VGPR to CR (n = 5); VGPR to sCR (n = 1); CR to sCR (n = 2)

With permission from Kumar SK et al. *Proc ASH* 2014;Abstract 82.

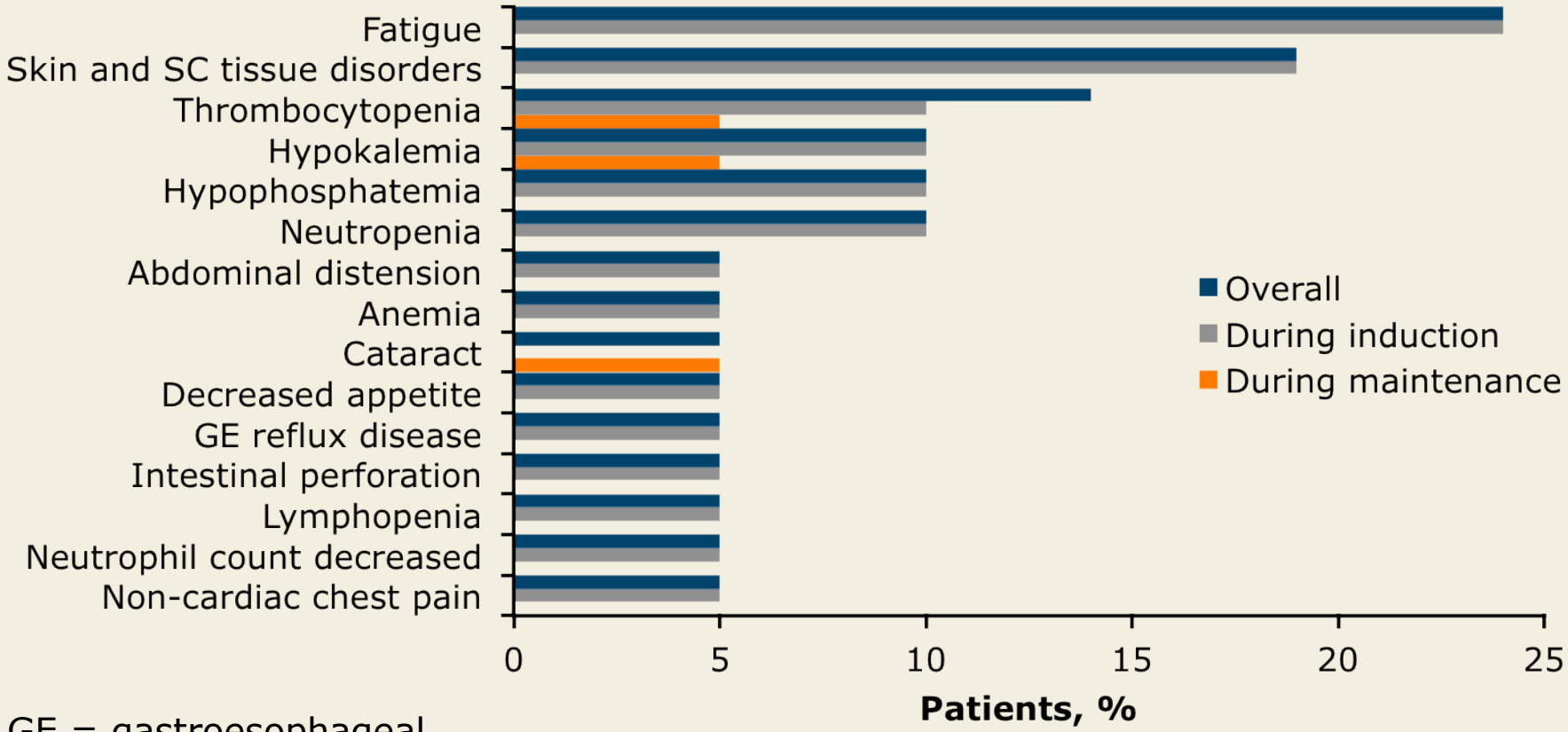
Progression-Free Survival (PFS)



- All 21 patients who received ixazomib maintenance were alive after a follow-up of 25.1-33.9 months

With permission from Kumar SK et al. *Proc ASH* 2014;Abstract 82.

Grade 3 Ixazomib-Associated Adverse Events (AEs)



GE = gastroesophageal

- Grade 3 AEs were reported in 13 (62%) patients overall: Induction (52%), maintenance therapy (14%)
- No Grade 4 AEs among the 21 patients who received ixazomib maintenance

With permission from Kumar SK et al. *Proc ASH* 2014;Abstract 82.

