5 Minute JournalClub

Hematologic Oncology

Issue 1, 2013

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CME Information

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in multiple myeloma, and consider this information in clinical practice.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors, immunomodulatory agents and novel antibodies alone or in combination with approved systemic treatments for patients with relapsed/refractory multiple myeloma.
- Assess the benefits and risks of carfilzomib in combination with an alkylating or immunomodulatory agent for patients with newly diagnosed multiple myeloma.
- Determine the effectiveness and tolerability of pomalidomide in combination with low-dose dexamethasone for patients with relapsed or refractory multiple myeloma and adverse cytogenetics or renal impairment.

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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CME Information (Continued)

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Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

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The revolution in treatment of multiple myeloma (MM) that occurred over the better part of the last decade is evident in the waiting room of every medical oncologist. Thanks to regimens that include immunomodulatory agents (IMiDs) — particularly lenalidomide (len) — and proteasome inhibitors, specifically bortezomib (bz), along with the widespread utilization of bisphosphonates, it is no longer uncommon to see patients on active treatment for 10 years or more. Of course much is still to be done with this challenging disease, and I met with a leader in the field, Dr Antonio Palumbo, for his take on where we are today and where we might be heading.

For some time Dr Palumbo has been a vocal proponent, along with many other MM investigators, of using the most effective therapies as early as possible in the disease course — often for prolonged durations. Based on his research and that of many others, for younger patients his standard is triple-agent induction followed by high-dose chemotherapy and autologous stem cell transplant and then long-term maintenance treatment. On the flip side, Dr Palumbo has taken a leadership role in the use of preemptive dose reductions for the elderly, allowing for longer-term therapy as opposed to what he calls “short flashes of treatment.”

From this clinical framework, Dr Palumbo commented on several new data sets from the ASCO and the European Hematology Association (EHA) annual meetings, attempting to better define the role of the 2 most recently approved agents for MM — carfilzomib (cz) and pomalidomide (pom) — and several other promising candidates in the later stages of development.

1. Cz triplets

At ASCO this year we saw more on CRd (cz/len/low-dose dexamethasone [lddex]), a cousin of RVD (len/bz/dex), currently one of the most commonly used IMiD/proteasome inhibitor induction regimens.

The final report from the Phase Ib/II trial in relapsed/refractory disease led by Dr Michael Wang that started it all in 2008 demonstrated excellent tolerability with CRd — particularly a lack of significant peripheral neuropathy — and impressive efficacy in patients with extensive prior treatment.

These findings inspired Dr Andrzej Jakubowiak and colleagues to launch an up-front trial that was again reported at ASCO. The antitumor activity in this study is interesting because the depth of response increased with more treatment, and by a median of 22 cycles 87% of patients had achieved a VGPR or better. In keeping with his approach of maximizing the depth of response as early in the disease course as possible, Dr Palumbo is hopeful that accumulating data on CRd and other cz-based up-front regimens will result in an important step forward in induction treatment.

In that context, Dr Palumbo presented at EHA the initial results from a **Phase II up-front trial** evaluating the CCd regimen (cz/cyclophosphamide [cy]/lddex), which resembles another major induction triplet in current practice, CyBorD (cy, bz and dex). CCd was not only well tolerated, but the efficacy seemed equivalent if not superior to that of the bz-based approach.

Similarly, at ASCO and then again at EHA we were treated to **data on CMP** (cz/melphalan/prednisone) as up-front therapy for elderly patients. Again there was significant activity and good tolerability, and while Dr Palumbo believes that both alkylating agent combinations with cz are effective, in his view cyclophosphamide-based regimens are the way forward because of better tolerability.

With the rapid emergence of impressive up-front data with cz regimens, it will be interesting to see whether regulatory agencies, investigators and payers will require direct head-to-head trials against bz-based treatments to see a change in practice. In this regard, the NCCN now lists CRd as a category 2A up-front option.

2. Pom/lddex

In December 2012 at ASH Dr Meletios Dimopoulos presented initial findings from the Phase III MM-003 trial documenting an overall survival benefit with the use of pom/lddex for patients with relapsed/refractory MM. At ASCO and EHA **the results were updated**, and **subset data from this seminal effort** provide

evidence of safety and efficacy in patients with moderate renal impairment and modest activity in patients with adverse cytogenetic profiles. In commenting on these studies, Dr Palumbo stated his belief that this regimen provides useful clinical responses in 30% to 50% of patients with disease progressing on len. He also predicted greater long-term benefit if pom/lddex were used earlier in the disease course, ideally soon after progression on another IMiD.

3. Monoclonal antibodies (mAbs)

The recent emergence of 2 distinct compounds with preliminary activity in MM may soon make this disease fertile ground for the regular use of mAbs. The first agent is elotuzumab, which targets the CS1 antigen, and at ASCO and then again at EHA we got more information from Dr Sagar Lonial's **Phase II trial** combining this drug with len and lddex. While this mAb has no single-agent activity, the combination resulted in an eye-popping median PFS of 25.8 months, and one wonders whether we are looking at the myeloma version of "R squared" in lymphoma (len/rituximab). However, Dr Palumbo cautions us to take a conservative view and hold our excitement until Phase III data are available.

Daratumumab, another FDA breakthrough designation recipient, is an anti-CD38 antibody that has shown significant single-agent activity, including an encouraging 31% clinical response rate in a single-arm **Phase I/II dose-escalation study** presented at ASCO and updated at EHA. In Dr Palumbo's eyes CD38 may be as important in MM as CD20 is in lymphoma, and while he won't

speculate as to whether the efficacy of this agent will even come close to what we have seen with rituximab in lymphoma, he is enthusiastic about this potential and recently began entering patients on trials of this agent in his own clinic.

4. Oral proteasome inhibitors

The promise of all-oral combination regimens has many excited about MLN9708 (ixazomib), which has a similar structure to bz but lacks the inconvenience of subcutaneous or IV administration. At ASCO Dr Shaji Kumar presented more from an **expanded Phase I study** of ixazomib demonstrating similar efficacy to what has been observed with bz but with improved tolerability. In that regard, Dr Palumbo is particularly interested in seeing this and other oral agents studied in elderly patients for whom the ease of drug delivery might allow more prolonged treatment and greater disease control.

Over the next few years, we shall see if the next generation of new agents and strategies typified by these EHA and ASCO papers bump ahead outcomes similarly to the initial introduction of IMiDs and proteasome inhibitors, but MM investigators including Dr Palumbo seem determined to push the disease at the least into CML-like control and maybe even cure. Next on this series we consider a number of summer papers on CLL, and one data set in particular that may signal a major shift in choice of anti-CD20 antibody in this disease.

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Treatment Outcome with the Combination of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) for Newly Diagnosed Multiple Myeloma (NDMM) After Extended Follow-Up[1]

Final Results from the Phase Ib/II Study (PX-171-006) of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Patients with Relapsed or Progressive Multiple Myeloma[2,3]

[1] **Jakubowiak AJ et al.**
Proc ASCO 2013;Abstract 8543.

[2] **Wang M et al.**
Proc ASCO 2013;Abstract 8529.

[3] **Niesvizky R et al.**
Proc EHA 2013;Abstract S577.

Treatment Outcome with the Combination of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) for Newly Diagnosed Multiple Myeloma (NDMM) After Extended Follow-Up

Jakubowiak AJ et al.

Proc ASCO 2013;Abstract 8543.

Background

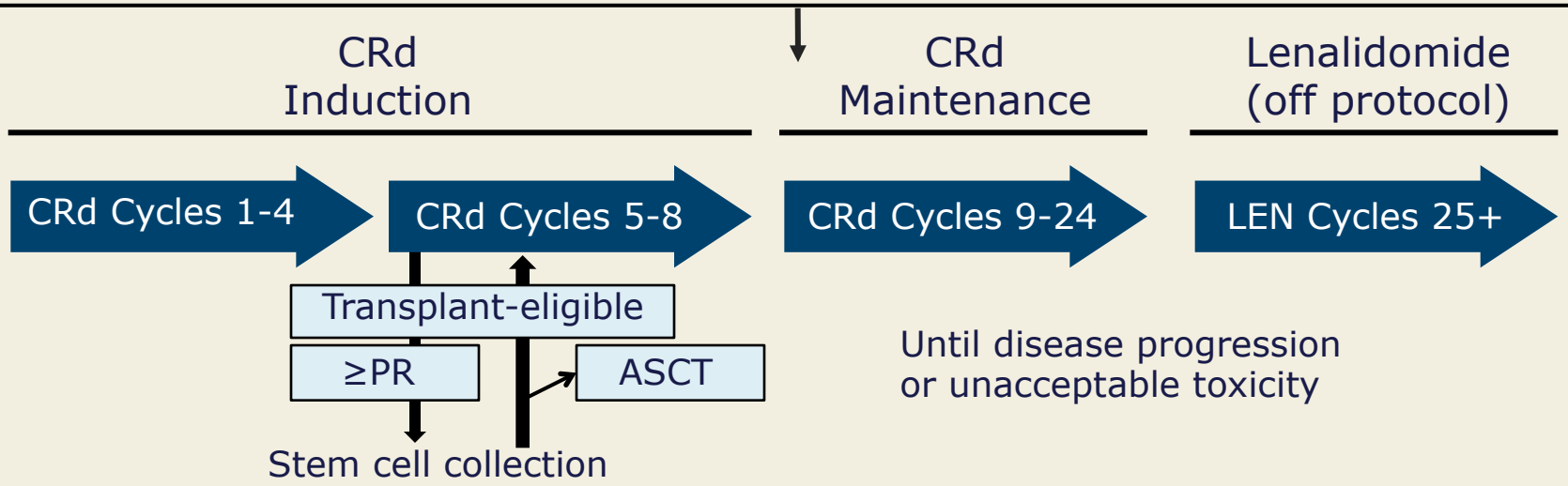
- Carfilzomib (CFZ) is a novel proteasome inhibitor with proven activity as a single agent and a manageable toxicity profile.
- It can be administered for an extended duration without significant treatment-related peripheral neuropathy (*Blood* 2012;120:2817).
- Earlier data from this Phase I/II trial of CFZ in combination with lenalidomide and low-dose dexamethasone (CRd) showed promising activity and depth of response in patients with NDMM (*Blood* 2012;120:1801).
  - Overall response rate: 98% after a median of 12 cycles
- **Study objective**: To report updated results from the Phase I/II trial for patients with NDMM after an extended treatment duration with CRd.

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Phase I/II Trial Design

Eligibility (n = 53)

Newly diagnosed Stages I-III multiple myeloma
Transplant eligible and ineligible
Symptomatic disease
No Grade 3/4 peripheral neuropathy



- **Primary endpoints:** Safety and maximum tolerated dose (Phase I); complete response (CR), near CR (nCR) and stringent CR (sCR) (Phase II)

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Best Response (n = 53*)

Response rate	Median: 12 cycles	Median: 22 cycles†
≥Partial response (PR)	98%	98%
≥Very good PR	81%	87%
≥nCR	62%	74%
CR	47%	62%
sCR	42%	55%
Immunophenotypic CR (iCR)	40%	50%‡

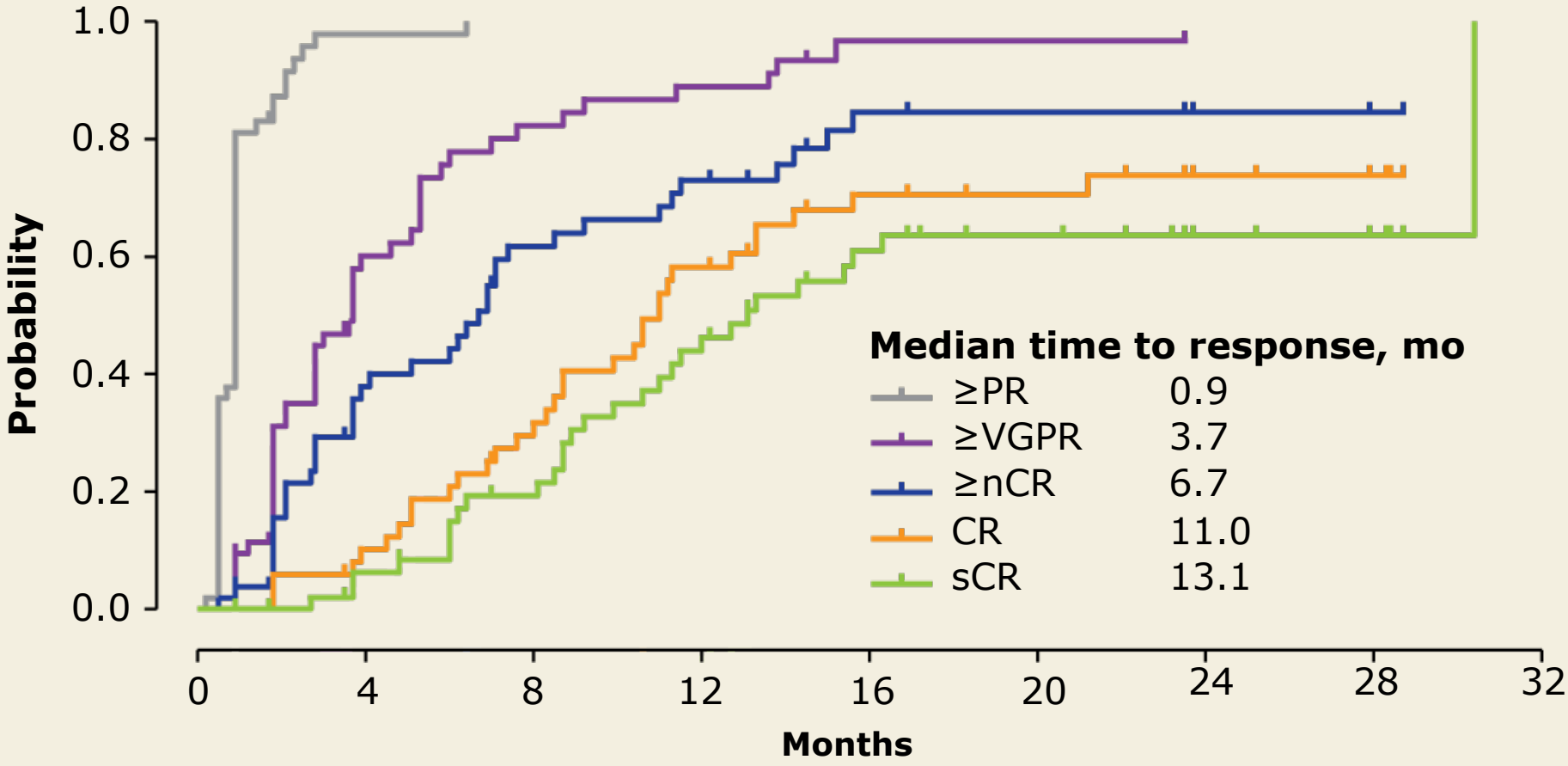
* Intention-to-treat population, including patients who stopped treatment early

† After an additional follow-up of 12 months

‡ Estimate of MRD-negative disease based on percentage of patients in sCR at 12 months (18/19) and at 22 months (22/24)