Author Conclusions

- The all-oral combination of ixazomib/len/dex is active as induction therapy, with a manageable safety profile at the recommended Phase II dose for patients with previously untreated MM:
  - ≥PR = 90% after up to 12 cycles of induction therapy
- Data on 21 patients indicate that single-agent ixazomib maintenance for up to 1.9 years was feasible, with a manageable profile for patients not undergoing ASCT:
  - Ixazomib maintenance improved responses
  - It contributed to durable responses
  - New onset of toxicity was limited during ixazomib maintenance
- A Phase III trial of ixazomib or placebo in combination with len/dex for patients with previously untreated MM is ongoing (TOURMALINE-MM2; NCT01850524).

Kumar SK et al. *Proc ASH* 2014;Abstract 82.

Investigator Commentary: Long-Term Efficacy and Safety of Ixazomib Maintenance Therapy After Induction Therapy with Ixazomib/Len/Dex for Previously Untreated MM

This is a study of the long-term use of single-agent ixazomib maintenance therapy after induction therapy with ixazomib/len/dex. In the Phase II portion of the study, 50 patients were followed up for about 1.5 years. The study showed that the continuation of ixazomib maintenance is well tolerated and improves responses. Also, it contributes to durable responses. This is extremely important. Evidence suggests that it will provide us with another oral maintenance agent, a proteasome inhibitor, beyond the immunomodulatory drug len. However, we need larger studies with longer follow-up to confirm these results. Though promising, ixazomib is investigational and cannot be used outside of a protocol setting. A study of ixazomib or placebo with len/dex in the relapsed/refractory setting is ongoing (NCT01564537). If that study is successful, ixazomib may become available.

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

Clinical Profile of Single-Agent Oprozomib in Patients with Multiple Myeloma: Updated Results from a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study

Vij R et al.

Proc ASH 2014;Abstract 34.

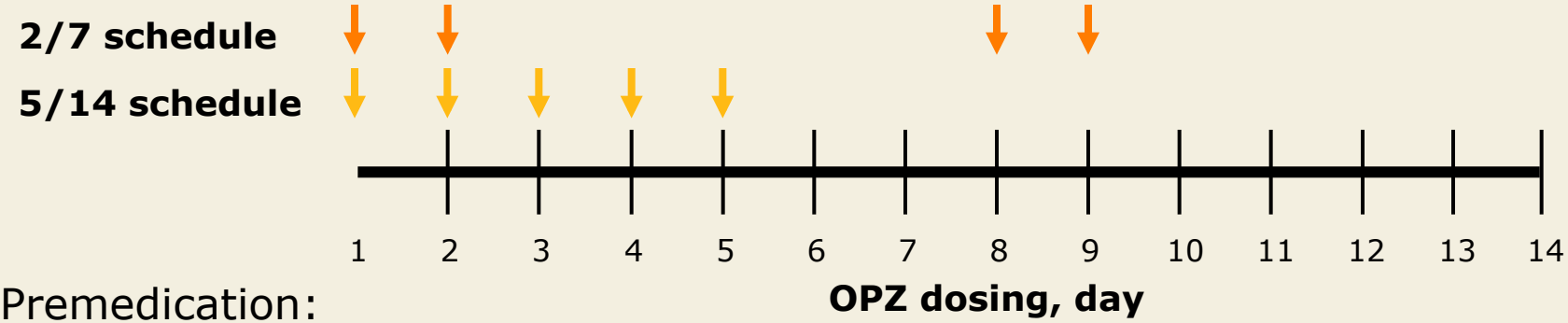
Background

- Oprozomib (OPZ) is an orally bioavailable epoxyketone proteasome inhibitor.
- It selectively and irreversibly binds to its target.
- Preliminary findings demonstrated promising antitumor activity of single-agent OPZ in patients with hematologic cancers, including multiple myeloma (MM) (*Proc ASH* 2013;Abstract 3184):
  - Clinical benefit rate (CBR) in MM, 23.1%
- **Study objective:** To determine the safety and efficacy of OPZ in the subset of patients with MM enrolled on a Phase Ib/II trial.