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Time to Response



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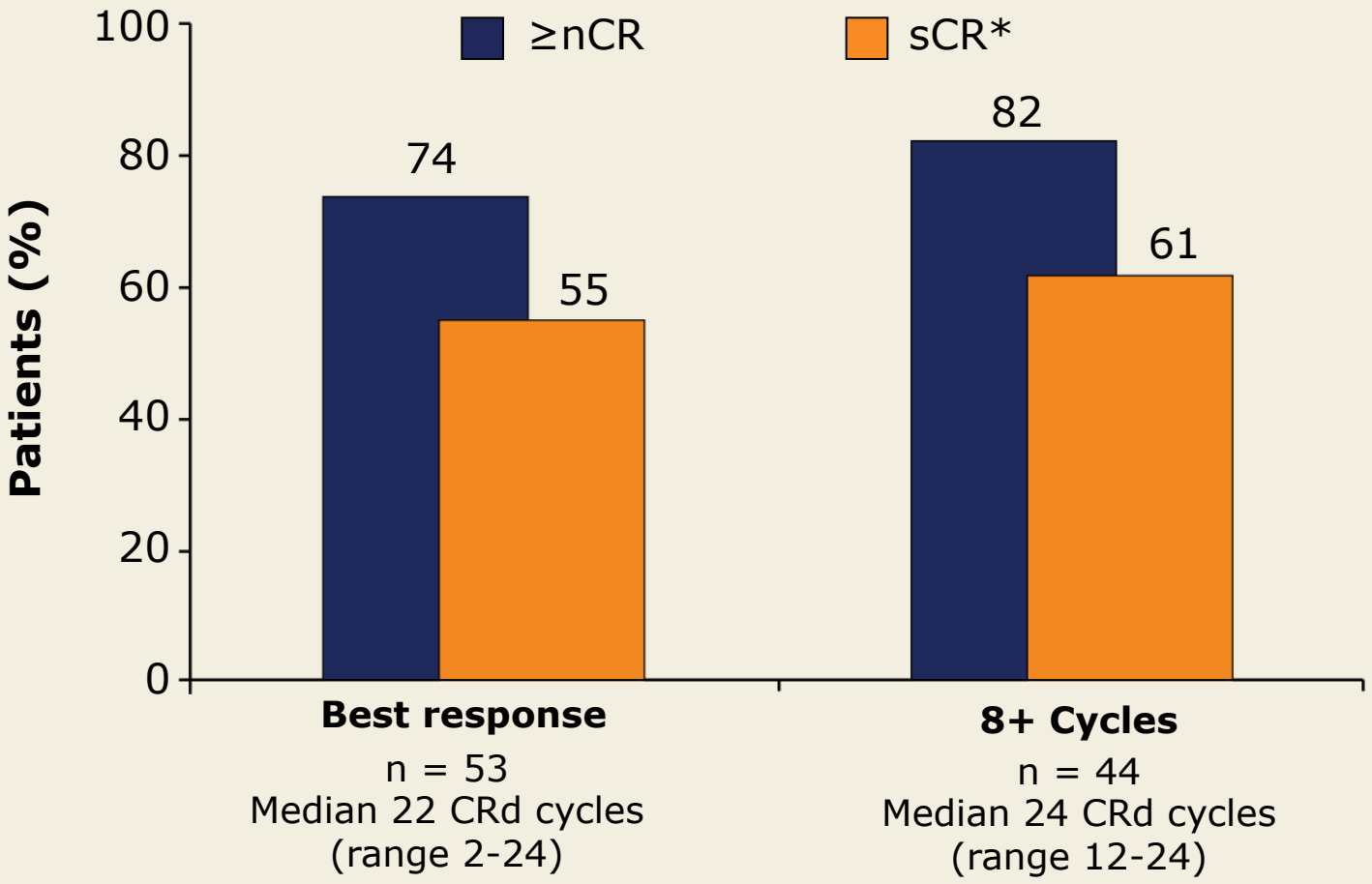
Response After Extended Treatment



* Of patients who achieved sCR, 25% had high-risk cytogenetics

With permission from Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Best Response in a Subset of Patients Who Did Not Proceed to Receive ASCT

Response rate	All patients (n = 53)	No transplant* (n = 46)
≥PR	98%	100%
≥Very good PR	87%	91%
≥nCR	74%	78%
sCR	55%	61%

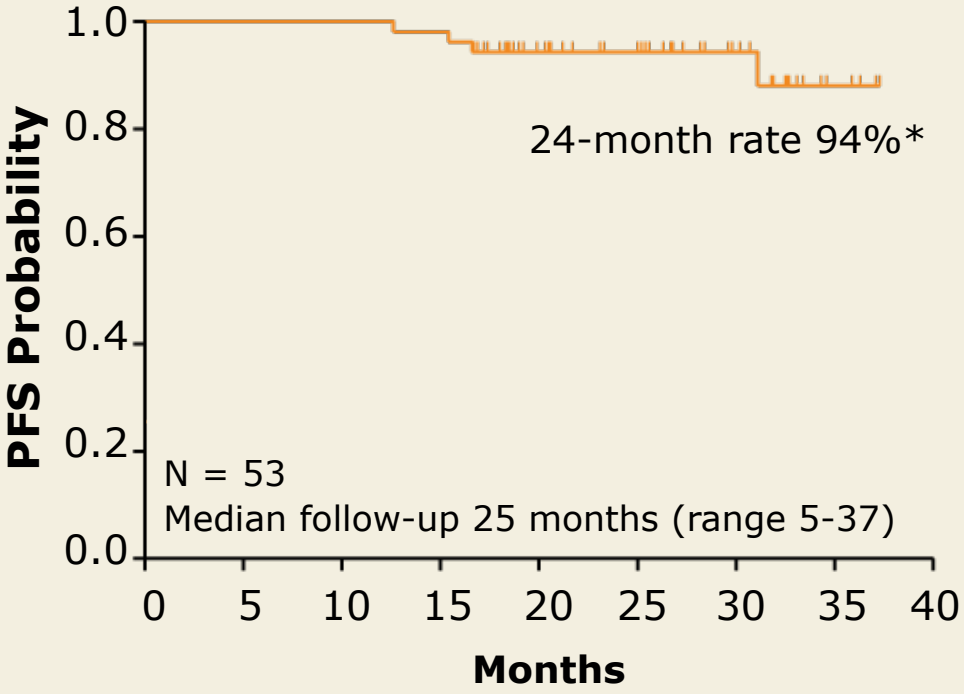
ASCT = autologous stem cell transplantation

* Includes transplant-ineligible patients and/or those who deferred transplantation for various reasons

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

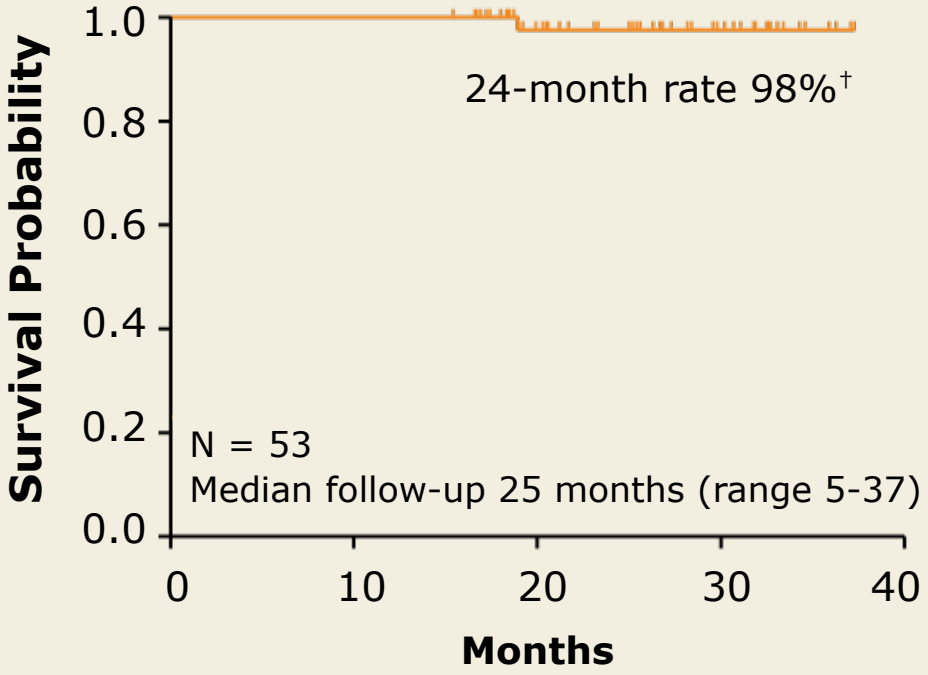
Survival Outcomes

Progression-free survival (PFS)



* For patients in sCR, the estimated 24-month PFS was 97%

Overall survival (OS)



† For patients in sCR, the estimated 24-month OS was 100%

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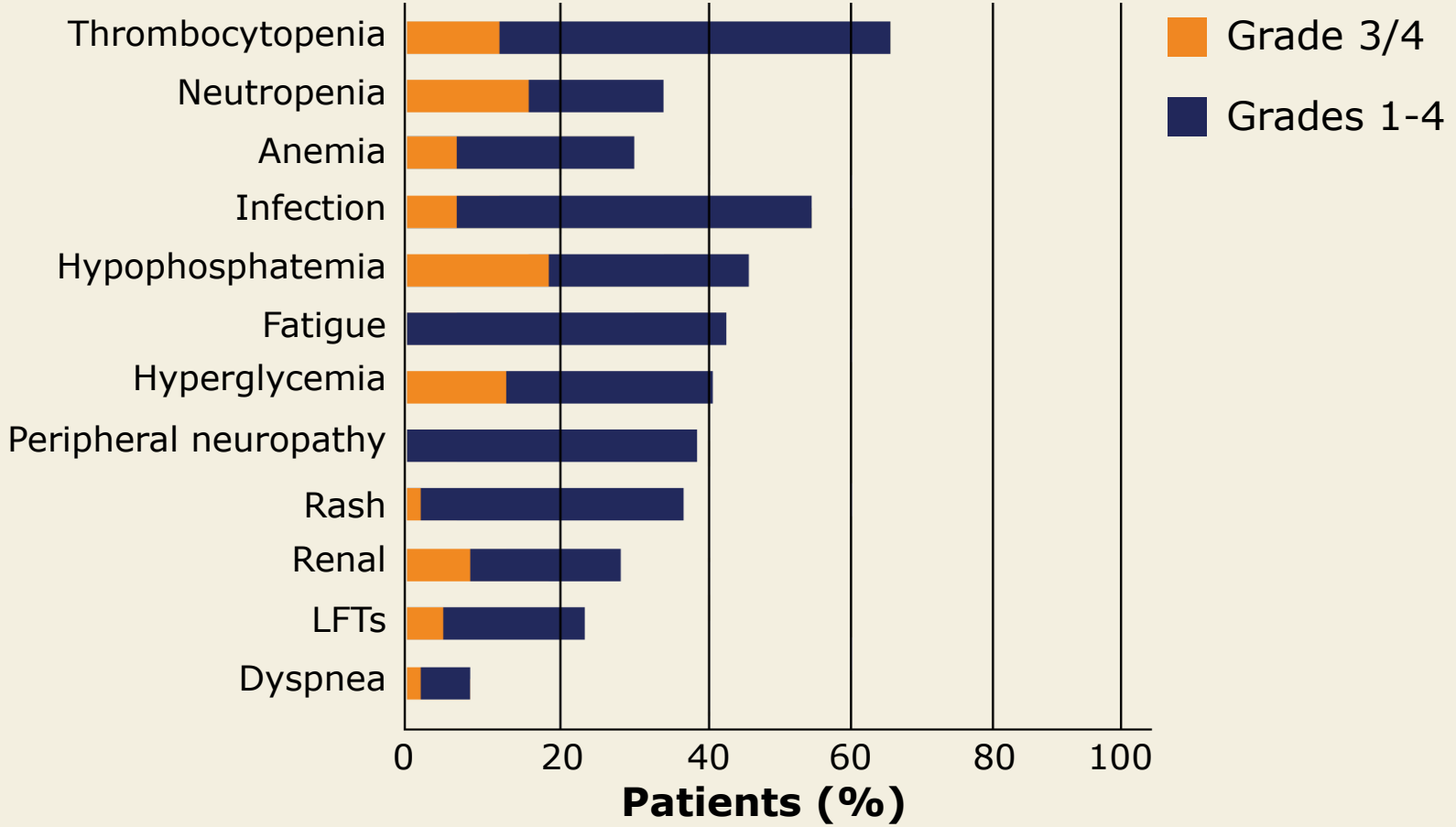
Adverse Events* (n = 44)



* After a median of 16 months of CRd maintenance

- Peripheral neuropathy was limited to Grade 1 (32%) and Grade 2 (9%)

With permission from Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Author Conclusions

- For patients with NDMM, CRd demonstrated rapid responses, with the depth of response improving over the duration of treatment.
- After an additional 12 months of CRd treatment and follow-up, the best response rates improved:
  - VGPR from 81% to 87%
  - ≥nCR from 62% to 74%
  - sCR from 42% to 55%
- Treatment with CRd resulted in a high rate of MRD-negative disease in 22 of 24 patients (92%) with sCR.
- The median PFS and OS were not reached after a median follow-up of 25 months.
  - 2-year PFS: 94%
  - 2-year OS: 98%

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

Author Conclusions (Continued)

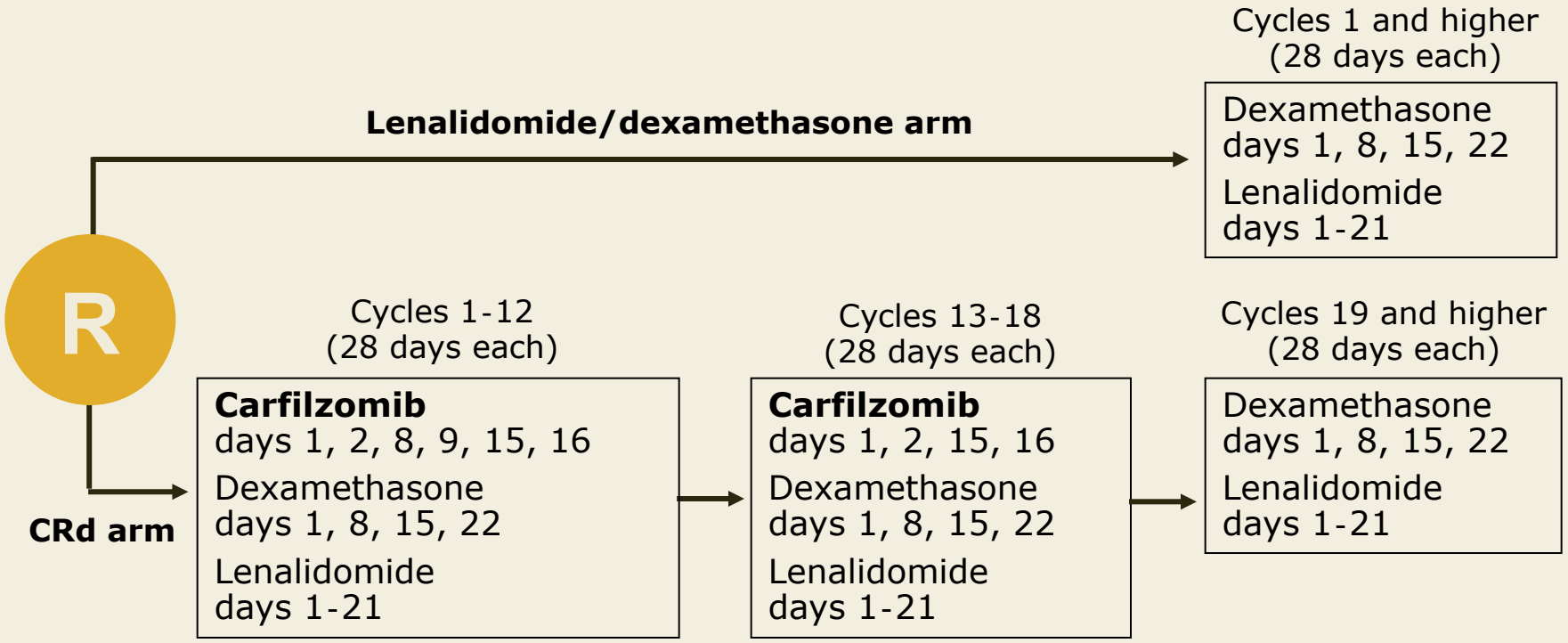
- The CRd regimen was well tolerated after an extended treatment period.
  - Generally, toxicities were of mild to moderate severity.
  - The most common hematologic adverse event was thrombocytopenia, and infection was the most common nonhematologic adverse event.
- The response rates achieved in this study compare favorably to those seen in previous studies (*Lancet Oncol* 2010;11:29).
- Other Phase II studies for patients with NDMM are ongoing (*Proc ASH* 2012;Abstract 732).
- The Phase III ASPIRE trial for patients with relapsed multiple myeloma has been initiated (NCT01080391).

Jakubowiak AJ et al. *Proc ASCO* 2013;Abstract 8543.

ASPIRE Phase III Trial Design

Estimated Enrollment: 780 (Closed)

Eligibility
Symptomatic, relapsed disease after 1 to 3 prior therapies No prior CFZ or intolerance to lenalidomide or dexamethasone



www.clinicaltrials.gov. Identifier NCT01080391, August 2013.

Investigator Commentary: Updated Results of the Phase I/II Trial of CRd for Patients with NDMM After Extended Follow-Up

The CRd regimen in this population of younger patients yielded a stringent complete response rate of 42% after 12 cycles and 55% after 22 cycles. This is certainly an improvement over cyclophosphamide-containing regimens or even the RVD regimen. The time-to-response results are interesting. I would stress that more time was required to achieve complete response and stringent complete response. One might consider that around 30% of patients will achieve stringent complete responses after 1 year of therapy.

The time-to-response curves demonstrate that stopping therapy after 4 to 6 months will result in about a 70% decrease in the complete response rate. This is a relevant message for a physician because it indicates that short-term treatment is not a good idea. With increased toxicity, treatment should be stopped or the dose reduced, but short flashes of treatment certainly reduce the opportunity to achieve good response rates that translate into long-term duration of remission.

Interview with Antonio Palumbo, MD, August 12, 2013

Final Results from the Phase Ib/II Study (PX-171-006) of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Patients with Relapsed or Progressive Multiple Myeloma

Wang M et al.

Proc ASCO 2013;Abstract 8529.

Niesvizky R et al.

Proc EHA 2013;Abstract S577.

Background

- Carfilzomib (CFZ) is a selective proteasome inhibitor that is FDA approved as a single agent in the treatment of patients with relapsed or refractory multiple myeloma (MM).
- Previously, data from the Phase Ib portion of the PX-171-006 trial of CFZ in combination with lenalidomide and low-dose dexamethasone (CRd) for relapsed or progressive MM were reported (*Clin Cancer Res* 2013;19:2248).
  - The maximum tolerated dose (MTD) was not reached.
  - The maximum planned dose (MPD) showed promising safety and efficacy and was recommended for the Phase II study.
- **Study objective:** To report the final efficacy and safety results from the Phase Ib/II PX-171-006 trial with particular attention to the MPD cohort.

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Phase Ib/II Trial Design

Eligibility (n = 84)

Relapsed or progressive MM
Symptomatic disease
1-3 prior regimens including bortezomib, lenalidomide and/or thalidomide
≥1 minimal response to prior therapy

→

CRd (n = 84)

CFZ: 15-27 mg/m^2 (IV), biweekly
Len: 10-25 mg (PO), days 1-21
Dex: 40 mg (PO), weekly
28-day cycle x ≤12

CFZ dosing was modified during cycles 13-18 (maintenance)

Len = lenalidomide; Dex = dexamethasone

- **Primary endpoints:** (Phase Ib) safety and determination of MTD or MPD
- **Secondary endpoints:** (Phase Ib/II) overall response rate (ORR), duration of response (DoR), progression-free survival (PFS)
- Response was assessed on day 15 of cycle 1 and on day 1 of subsequent cycles

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Study Cohorts

Cohort	CFZ	Len	Dex
1 (n = 6)	15 mg/m^2	10 mg	40 mg
2 (n = 6)	15 mg/m^2	15 mg	40 mg
3 (n = 8)	15 mg/m^2	20 mg	40 mg
4 (n = 6)	20 mg/m^2	20 mg	40 mg
5 (n = 6)	20 mg/m^2	25 mg	40 mg
6/7 (MPD, n = 52)	20/27 mg/m^{2*}	25 mg	40 mg

* CFZ: 20 mg/m^2, d1-2 during cycle 1; 27 mg/m^2 thereafter

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Best Response

Response	MPD cohort (n = 52)	Overall (n = 84)
ORR	76.9%	69.0%
Stringent CR	3.8%	3.6%
Complete response (CR)	1.9%	1.2%
Very good PR	36.5%	35.7%
Partial response (PR)	34.6%	28.6%
Minimal response	0%	6.0%

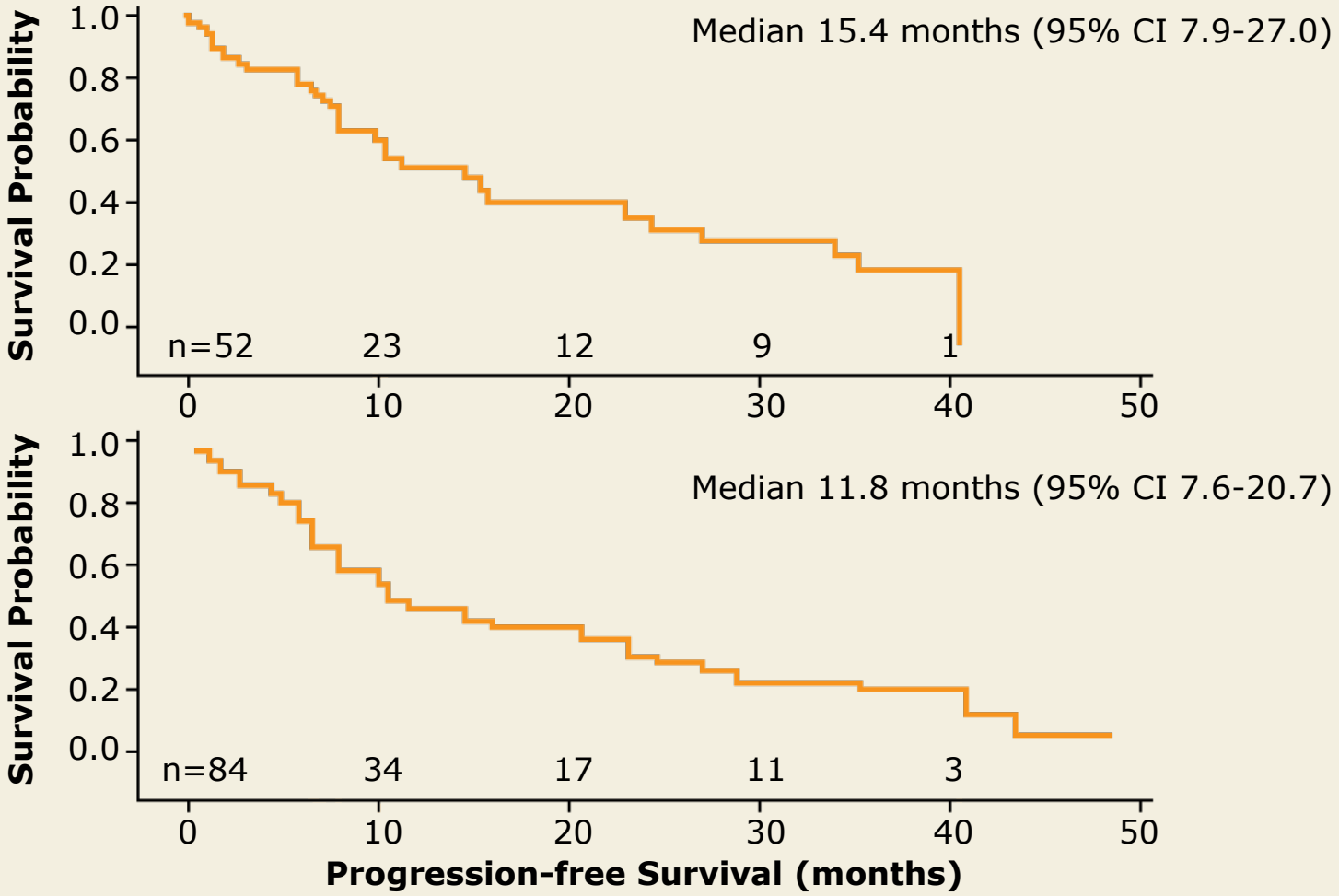
Median duration of response: 22.1 mo (MPD cohort), 18.8 mo (overall)
Median time to response ≥PR: 1.0 mo for both groups

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

PFS Outcomes

MPD Cohort (N=52)

Overall (N=84)



Wang M et al. *Proc ASCO* 2013;Abstract 8529; With permission from Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Efficacy Results by Patient Subgroup

Len naïve	**ORR**	**Median DoR**	**Median PFS**
MPD cohort (n = 14)	85.7%	Not reached	Not reached
Overall (n = 25)	80%	21.4 mo	28.7 mo
Len refractory	**ORR**	**Median DoR**	**Median PFS**
MPD cohort (n = 22)	68.2%	23.5 mo	9.9 mo
Overall (n = 29)	58.6%	13.8 mo	9.9 mo
Bortezomib refractory	**ORR**	**Median DoR**	**Median PFS**
MPD cohort (n = 14)	71.4%	18.5 mo	12.9 mo
Overall (n = 17)	58.8%	18.5 mo	9.9 mo

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Select Treatment-Emergent Adverse Events

Grade	MPD cohort (n = 52)		Overall (n = 84)	
	Any	3/4	Any	3/4
Fatigue	69.2%	11.5%	65.5%	7.1%
Diarrhea	57.7%	5.8%	56.0%	6.0%
Lymphopenia	40.4%	36.5%	33.3%	31.0%
Hypophosphatemia	38.5%	25.0%	28.6%	20.2%
Neutropenia	36.5%	30.8%	45.2%	36.9%
Anemia	32.7%	17.3%	38.1%	17.9%
Thrombocytopenia	30.8%	19.2%	34.5%	25.0%
Peripheral neuropathy	26.9%	1.9%	21.4%	1.2%
Hypokalemia	23.1%	7.7%	25.0%	8.3%
Pneumonia	17.3%	11.5%	16.7%	9.5%

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Author Conclusions

- The CRd regimen provided robust, rapid and durable responses in patients with relapsed or progressive MM.
  - This included 35% of patients in the overall population with lenalidomide-refractory MM.
  - Median PFS in the 30% of patients in the overall population with lenalidomide-naïve MM was 28.7 months.
  - Response rates and safety data in the MPD cohort compared favorably to the overall study population.
- CRd had an acceptable safety and tolerability profile with infrequent CFZ dose reductions (data not shown) and Grade 3 neuropathy and moderate discontinuation rates due to adverse events.
- Ongoing studies evaluating the CRd regimen include several Phase II trials in NDMM and the Phase III ASPIRE trial for patients with relapsed MM (NCT01080391).

Wang M et al. *Proc ASCO* 2013;Abstract 8529; Niesvizky R et al. *Proc EHA* 2013;Abstract S577.

Investigator Commentary: Final Results of the Phase Ib/II PX-171-006 Trial of CRd in Relapsed or Progressive MM

This important Phase Ib/II trial with 84 patients with relapsed/refractory MM has been presented before, and in fact it was the initial unpublished data from this study that gave us confidence to evaluate CRd in our up-front trial. However, the maximum planned dose of carfilzomib in this trial was 27 mg/m^2 and it was not escalated further, whereas in our trial our maximum planned dose was 36 mg/m^2 and we never reached MTD. This is important because the activity of carfilzomib is dose dependent. It is also clear that carfilzomib is more active in patients with less prior treatment. Currently I almost exclusively use carfilzomib in combination with other agents, both approved and as part of trials such as those combining it with HDAC inhibitors.

Interview with Andrzej J Jakubowiak, MD, PhD, August 28, 2013

Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma (MM) Patients: Initial Results of a Multicenter, Open Label Phase II Study

Bringhen S et al.

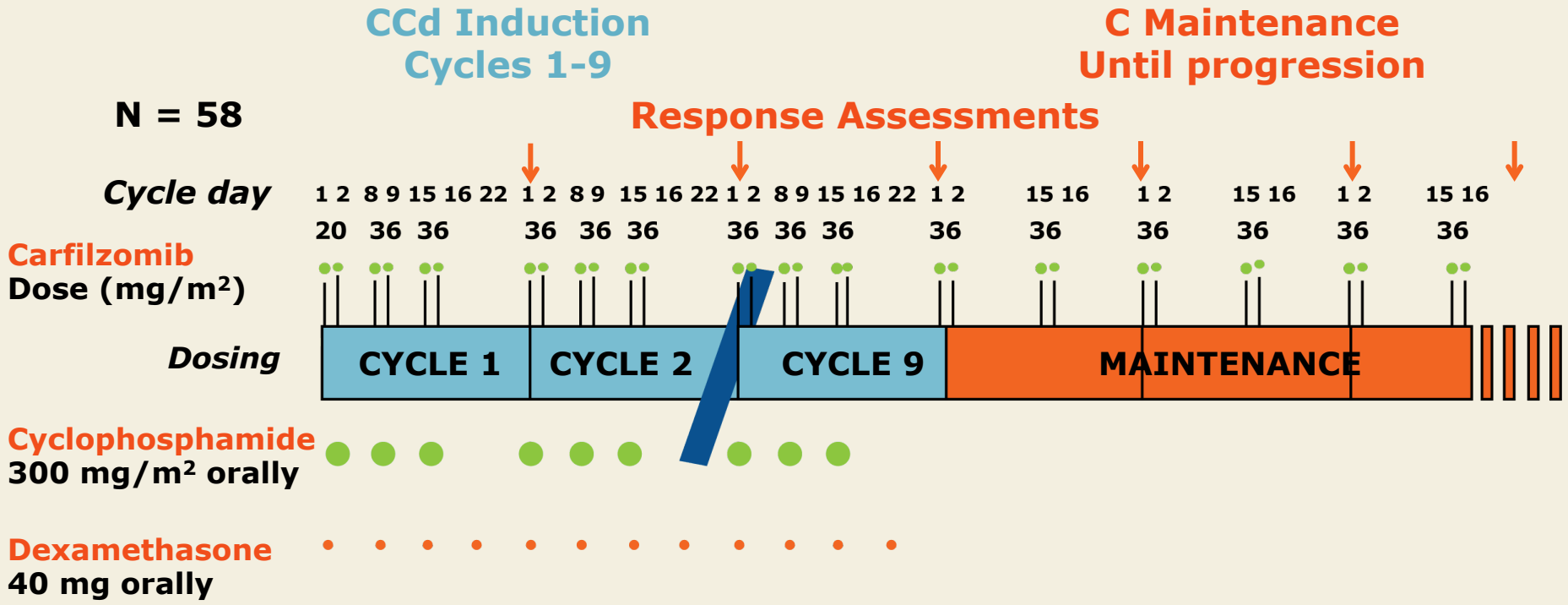
Proc EHA 2013;Abstract S578.

Background

- VMP and MPT, which are standard therapies for elderly patients with newly diagnosed multiple myeloma (NDMM), induce about a 30% near-complete response/complete response rate, with a 35% discontinuation rate due to adverse events.
- Carfilzomib, an irreversible proteasome inhibitor, has shown significant activity and favorable toxicity in MM.
- Preliminary results with a combination of carfilzomib with cyclophosphamide and dexamethasone (CCd) showed encouraging activity in elderly patients with NDMM (*Proc ASH* 2012;Abstract 730).
- **Study objective:** To present updated efficacy and safety results with the CCd regimen after 8 months of follow-up for patients with symptomatic NDMM who are ≥65 years old or ineligible for autologous stem cell transplantation.

Bringhen S et al. *Proc EHA* 2013;Abstract S578.