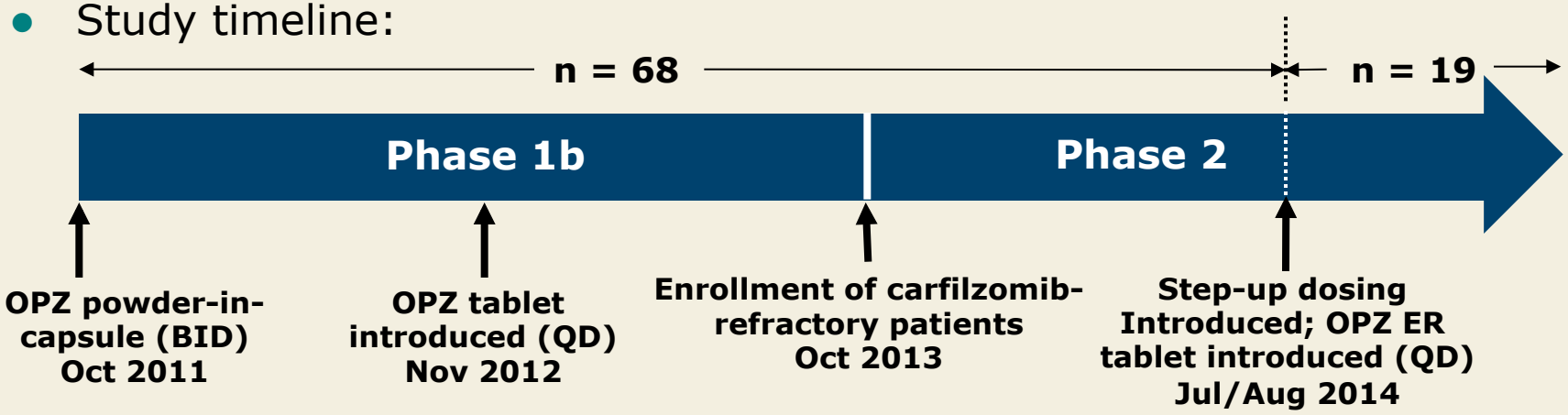
Vij R et al. *Proc ASH* 2014;Abstract 34.

Ongoing Phase Ib/II Trial Design(NCT01416428)

- Study dosing schema:



- Premedication:
  - 5-HT3 inhibitor (phase 1b and phase 2)
  - Dexamethasone (4 mg PO or IV; phase 2 only)
- Study timeline:



With permission from Vij R et al. *Proc ASH* 2014;Abstract 34.

Eligibility Criteria and Endpoints

- Target accrual (n = 349)
- Patients with hematologic cancer
  - Relapsed after ≥1 line of therapy (Phase Ib)
  - Relapsed and/or refractory after 1 to 3 lines of therapy (Phase II)
- No evidence of CNS lymphoma
- No New York Heart Association Class III/IV congestive heart failure
- No Grade ≥3 peripheral neuropathy (PN) or Grade 2 PN with pain
- **Primary endpoints**
  - Phase I: Determination of the maximum tolerated dose (MTD)
  - Phase II: Overall response rate (ORR)
- **Secondary endpoints** include safety/tolerability and CBR

Vij R et al. *Proc ASH* 2014;Abstract 34.

Enrollment to Date

- As of November 3, 2014, patients with hematologic cancer receiving OPZ (n = 129)
  - Patients with MM (n = 87):
    - Phase Ib, 2/7 schedule (n = 21)
    - Phase Ib, 5/14 schedule (n = 20)
    - Phase II cohort:
      - 5/14 schedule, 240 mg/d (n = 27)
      - 2/7 step-up schedule, 240 then 300 mg/d (n = 10)
      - 5/14 step-up schedule, 150 then 180 mg/d (n = 9)

Vij R et al. *Proc ASH* 2014;Abstract 34.

Duration of Treatment (DoT)