Phase II Study Design

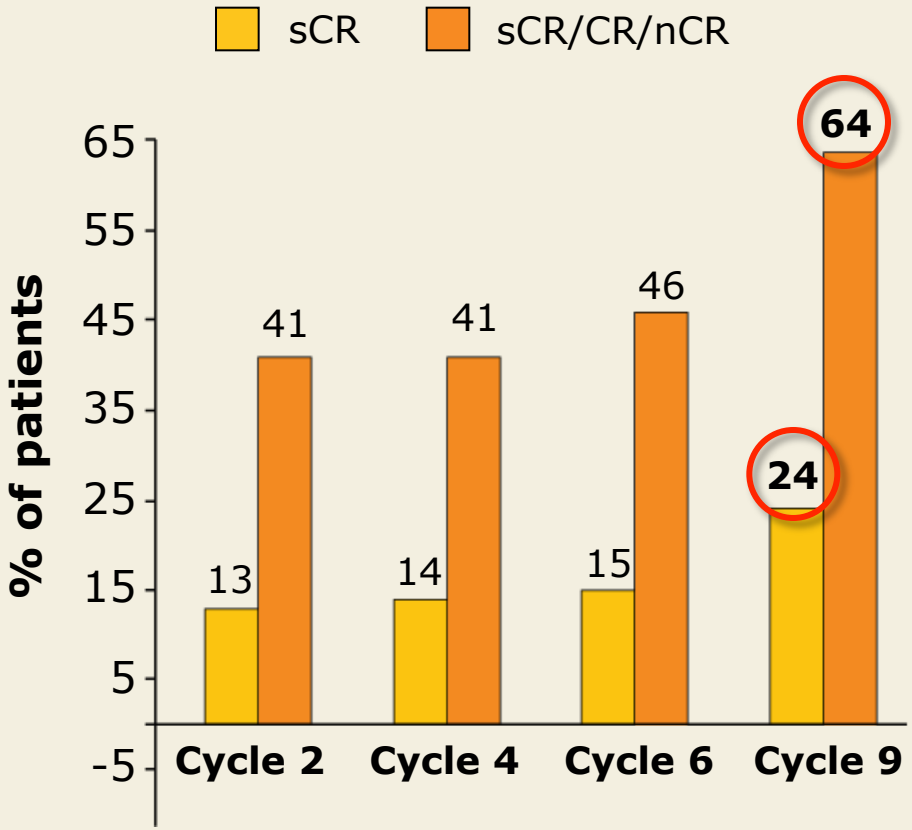


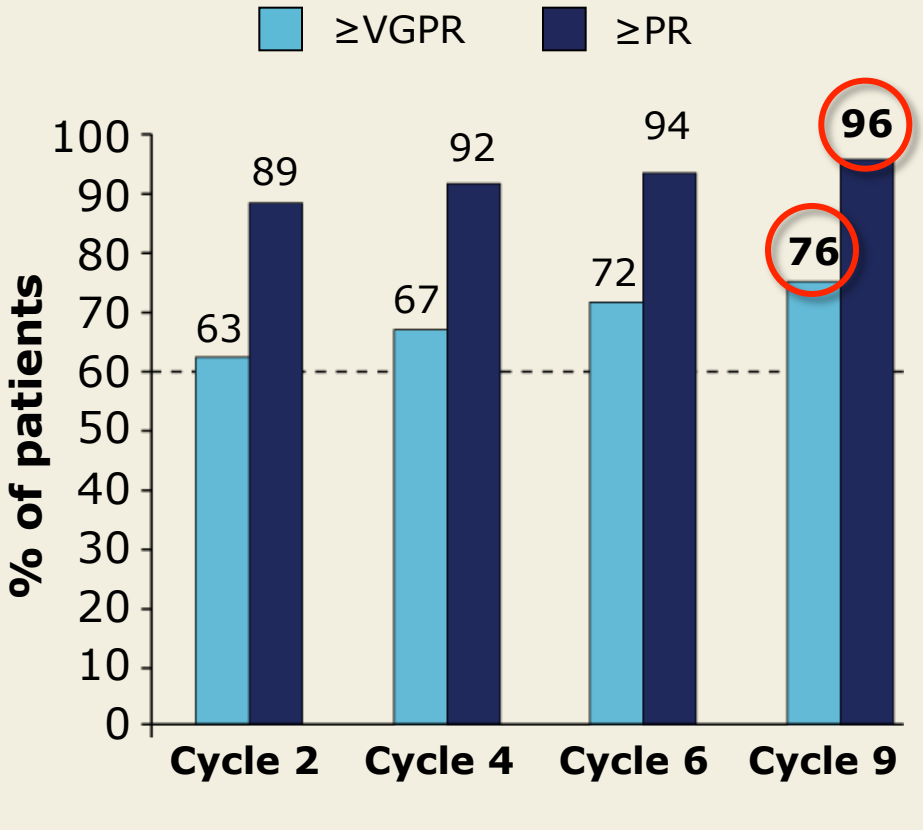
Primary objectives:

- Safety: Grade 4 neutropenia (>3 d), Grade 4 thrombocytopenia (>7 d), Grade ≥3 nonhematologic toxicity
- Efficacy: Partial response (PR)

Bringhen S et al. *Proc EHA* 2013;Abstract S578.

Response Rate by Treatment Duration





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

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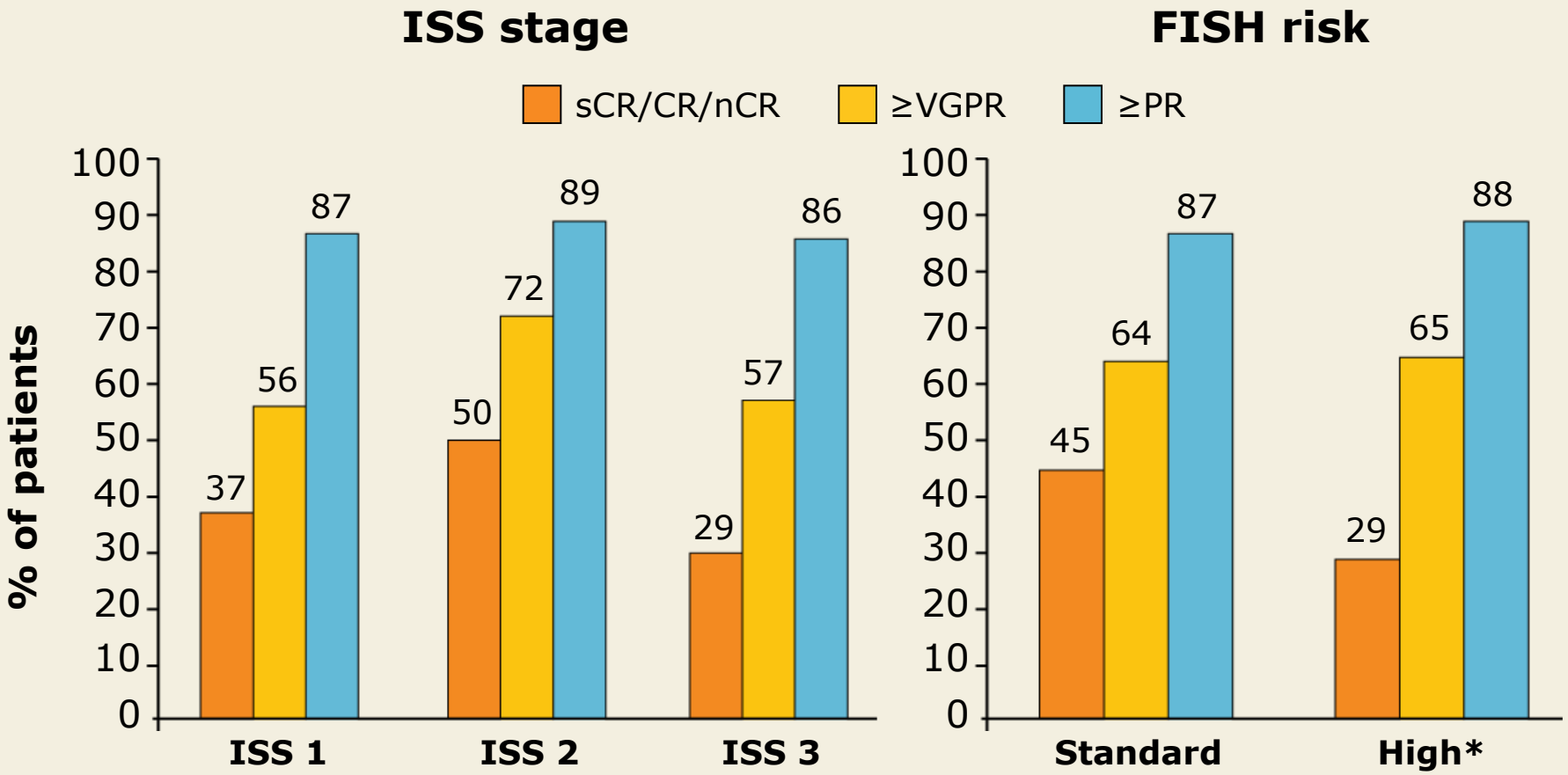
Subgroup Analysis of Best Response Rates



* Defined as presence of t(4;14) or t(14;16) or del17p

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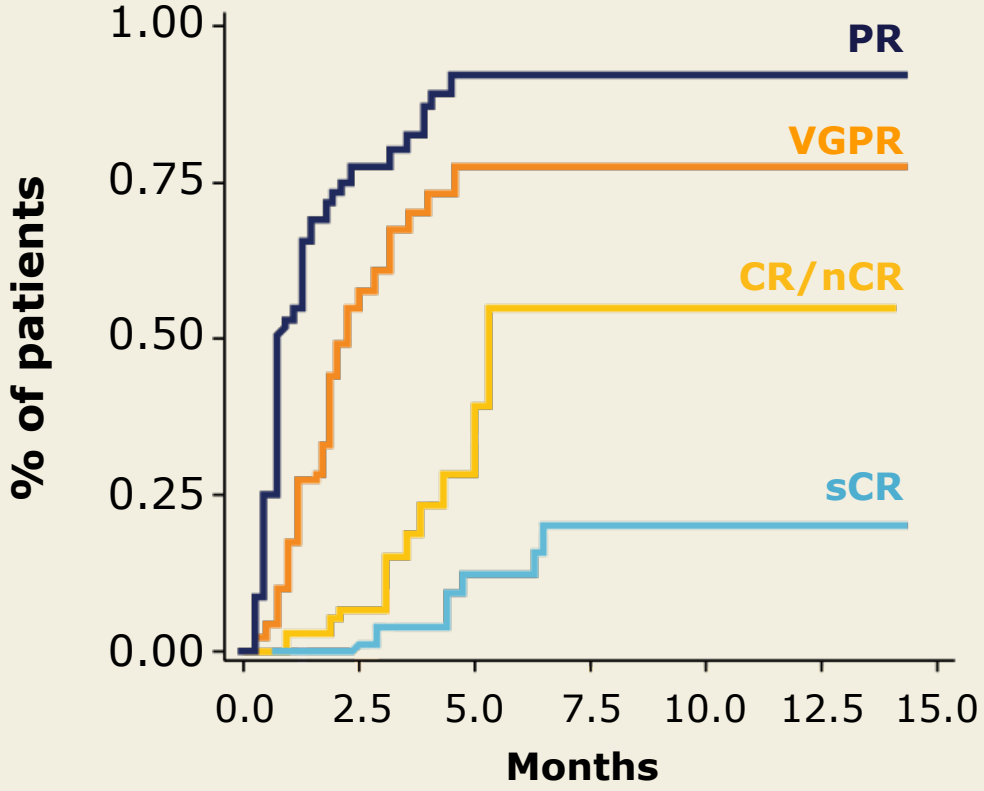
Time to Response

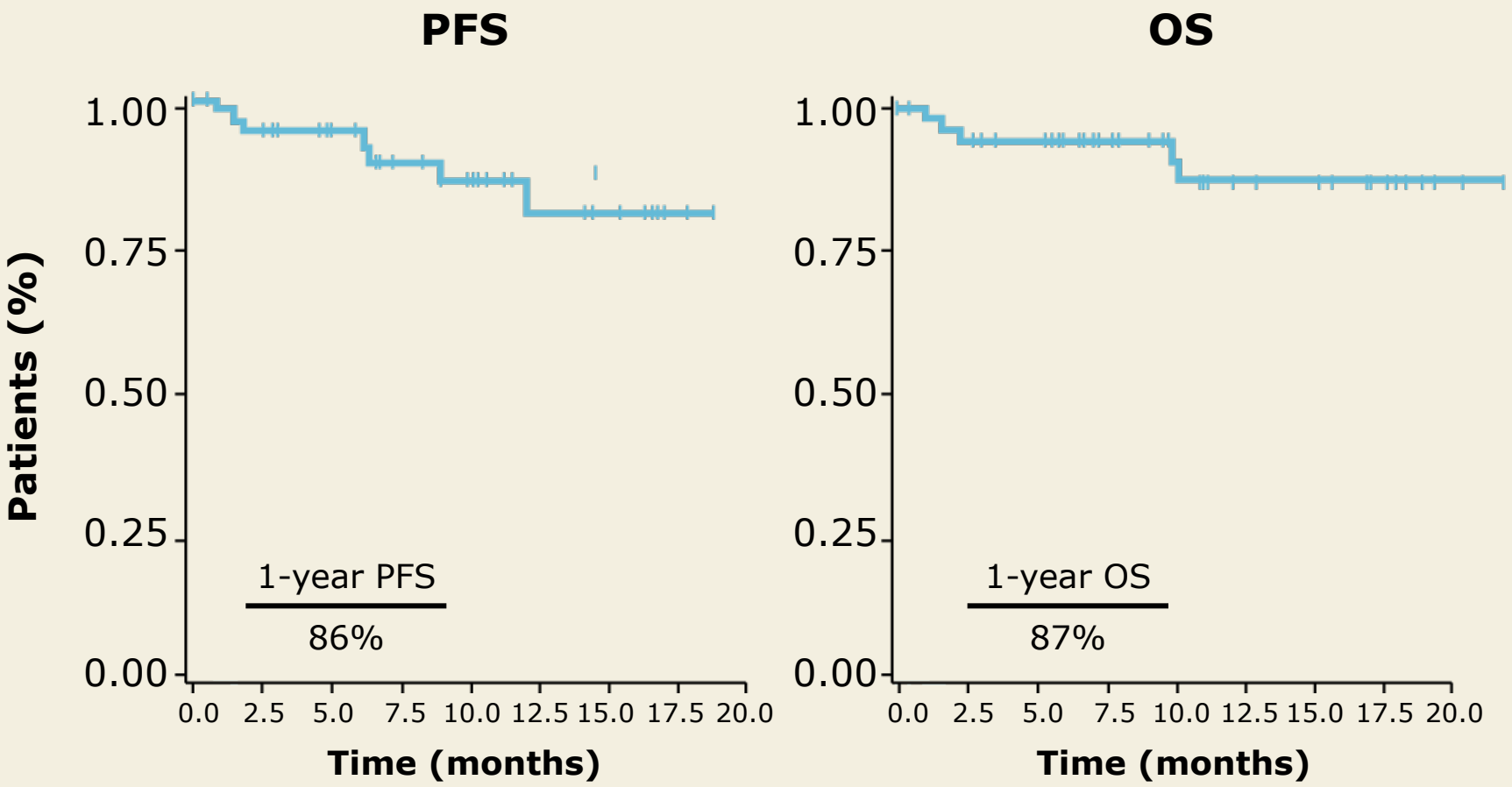
Median treatment duration, cycles (range): 8 (1-9)



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

With permission from Bringhen S et al. *Proc EHA* 2013;Abstract S578.

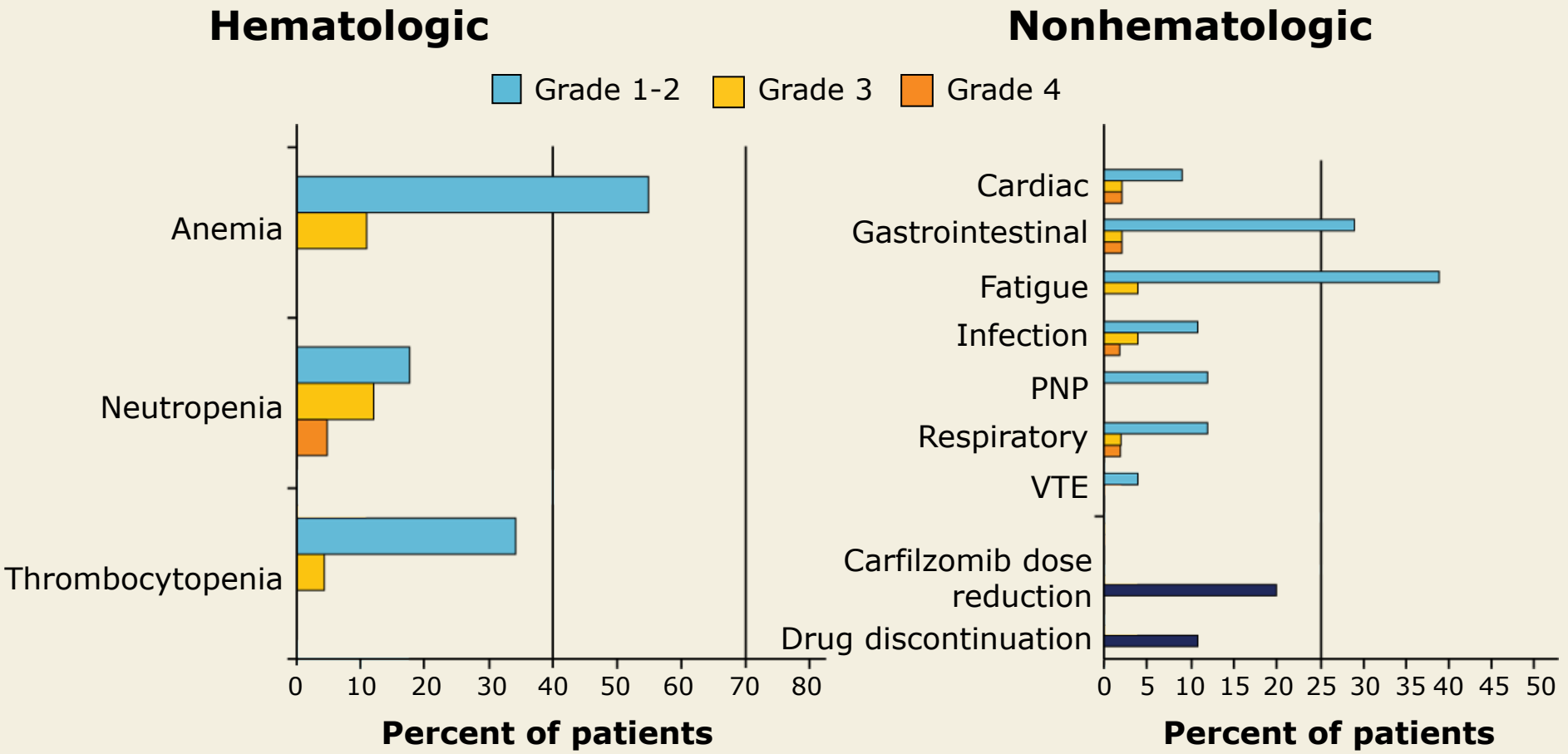
Progression-Free and Overall Survival



PFS = progression-free survival; OS = overall survival

With permission from Bringhen S et al. *Proc EHA* 2013;Abstract S578.