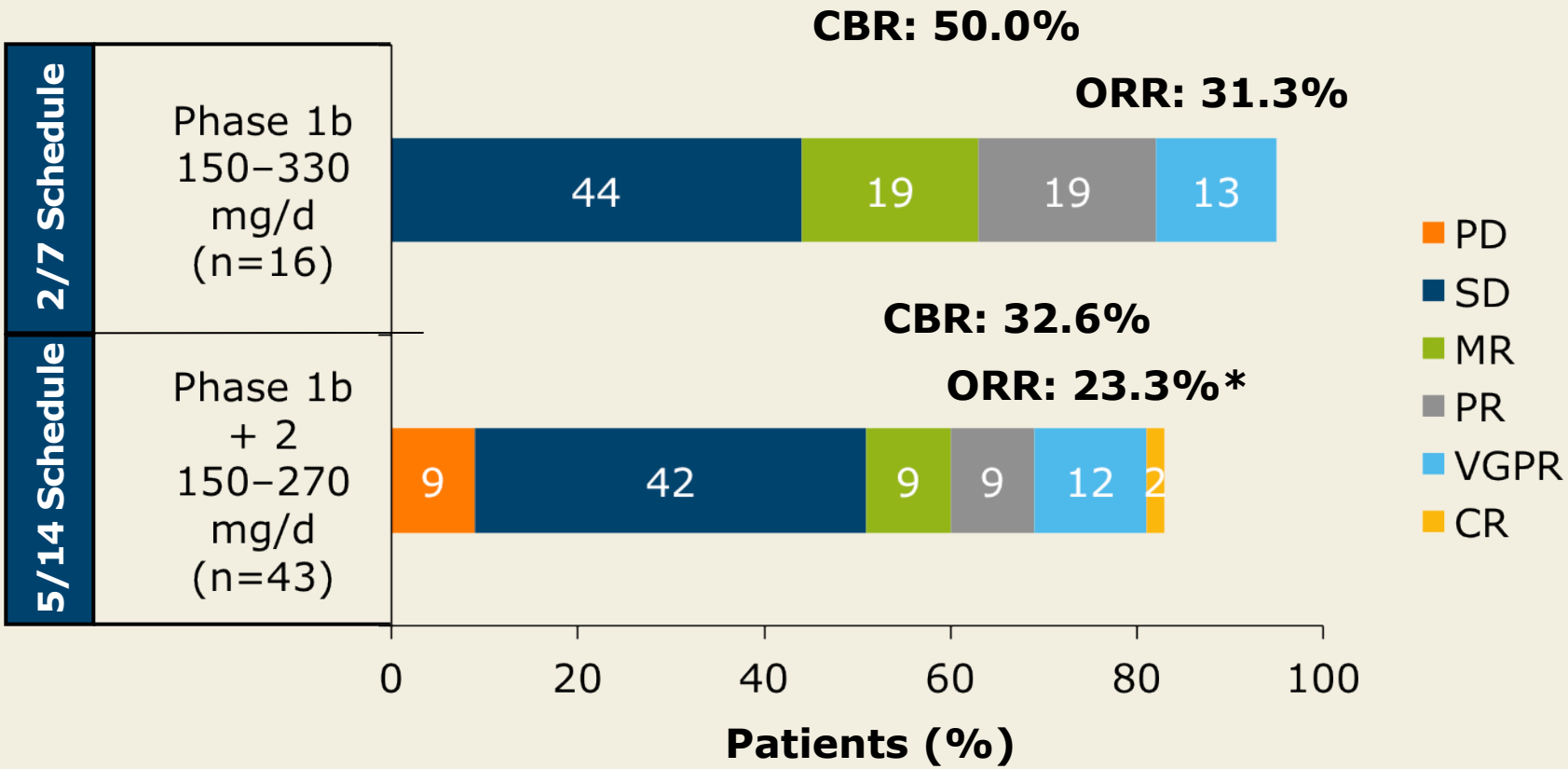
Phase Ib	**2/7 Schedule**	**5/14 Schedule***
	150-330 mg/d (n = 21)	**150-270 mg/d (n = 47)**
Median DoT	23.4 weeks	6.7 weeks
Phase II	**2/7 Step-up**	**5/14 Step-up**
	240 then 300 mg/d (n = 10)	**150 then 180 mg/d (n = 9)**
Median DoT	5.6 weeks	6.7 weeks

* Phase Ib + II

- Treatment duration in the step-up cohorts (Phase II) was limited by the recent enrollment of patients.
- Phase Ib: 2/7 schedule, MTD = 300 mg/d
  5/14 schedule, MTD = 240 mg/d

Vij R et al. *Proc ASH* 2014;Abstract 34.

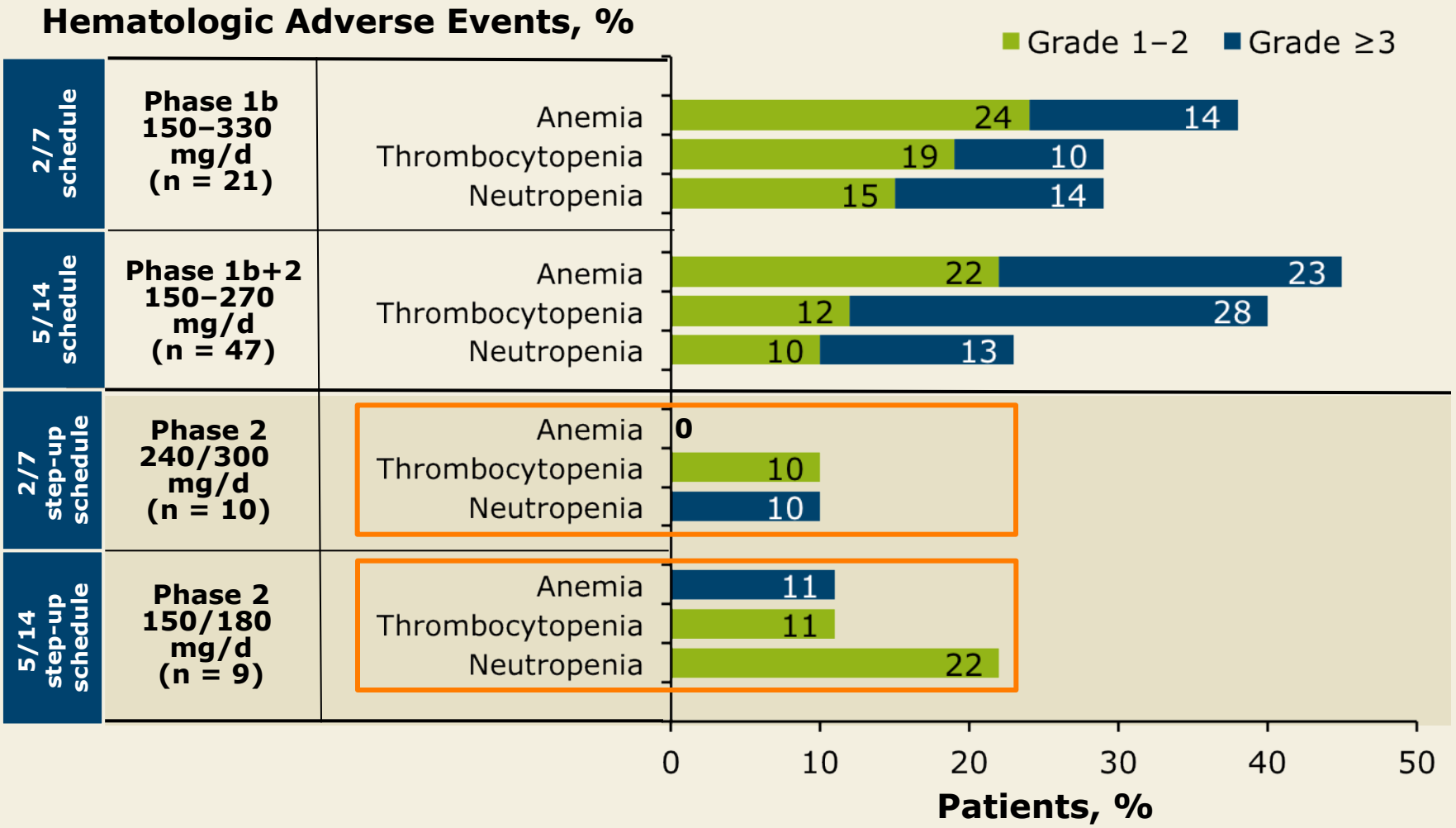
Response (Phase Ib – 2/7 Schedule)



- ORR for 11 patients with carfilzomib-refractory MM (Phase II): 18.2%
- Response data not shown for step-up cohorts because of limited treatment exposure

With permission from Vij R et al. *Proc ASH* 2014;Abstract 34.