Adverse Events of All Grades



Grade 3-5 adverse events — Cardiac: Acute myocardial infarction, atrial fibrillation, heart failure, hypertension; gastrointestinal: Ileum perforation; infections: Pneumonia, bronchitis

With permission from Bringhen S et al. *Proc EHA* 2013;Abstract S578.

Author Conclusions

- CCd showed encouraging activity in elderly patients with NDMM in comparison to results with MPT and VMP from other studies.[1-3]
  - ≥VGPR: 76% vs 36% (MPT) or 41% (VMP)
  - nCR/CR/sCR: 64% vs 27% (MPT) or 30%* (VMP)
  - sCR: 24% (not reported for MPT or VMP)
- The CCd combination was well tolerated. Grade 3 or 4 adverse events included
  - Thrombocytopenia: 4% vs 3% (MPT) or 37% (VMP)
  - Peripheral neuropathy: 0% vs 6% (MPT) or 14% (VMP)
  - Venous thromboembolic events: 0% vs 9% (MPT) or 1% (VMP)
  - Treatment discontinuation: 11% vs 35% (MPT) or 33% (VMP)

* CR only, nCR not reported

[1] *Blood* 2011;118:1239; [2] *New Engl J Med* 2008;359:906; [3] *Lancet* 2006;367:825

Bringhen S et al. *Proc EHA* 2013;Abstract S578.

Investigator Commentary: Initial Results of the Phase II Study of CCd for Patients with NDMM

From this and several other studies, it is increasingly obvious that melphalan is much more toxic than dexamethasone and cyclophosphamide. Melphalan probably adds some benefit over cyclophosphamide and dexamethasone, but in continuous or maintenance therapy the advantages are limited and do not counterbalance the disadvantages of its toxicity. Cyclophosphamide is better tolerated than melphalan, including by patients older than 75 years.

More importantly, this study showed that it is possible to double the rate of CR or nCR with CCd (64%) in comparison to the VMP regimen (30%). Patients achieved a stringent CR of 24% with CCd. As other studies have demonstrated, carfilzomib is well tolerated. When it was used in doses up to 36 mg/m^2 in patients older than 75, no major side effects were observed.

Interview with Antonio Palumbo, MD, August 12, 2013

Effect of CMP, Carfilzomib (CFZ) plus Melphalan-Prednisone (MP), on Response Rates in Elderly Patients (pts) with Newly Diagnosed Multiple Myeloma (NDMM): Results of a Phase (Ph) I/II Trial[1]

CMP — Carfilzomib (CFZ) plus Melphalan-Prednisone (MP) — in Elderly Patients (pts) with Newly Diagnosed Multiple Myeloma (NDMM): Results of a Phase (Ph) I/II Trial[2]

[1] **Touzeau C et al.**
Proc ASCO 2013;Abstract 8513.

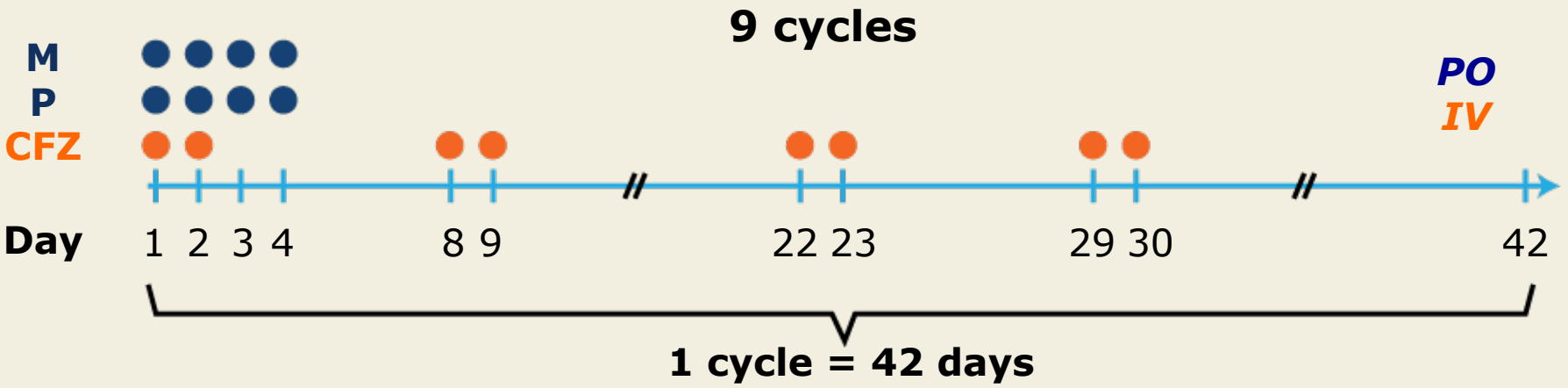
[2] **Moreau P et al.**
Proc EHA 2013;Abstract P224.

Background

- MP in combination with bortezomib (VMP) and with thalidomide (MPT) have shown benefits in progression-free and overall survival for patients with NDMM who are ineligible for stem cell transplantation.
- However, VMP and MPT are associated with significant peripheral neuropathy (*NEJM* 2008;359(9):906; *Hematology Am Soc Hematol Educ Program* 2009:566).
- CFZ is a novel proteasome inhibitor with demonstrated activity in relapsed or refractory multiple myeloma and low rates of peripheral neuropathy.
- **Study objective:** To determine the maximum tolerated dose (MTD) as well as the efficacy and safety of carfilzomib combined with MP (CMP) in elderly patients (>65 years) with NDMM.

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Study Design



- Melphalan (oral): d1 to d4: 9 mg/m²/d
- Prednisone (oral): d1 to d4: 60 mg/m²/d
- Carfilzomib (30 min IV)

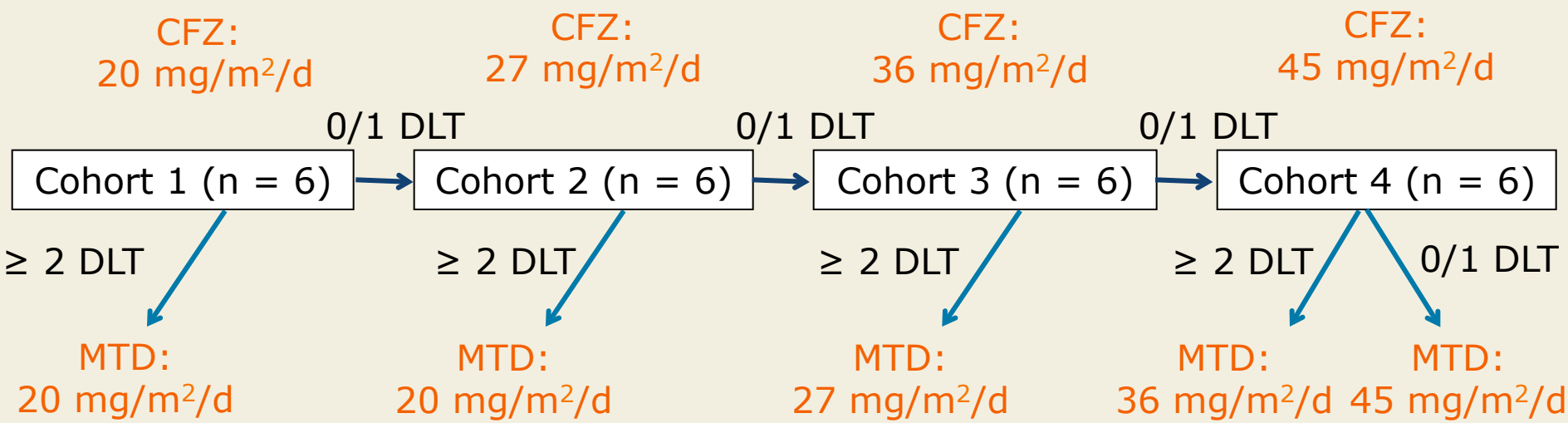
Day 1 → **d1-2: 20 mg/m²/d**
→ **d8-9, 22-23, 29-30**

Cycles 2 to 9 → **d1-2, 8-9, 22-23 29-30**

20 or 27 or 36 or 45 mg/m²/d
(cohort 1, 2, 3 or 4)

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

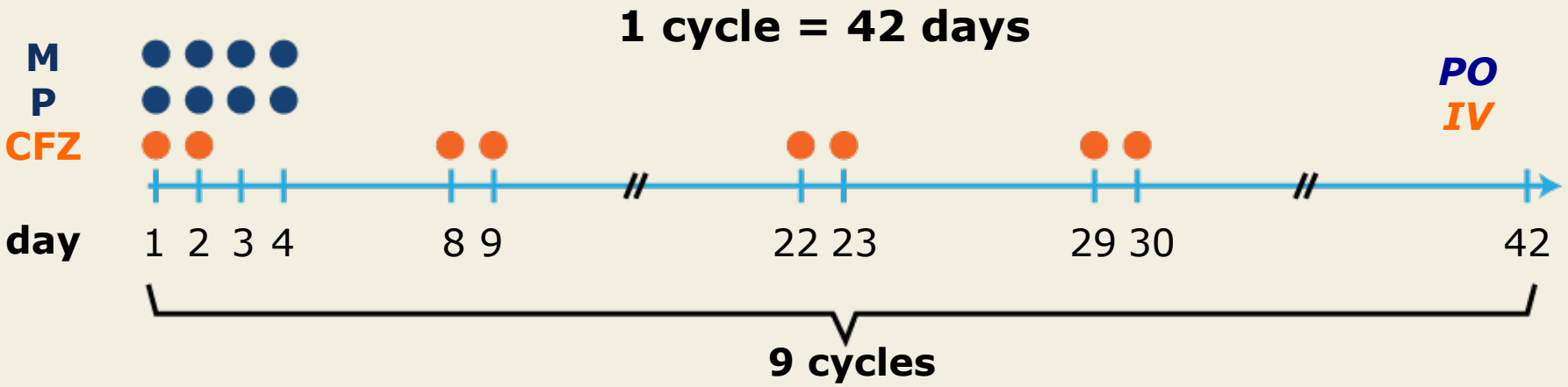
Phase I Design to Define MTD by Dose-Limiting Toxicity (DLT)



- Cohorts 1, 2 and 3: 1 DLT occurred in each cohort
- Cohort 4: 2 DLTs occurred
- MTD for CFZ defined at 36 mg/m²/d

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Phase II Trial Design (N = 44)



M: 9 mg/m^2 (PO), d1-4; P: 60 mg/m^2 (PO), d1-4

CFZ: 36 mg/m^2 (IV), d1-2, 8-9, 22-23, 29-30

- Patients enrolled in Phase I and Phase II of the trials were included in efficacy and safety analyses.

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Patient Characteristics (Phase I and II Patients)

Characteristic	Patients (n = 68)
Median age (range)	72 y (61-86)
Male/female, %	51/49
ISS	
1	34%
2	30%
3	36%
t(4;14) or t(14;16) or 17p del	17%

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Best Responses

Response rate	Patients (n = 66)
Overall response rate (ORR)	91%
Complete response	6%
Very good partial response	50%
Partial response	35%
Stable disease	9%
Progressive disease	0%

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Survival Outcomes

Outcome	N = 68
Median PFS	22 months
OS rate	87%

PFS = progression-free survival; OS = overall survival

- Median follow-up = 12 months
- Eight deaths due to:
  - Progression (n = 3)
  - Infection (n = 3)
  - Congestive heart failure (n = 2)

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Adverse Events (AEs)

AEs (n = 68)	All grades	Grade 3/4
Anemia	54%	21%
Thrombocytopenia	35%	7%
Neutropenia	35%	22%
Deep vein thrombosis	7%	1.5%
Congestive heart failure	6%	4.5%
Peripheral neuropathy*	23.5%	1.5%
Nausea	31%	4.5%
Infection	52%	9%
Elevated liver enzymes	29%	4.5%

* Grade 1 (19%); Grade 2 (4.5%); Grade 3 (1.5%); Grade 4 (0%)

Eight patients discontinued CMP due to AEs.

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Author Conclusions

- CFZ at 36 mg/m^2 in combination with MP is manageable with a few neurotoxic effects observed.
- The study demonstrated an ORR of 91%.
  - ≥Very good partial response rate: 56%
- The response rates compared favorably to those in other studies of front-line therapeutic combinations for patients >65 years old:
  - ORR for VMP: 71% (*NEJM* 2008;359:906)
  - ORR for MPT: 76% (*Lancet* 2007;370:1209)
  - ORR for MPR: 80% (*JCO* 2007;25:4459)
  - ORR for lenalidomide/dexamethasone: 76% (*Lancet Oncol* 2010;11:29)
- The median PFS was promising at 22 months.
- The study is ongoing as a longer follow-up period is needed.

Touzeau C et al. *Proc ASCO* 2013;Abstract 8513; Moreau P et al. *Proc EHA* 2013;Abstract P224.

Investigator Commentary: Phase I/II Trial of Carfilzomib with Melphalan/Prednisone for Elderly Patients with NDMM

This Phase I/II trial of carfilzomib/melphalan/prednisone (CMP) clearly demonstrated that carfilzomib is well tolerated even at a dose of 36 mg/m^2 in elderly patient populations with a median age of 72. In comparison to bortezomib-containing regimens, CMP was associated with limited rates of Grade 3 and 4 peripheral neuropathy, dermatologic toxicity, thrombocytopenia and neutropenia. This makes carfilzomib one of the most interesting agents to use in combination with alkylating agents such as melphalan/prednisone.

Interview with Antonio Palumbo, MD, August 12, 2013

Efficacy, Safety, and QoL in MM-003, a Phase 3, Multicenter, Randomized, Open-Label Study of Pomalidomide (POM) + Low-Dose Dexamethasone (LoDEX) vs High-Dose Dexamethasone (HiDEX) in RRMM[1]

MM-003: A Phase III, Multicenter, Randomized, Open-Label Study of Pomalidomide (POM) plus Low-Dose Dexamethasone (LoDEX) versus High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM)[2]

San Miguel JF et al.

[1] *Proc EHA* 2013;Abstract S1151.