Hematologic Adverse Events



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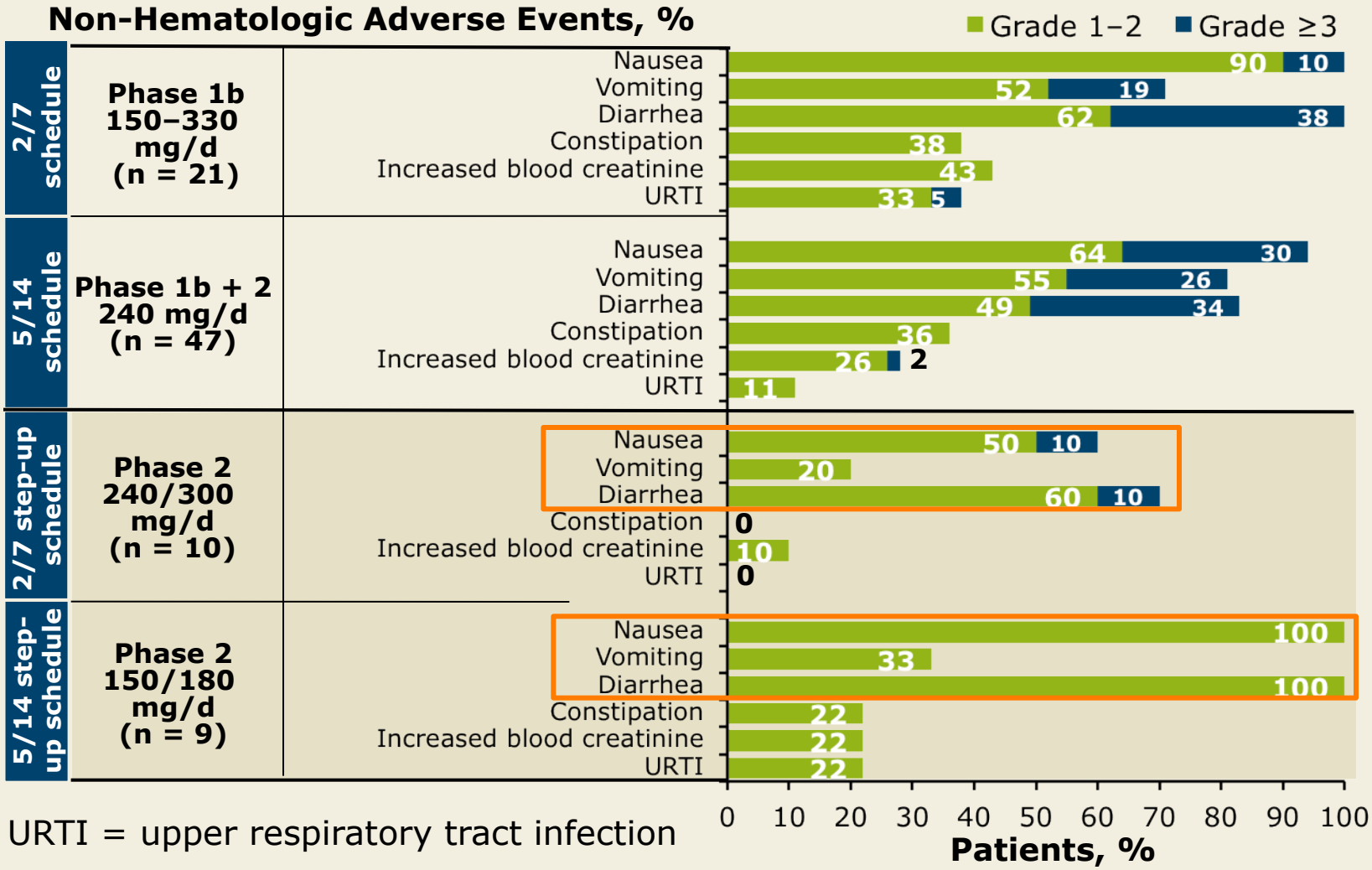
Nonhematologic Adverse Events



URTI = upper respiratory tract infection

With permission from Vij R et al. *Proc ASH* 2014;Abstract 34.

PN, Rash, Gastrointestinal (GI) Bleeding and Deaths

- Treatment-emergent or worsening PN occurred in 5 patients (6%).
  - Patients with Grade ≥3 PN: 1 (1%)
- Treatment-emergent rash occurred in 6 patients (7%).
  - No Grade ≥3 rash was observed
- Patients who developed serious adverse events: 28
- Patients who died: 3 (6%)
  - Patients who died of upper GI bleeding on the 5/14 schedule (Phase II, 240 mg/d): 2
  - Patient who died of disease progression on the 5/14 schedule (Phase II, 240 mg/d): 1

Vij R et al. *Proc ASH* 2014;Abstract 34.

Author Conclusions

- The most common Grade ≥3 nonhematologic adverse events with single-agent OPZ were diarrhea, nausea and vomiting.
- The rates of treatment-emergent PN and rash were low.
- The recommended Phase II dose and schedule are
  - 2/7 step-up schedule: 240 then 300 mg/d
  - 5/14 step-up schedule: 150 then 180 mg/d
- Preliminary data suggest that step-up dosing is associated with improved tolerability, with few Grade ≥3 GI AEs.
- Accrual on the 2/7 and 5/14 schedules (Phase II) is ongoing.
  - Target enrollment for Phase II: 94 patients with MM
  - All current and newly enrolled patients are receiving a new formulation of OPZ (extended-release tablets)
- Single-agent OPZ continues to show promising antitumor activity with responses in carfilzomib-refractory disease.

Vij R et al. *Proc ASH* 2014;Abstract 34.

Investigator Commentary: Efficacy and Safety Results of a Phase Ib/II Trial of Single-Agent OPZ in Hematologic Cancer

OPZ is the fourth proteasome inhibitor that has been evaluated in patients with MM. The preceding proteasome inhibitors are bortezomib, carfilzomib and ixazomib. Both ixazomib and OPZ are orally bioavailable. This dose-escalation Phase Ib/II study is in its early stages. So far, it is fair to say that drug development focusing on OPZ has been hampered by toxicities that relate to GI symptoms — nausea, diarrhea and vomiting. It appears that OPZ is effective but associated with these toxicities. Hence, the dosing and schedule are being adjusted. Although OPZ is a promising agent, more data are needed to confirm its efficacy and tolerability.

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

Serum Free Light Chains Should Be the Target of Response Evaluation in Light Chain Multiple Myeloma Rather Than Urines: Results from the IFM/DFCI 2009 Trial

Corre J et al.

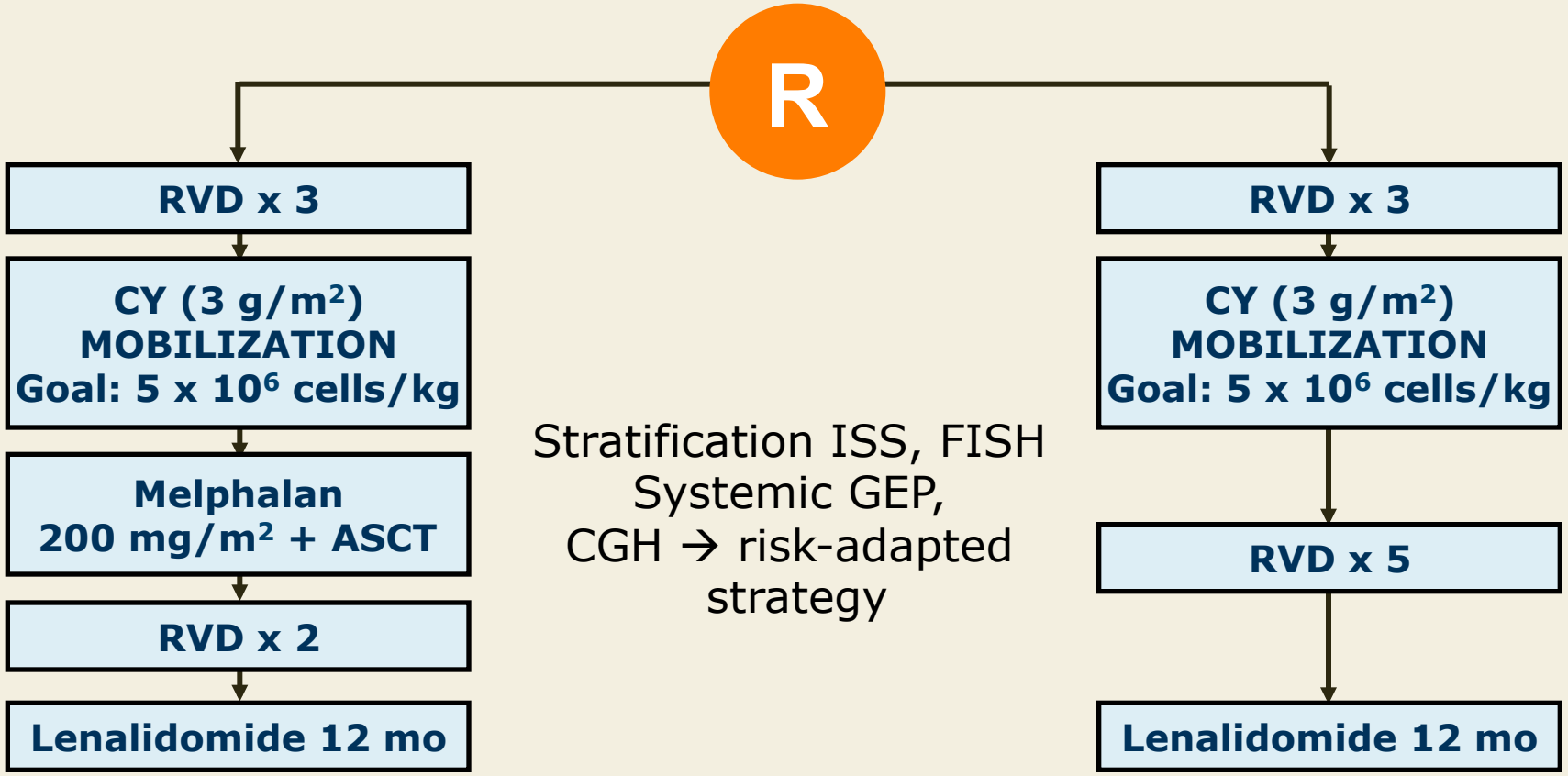
Proc ASH 2014;Abstract 180.