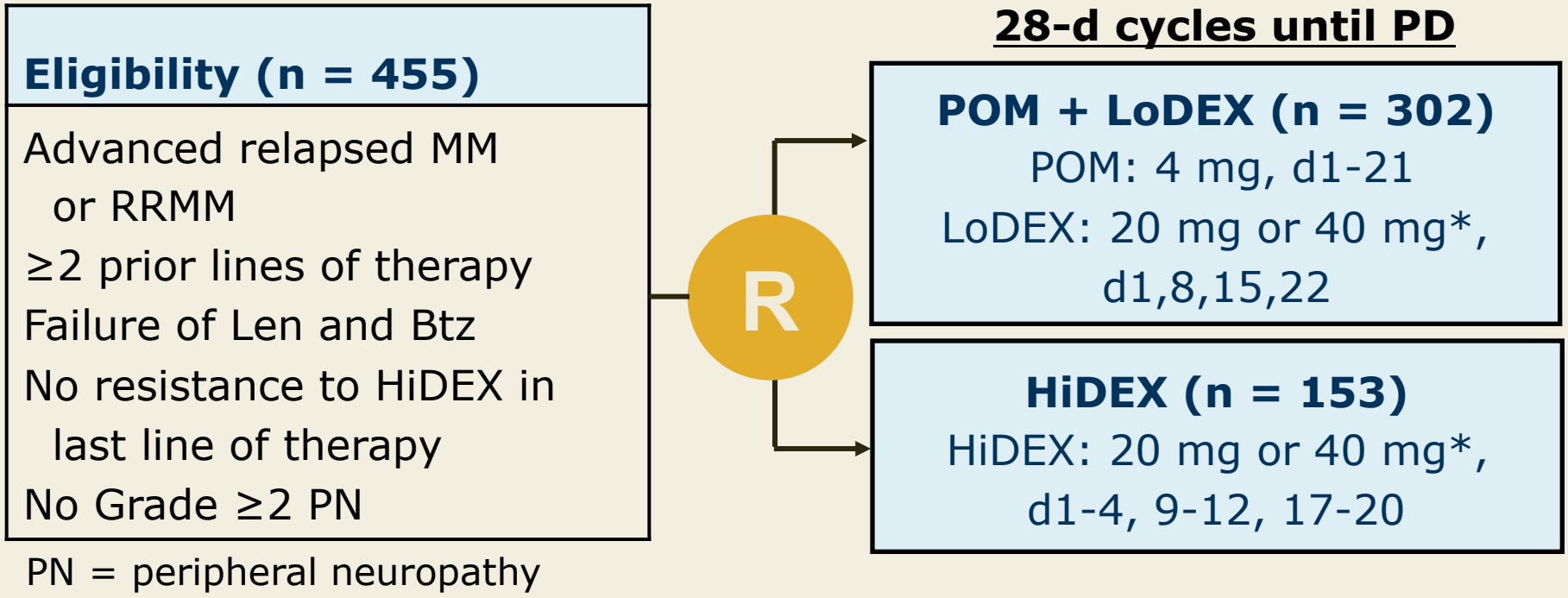
[2] *Proc ASCO* 2013;Abstract 8510.

Background

- Patients with RRMM with disease progression after treatment with bortezomib (Btz) and lenalidomide (Len) or thalidomide have a poor prognosis with a short overall survival (OS) and reduced quality of life.
- HiDEX is an established treatment for RRMM.
- POM demonstrated efficacy in patients with RRMM after Len and/or Btz therapy (*Blood* 2013;121:1968).
- Recently, pomalidomide (POM) was FDA approved for the treatment of MM in patients who have received ≥2 prior therapies, including Len and Btz, and have experienced disease progression within 60 days of their last therapy.
- **Study objective:** To determine the efficacy and safety of POM + LoDEX versus HiDEX in advanced RRMM.

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Phase III MM-003 Trial Design



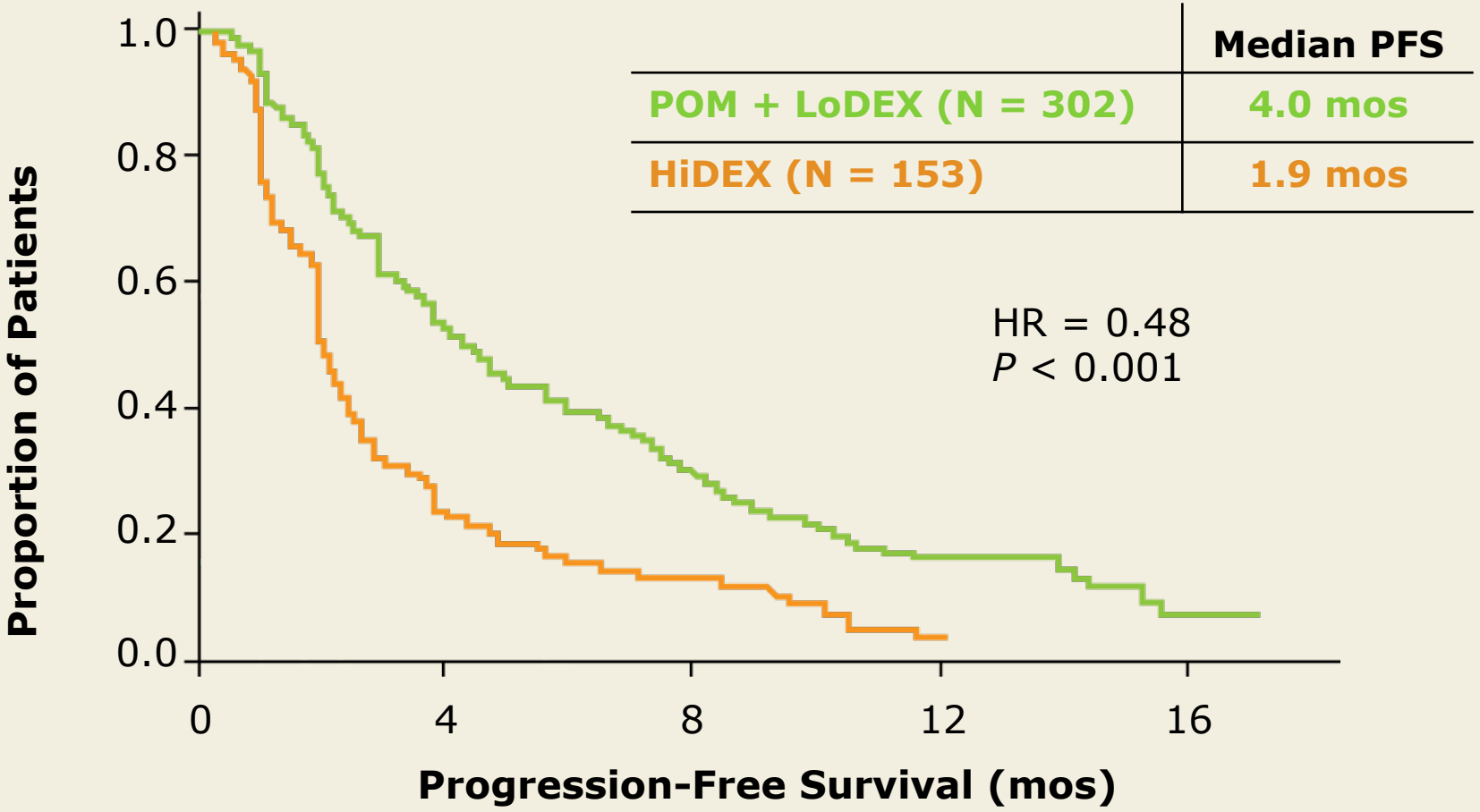
PN = peripheral neuropathy

* LoDEX or HiDEX: 20 mg (>75 years) or 40 mg (≤75 years)

- Thromboprophylaxis with lose-dose aspirin, low-molecular-weight heparin or equivalent was required for all patients receiving POM and those at high risk of thromboembolic events
- **Primary endpoint:** Progression-free survival (PFS)

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

PFS — Intention-to-Treat (ITT) Population (Median Follow-Up: 10 Months)

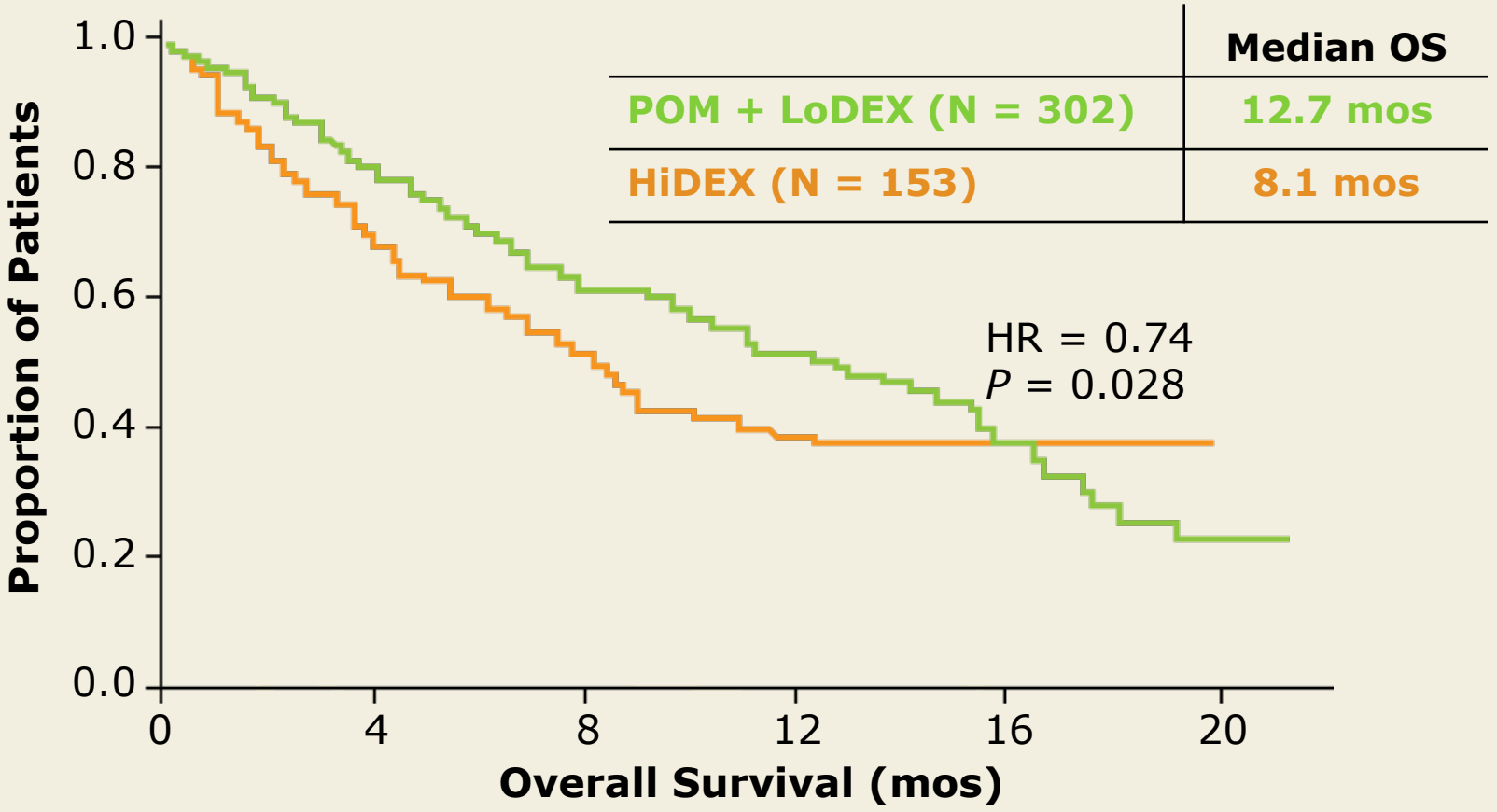


	Median PFS
POM + LoDEX (N = 302)	4.0 mos
HiDEX (N = 153)	1.9 mos

HR = 0.48
P < 0.001

With permission from San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

OS — ITT Population (Median Follow-Up: 10 Months)



- Nearly 50% of patients (n = 76) on the HiDEX arm received POM

With permission from San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Subgroup Analyses of PFS and OS

Subgroup (POM + LoDEX vs HiDEX)	HR	
	PFS	OS
ITT population (n = 302, 153)	0.48	0.74
Len and Btz refractory (n = 225, 113)	0.52	0.77
Len as last prior Tx (n = 85, 49)	0.38	0.53
Btz as last prior Tx (n = 132, 66)	0.52	0.87

- HR <1.0 favors POM + LoDEX

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Response Rates: ITT Population

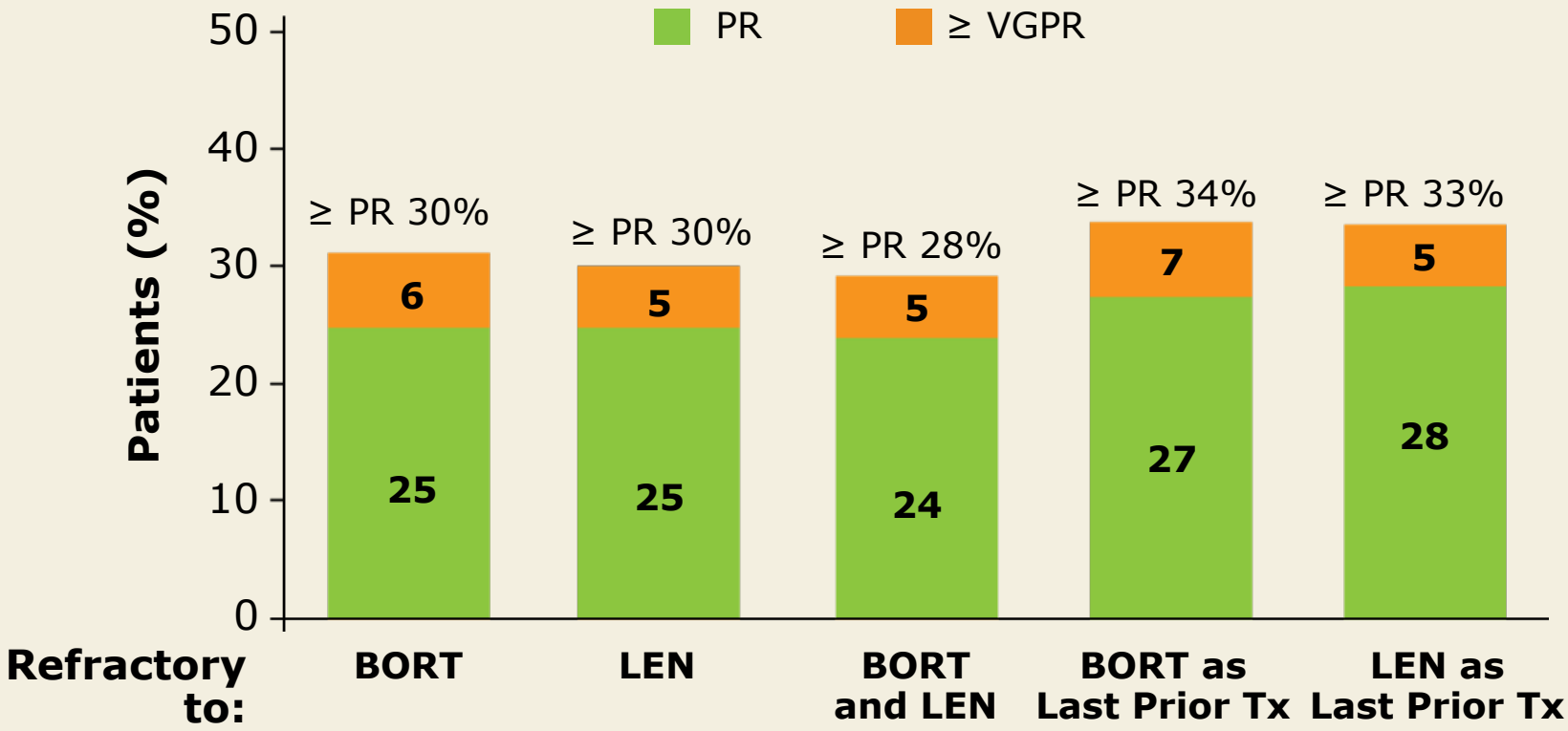
Response	POM + LoDEX (n = 302)	HiDEX (n = 153)	*p*-value
ORR	31%	10%	<0.001
≥VGPR	6%	1%	—
sCR/CR	1%	0%	—
≥MR	39%	16%	—
≥SD	82%	61%	—

ORR = overall response rate; VGPR = very good partial response; CR = complete response; sCR = stringent CR; MR = minimal response; SD = stable disease

- PFS of ≥MR with POM + LoDEX: 8 months

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Response Rates by Last Prior Therapy for Patients in the POM + LoDEX Arm



- Response rate was consistent among all subgroups, including patients who received Len or Btz as last prior therapy.