Background

- According to the International Myeloma Working Group (IMWG) criteria, evaluation of response in multiple myeloma (MM) is based on measurement of the monoclonal protein in serum and/or urine.
- For patients secreting only light chains, evaluation is based on urine electrophoresis, and measurable disease is defined by the presence of >200 mg/24 h light chains in the urine. However, this definition and recommendation have several pitfalls:
  - It is difficult to be sure that the 24-hour urine collection is complete, especially with elderly patients.
  - Even if collection is complete, evaluation of response is difficult and may not reflect the response at the plasma cell level.
- **Study objective:** To determine the usefulness of serum free light chain (sFLC) measurement with the Freelite® kit, which has been in use for over 10 years, in evaluating response.

Corre J et al. *Proc ASH* 2014;Abstract 180.

Phase III IFM/DFCI 2009 Trial Design



Cy = cyclophosphamide; SCT = stem cell transplantation

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Study Methods

- Patients enrolled on the IFM/DFCI trial from November 2010 to December 2012: n = 700
- All patients received 1 year of lenalidomide maintenance after induction therapy
- Patients who were identified as secreting only light chains (LCMM): 115 (16.4%)
  - All patients presented with an abnormal sFLC ratio
  - All patients had measurable disease (>100 mg/L) as described by the IMWG
  - All patients were centrally evaluated for response at the end of the induction (3 RVD courses) with urine electrophoresis and sFLC measurement
  - Measurement of sFLC was performed using the Freelite kit

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Study Outcomes

- Patients with negative urine electrophoresis: 88/112 (79%)
  - Patients not evaluated: n = 3
- Based on sFLC evaluation, a normal ratio and/or normal kappa and lambda levels were observed in 58/112 patients (52%)
- Discordances were always in the group of patients with normal urine electrophoresis and abnormal FLC
- To evaluate the speed of response on urine electrophoresis, results were collected from samples on which tests were performed locally in each IFM center after only 1 cycle of RVD
- Data were available for 84 patients
  - Patients presenting with a normal electrophoresis: 52 (62%)

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Response Assessment by Freelite versus Classical MM Assessment

- Response assessment by Freelite versus that observed in classical MM (IgG and IgA) was analyzed for patients who presented at diagnosis with an abnormal sFLC level and measurable disease (>100 mg/L)
- Number of patients identified in this category: 331/585
- Patients who achieved near complete response or complete response and had a normal sFLC ratio and/or normal kappa and lambda levels of sFLC: 65/70

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Response Assessment by Freelite versus Classical MM Assessment (continued)

- Among patients with very good partial response, 98/120 displayed normal Freelite results.
- For patients with partial response or less, only 29/141 presented with normal Freelite results.
- Based on Freelite assessments, 58% of those with classical MM presented with a normal sFLC ratio:
  - Individual FLC levels were not statistically different from the 52% observed in LCMM.

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Author Conclusions

- This study confirmed that response evaluation based on urine electrophoresis is not reliable because of the rapid clearance of serum light chains in urine.
- In contrast, sFLC assessment is much more reliable, with response evaluations statistically similar to those observed in classical IgG or IgA MM.
- These results suggest that it is important to reevaluate the IMWG response criteria for LCMM and incorporate sFLC assessment.

Corre J et al. *Proc ASH* 2014;Abstract 180 (Abstract only).

Investigator Commentary: sFLCs Should Be the Target of Response Evaluation in LCMM Instead of Urine Tests

This study focuses on sFLCs for response evaluation in LCMM. This is an important study, based on the large IFM/Dana-Farber Cancer Institute study that has enrolled about 700 patients. Patients were randomly assigned to receive RVD with or without up-front autologous stem cell transplant. Patients who release light chains instead of M spikes were selected for observation. Of all patients who were diagnosed with MM, about 20% had LCMM.

This study investigated the conventional assessment of response to therapy using light-chain secretion in urine, which is part of the IMWG criteria. Results were compared head to head with results of the sFLC test that was developed about 10 years ago. For many patients, information from urine is not available, and for many the urine result was negative while the serum result was positive. So evidence is provided to support the notion that urine is not the optimal site in which to look for these light chains in these patients. It's cumbersome to collect 24-hour urine samples from patients, and the practice is associated with several practical and methodological issues. In conclusion, it is proposed that the sFLC blood test should become part of new criteria for the IMWG. I agree that it is time to use the serum test instead of the urine test.

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