With permission from San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

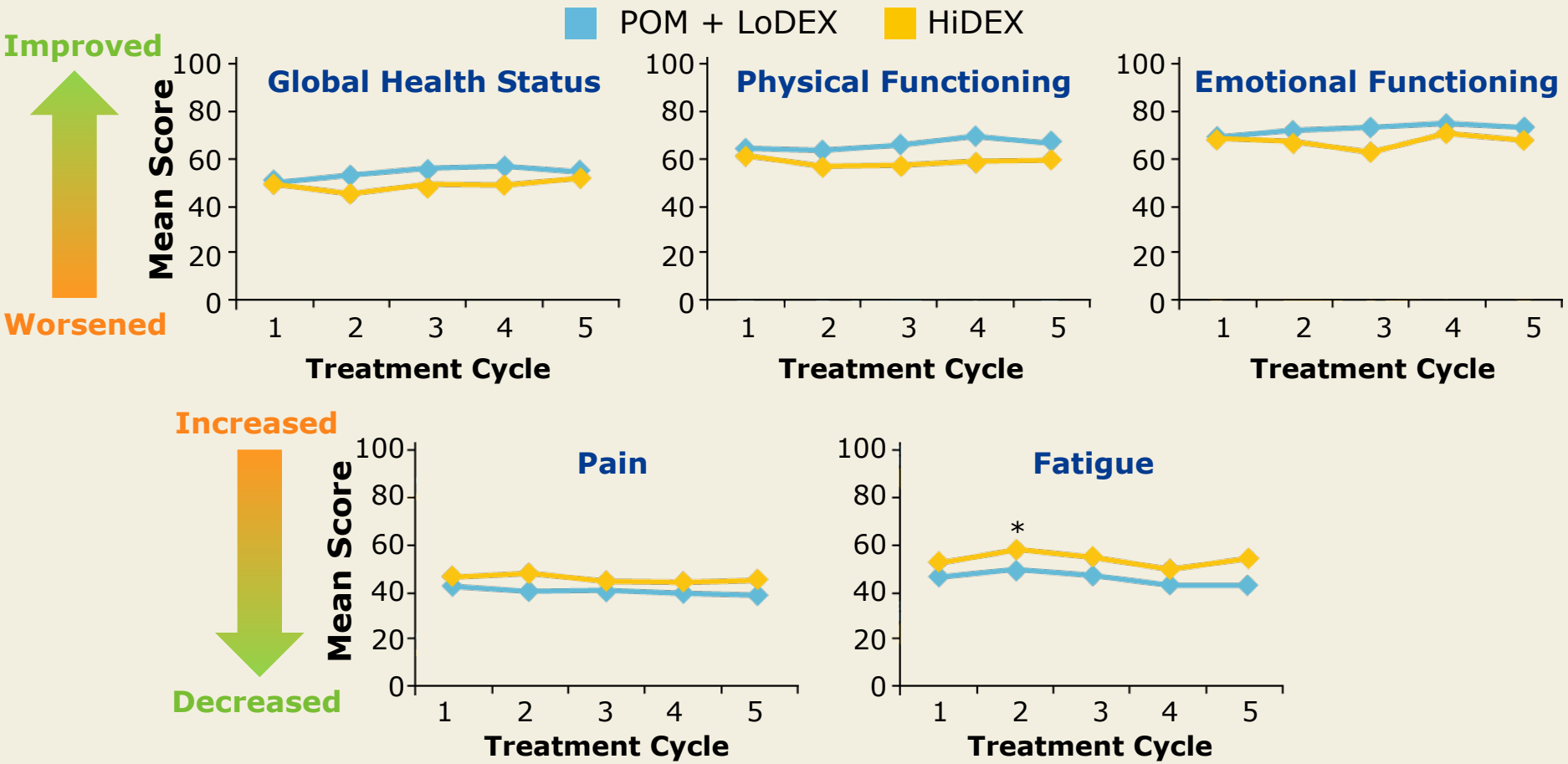
Grade 3 or 4 Adverse Events

Event	POM + LoDEX (n = 300)	HiDEX (n = 150)
Neutropenia Febrile neutropenia	48% 9%	16% 0%
Anemia	33%	37%
Thrombocytopenia	22%	26%
Infections Pneumonia	30% 13%	24% 8%
Bone pain	7%	5%
DVT/PE	1%	0%
Peripheral neuropathy	1%	1%

DVT/PE = deep vein thrombosis/pulmonary embolism

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Health-Related Quality of Life (HRQoL): Changes Over Time



POM + LoDEX consistently improved HRQoL measurements vs HiDEX
Improved in physical functioning and decreased pain and fatigue

* $P < .05$

With permission from San Miguel JF et al. *Proc EHA* 2013;Abstract S1151.

Author Conclusions

- Updated analyses reconfirm the advantage of POM + LoDEX compared to HiDEX despite 50% of patients in the HiDEX arm receiving subsequent POM.
- POM + LoDEX significantly improved PFS and OS compared to HiDEX.
- The benefit of POM + LoDEX was maintained regardless of refractoriness to Btz and Len, even as last prior treatment.
- The safety profile of POM + LoDEX is predictable and manageable. POM + LoDEX is generally well tolerated in patients with heavily pretreated RRMM.
- POM + LoDEX consistently improved HRQoL versus HiDEX for patients with heavily pretreated RRMM who had fully benefited from Btz and Len.
- In light of the OS advantage, POM + LoDEX, an oral treatment option, should be considered a new standard approach for patients with RRMM.

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151*; Proc ASCO* 2013;Abstract 8510.

Investigator Commentary: Phase III MM-003 Study of POM + LoDEX versus HiDEX for Patients with Advanced RRMM

POM is an excellent way to continue therapy with an immunomodulatory agent after Len. Therapy for patients who have developed Len-refractory disease should be switched to POM. This may represent an extension phase, maintaining disease remission for 30% to 50% of patients.

POM should not be administered at the end stage of myeloma treatment because it is less effective then. For end-stage MM, POM yielded a median PFS of 4 months versus 2 months with HiDEX in the Phase III MM-003 study. I am sure that if POM had been used immediately after Len, after first relapse, the median PFS might have been prolonged to 6 or 8 months. Additionally, the study resulted in a median OS of about 13 months with POM versus 8 months with HiDEX. The combination of POM with LoDEX improved the quality of life for patients with relapsed or refractory MM.

Interview with Antonio Palumbo, MD, August 12, 2013

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): MM-003 Analysis of Patients (pts) with Moderate Renal Impairment (RI)[1]

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): Impact of Cytogenetics in MM-003[2]

[1] **Weisel KC et al.**

Proc ASCO 2013;Abstract 8527.

[2] **Goldschmidt H et al.**

Proc ASCO 2013;Abstract 8528.

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): MM-003 Analysis of Patients (pts) with Moderate Renal Impairment (RI)

Weisel KC et al.

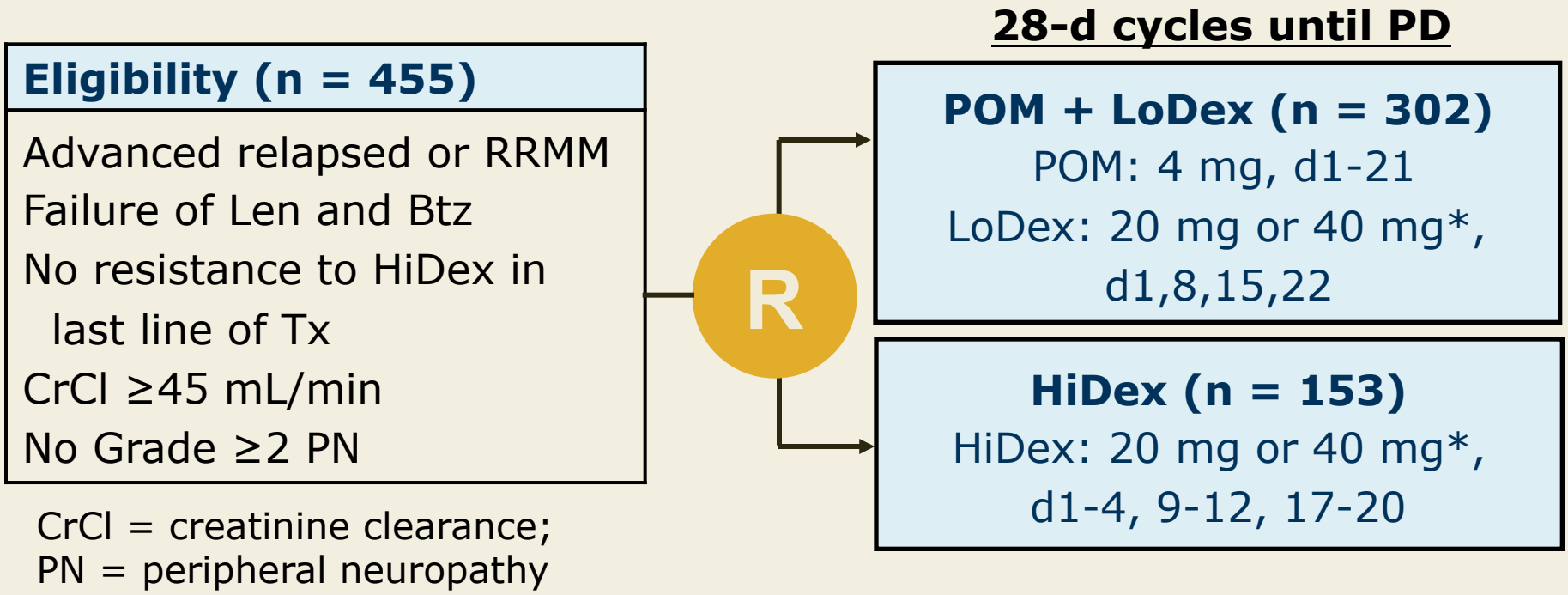
Proc ASCO 2013;Abstract 8527.

Background

- Patients with multiple myeloma (MM) that is refractory to lenalidomide (Len) and bortezomib (Btz) have a poor prognosis.
- In addition, renal impairment (RI), which is experienced by 20% of patients with MM at diagnosis, is associated with poor outcomes (*JCO* 2005;23:9219).
- Pomalidomide (POM) in combination with LoDex is effective against RRMM previously treated with Btz and Len, including in patients with RI (*Proc ASH* 2012;Abstract 4072).
- Recently, POM was FDA approved for the treatment of MM after ≥2 prior therapies, including Len and Btz.
- **Study objective:** To determine the efficacy and safety of POM + LoDex versus HiDex for patients with advanced RRMM with or without moderate RI.

Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Phase III MM-003 Trial Design



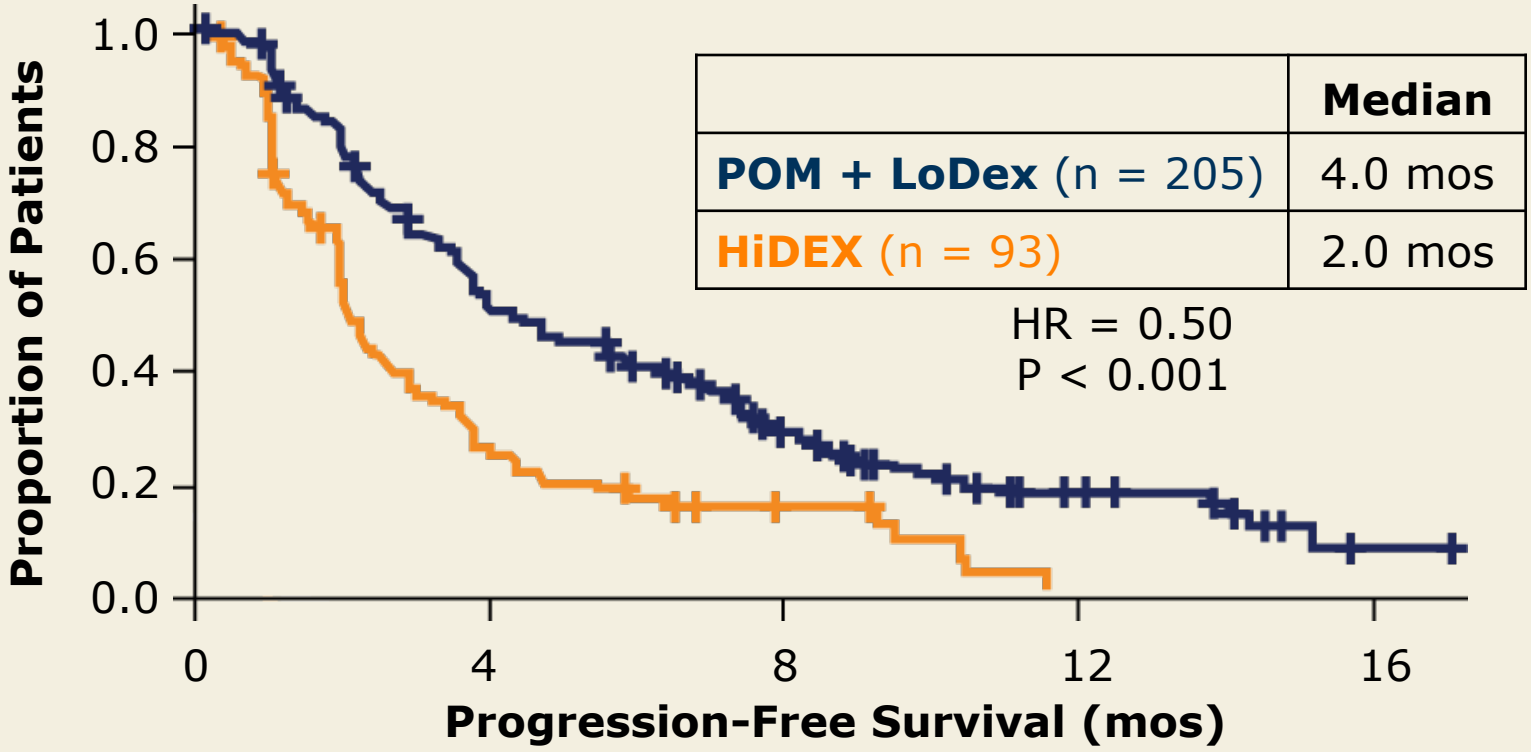
CrCl = creatinine clearance;
PN = peripheral neuropathy

* LoDex or HiDex: 20 mg (>75 years) or 40 mg (≤75 years)

- The study arms were evaluated with regard to patients with or without moderate RI (baseline CrCl <60 mL/min versus ≥60 mL/min)
- **Primary endpoint:** Progression-free survival (PFS)

Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

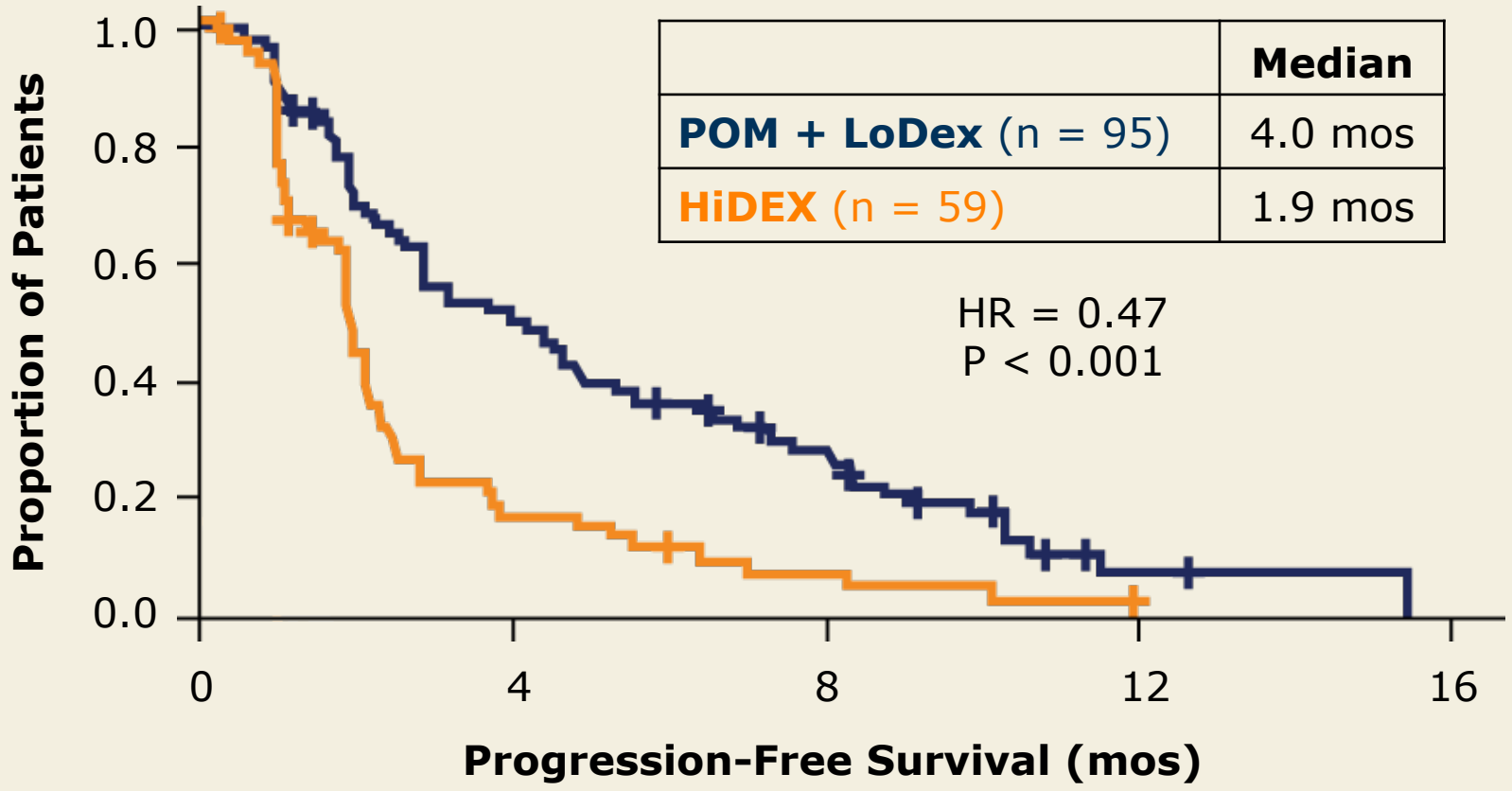
PFS for Patients without RI (CrCl ≥60 mL/min)



- Patients with baseline CrCl ≥60 mL/min were more likely to be younger, male and with better performance status than those with baseline CrCl <60 mL/min.
- 55% of patients on the HiDex arm subsequently received POM.

With permission from Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

PFS for Patients with Moderate RI (CrCl <60 mL/min)

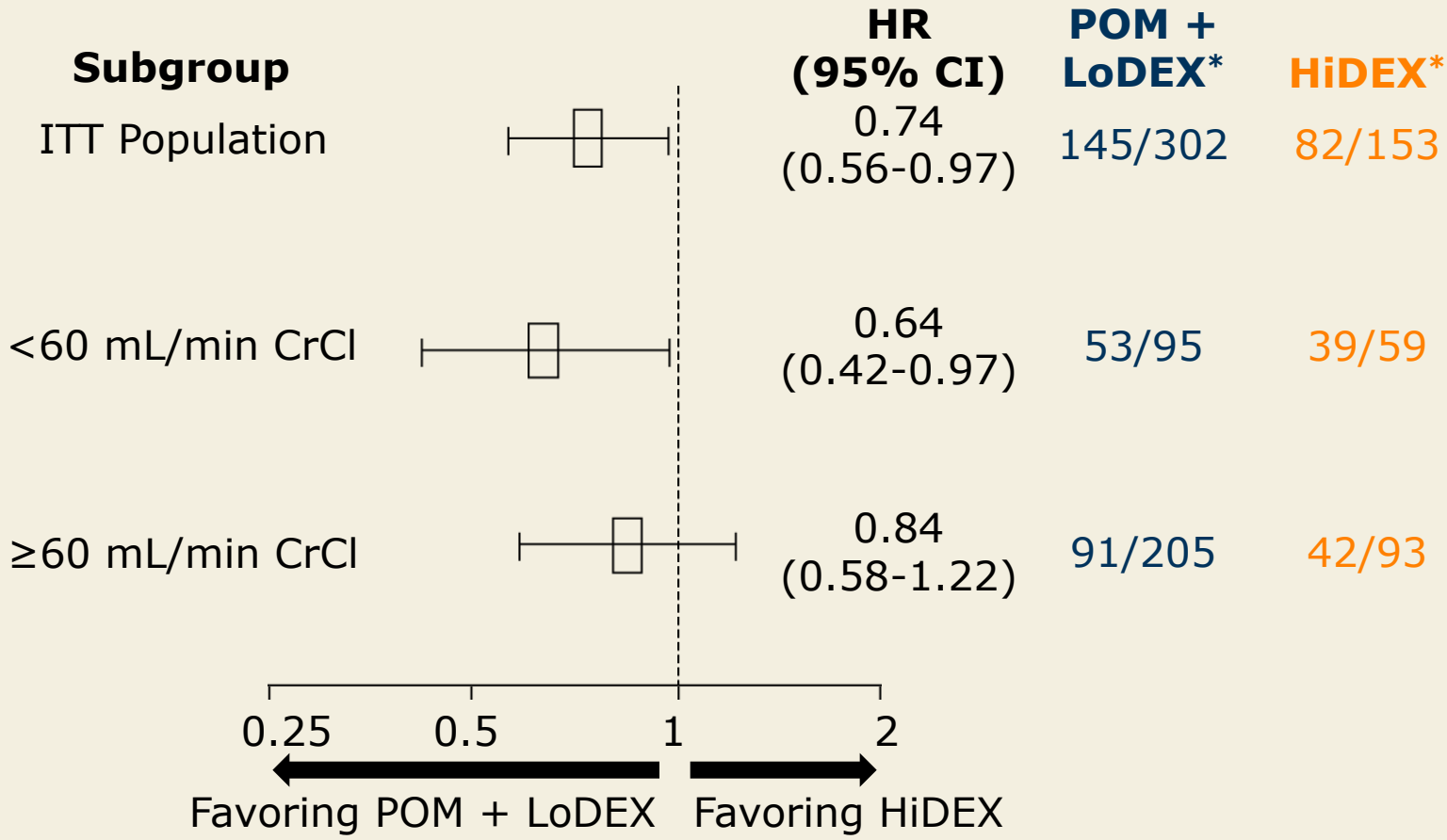


- 42% of patients on the HiDex arm subsequently received POM.

With permission from Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Overall Survival (OS) by Baseline Renal Function

HR by Subgroup



* Number of events/number of patients

With permission from Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Response Rates by Baseline Renal Function

Response	CrCl <60 mL/min		CrCl ≥60 mL/min	
	POM + LoDex (n = 95)	HiDex (n = 59)	POM + LoDex (n = 205)	HiDex (n = 93)
ORR (≥PR)	28%	8%	33%	11%
≥MR	36%	12%	41%	17%

ORR = overall response rate; PR = partial response; MR = minimal response

- Regardless of baseline renal function, ORR was significantly improved with POM + LoDex versus HiDex ($p < 0.001$)

Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Grade 3/4 Adverse Events in ≥10% of Patients

Event	CrCl <60 mL/min		CrCl ≥60 mL/min	
	POM + LoDex (n = 95)	HiDex (n = 59)	POM + LoDex (n = 203)	HiDex (n = 90)
Neutropenia	48%	19%	48%	14%
FN	5%	0%	11%	0%
Anemia	39%	42%	30%	32%
Thrombocytopenia	20%	36%	23%	20%
Infections	33%	25%	30%	23%
DVT/PE	0%	0%	2%	0%
PN	1%	2%	2%	1%
Discontinuations	12%	10%	7%	10%

FN = febrile neutropenia; DVT/PE = deep vein thrombosis/pulmonary embolism

Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Author Conclusions

- This study demonstrates that poor renal function (baseline CrCl <60 mL/min but ≥45 mL/min) does not affect the efficacy and safety of POM + LoDex in RRMM.
- Similar to the overall study population, POM + LoDex extended PFS compared to HiDex for patients with RRMM in both renal function subgroups.
- POM + LoDex improved OS in the ITT population and in patients with moderate RI.
  - ORR was similar between renal subgroups
- The tolerability of POM + LoDex was acceptable and comparable across subgroups, with few discontinuations due to adverse events.
- Prescribing information for POM will be updated with dose recommendations for patients with RI after the completion of the ongoing MM-008 trial.

Weisel KC et al. *Proc ASCO* 2013;Abstract 8527.

Pomalidomide + Low-Dose Dexamethasone (POM + LoDex) vs High-Dose Dexamethasone (HiDex) in Relapsed/Refractory Multiple Myeloma (RRMM): Impact of Cytogenetics in MM-003

Goldschmidt H et al.

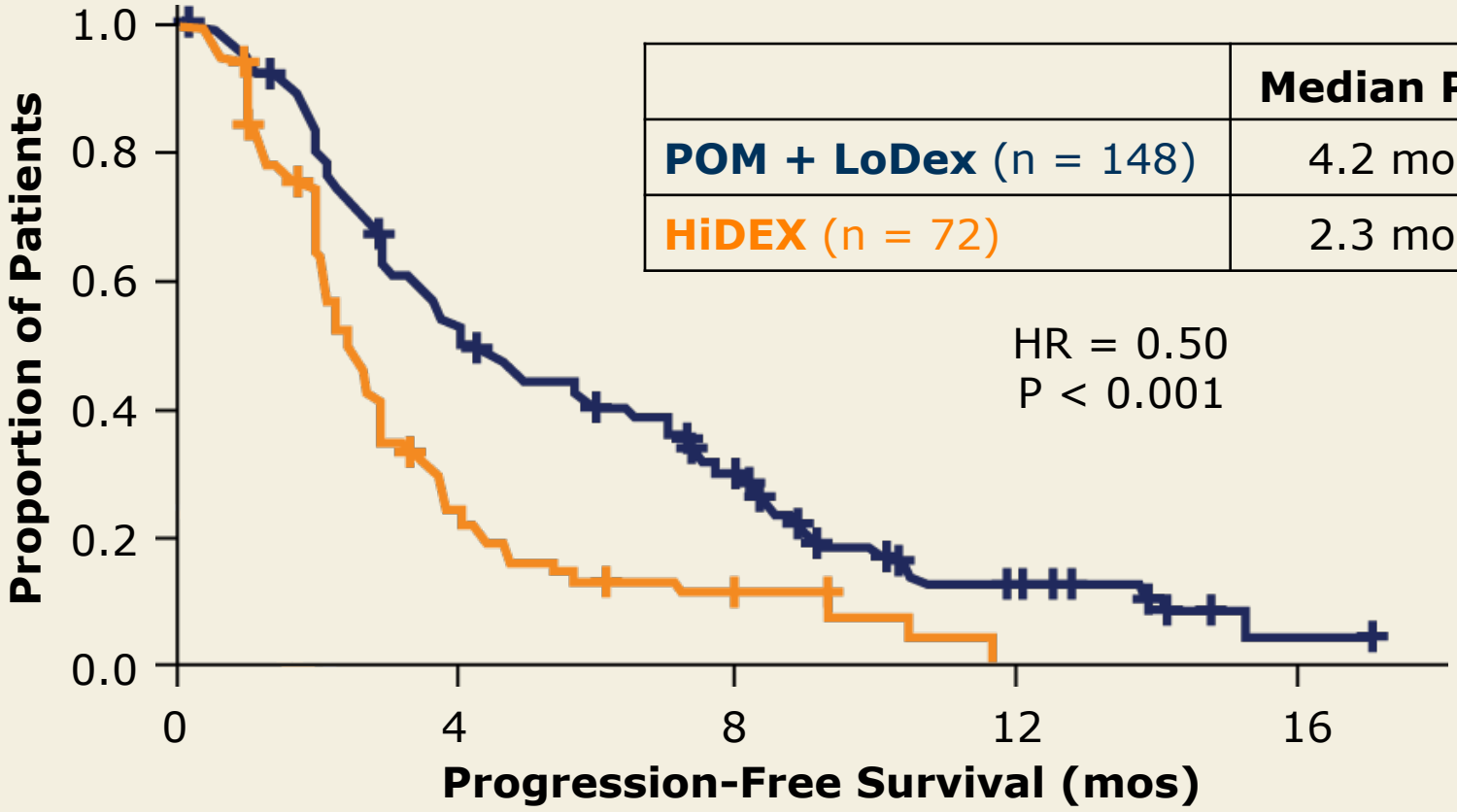
Proc ASCO 2013;Abstract 8528.

Background

- MM harboring cytogenetic abnormalities such as del17p and t(4;14) is associated with poor outcomes.
- Patients with MM who have exhausted treatment with bortezomib (Btz) and lenalidomide (Len) have a poor prognosis and limited effective treatment options.
  - Presence of high-risk cytogenetics also predicts shorter survival (*Leukemia* 2012;26:149)
- POM + LoDex demonstrated clinical efficacy in patients with RRMM and high-risk cytogenetics previously treated with Btz and/or Len (*Clin Lymphoma Myeloma Leuk* 2013;13:S44).
- **Study objective:** To prospectively examine the efficacy and safety of POM + LoDex versus HiDex for patients with RRMM in the MM-003 trial meeting the modified high-risk cytogenetic criteria, defined as presence of del17p and/or t(4;14).

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

PFS for Patients with Standard-Risk Cytogenetics



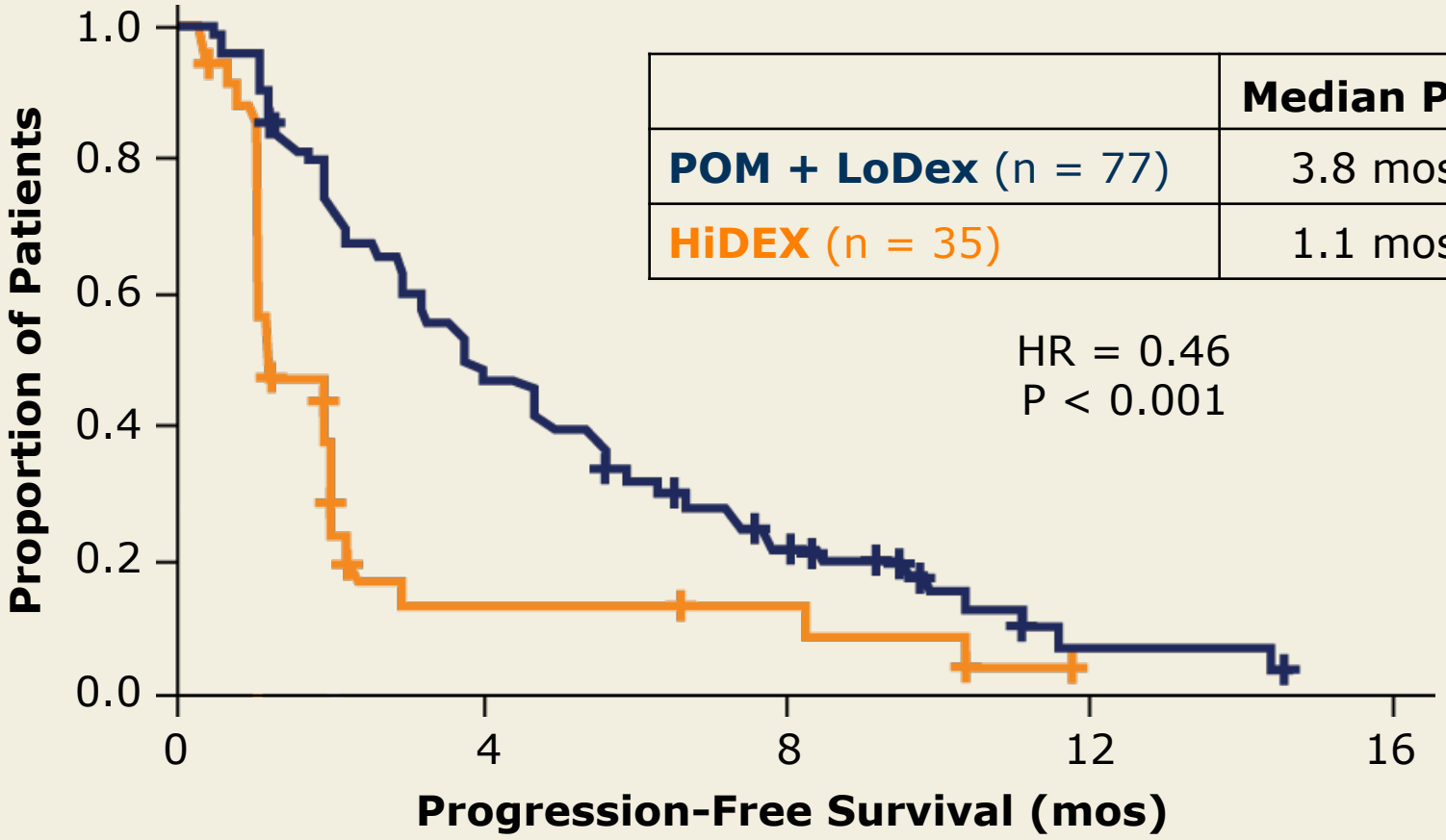
	Median PFS
POM + LoDex (n = 148)	4.2 mos
HiDEX (n = 72)	2.3 mos

HR = 0.50
P < 0.001

- 56% of patients on the HiDex arm subsequently received POM.

With permission from Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

PFS for Patients with Modified High-Risk Cytogenetics



	Median PFS
POM + LoDex (n = 77)	3.8 mos
HiDEX (n = 35)	1.1 mos

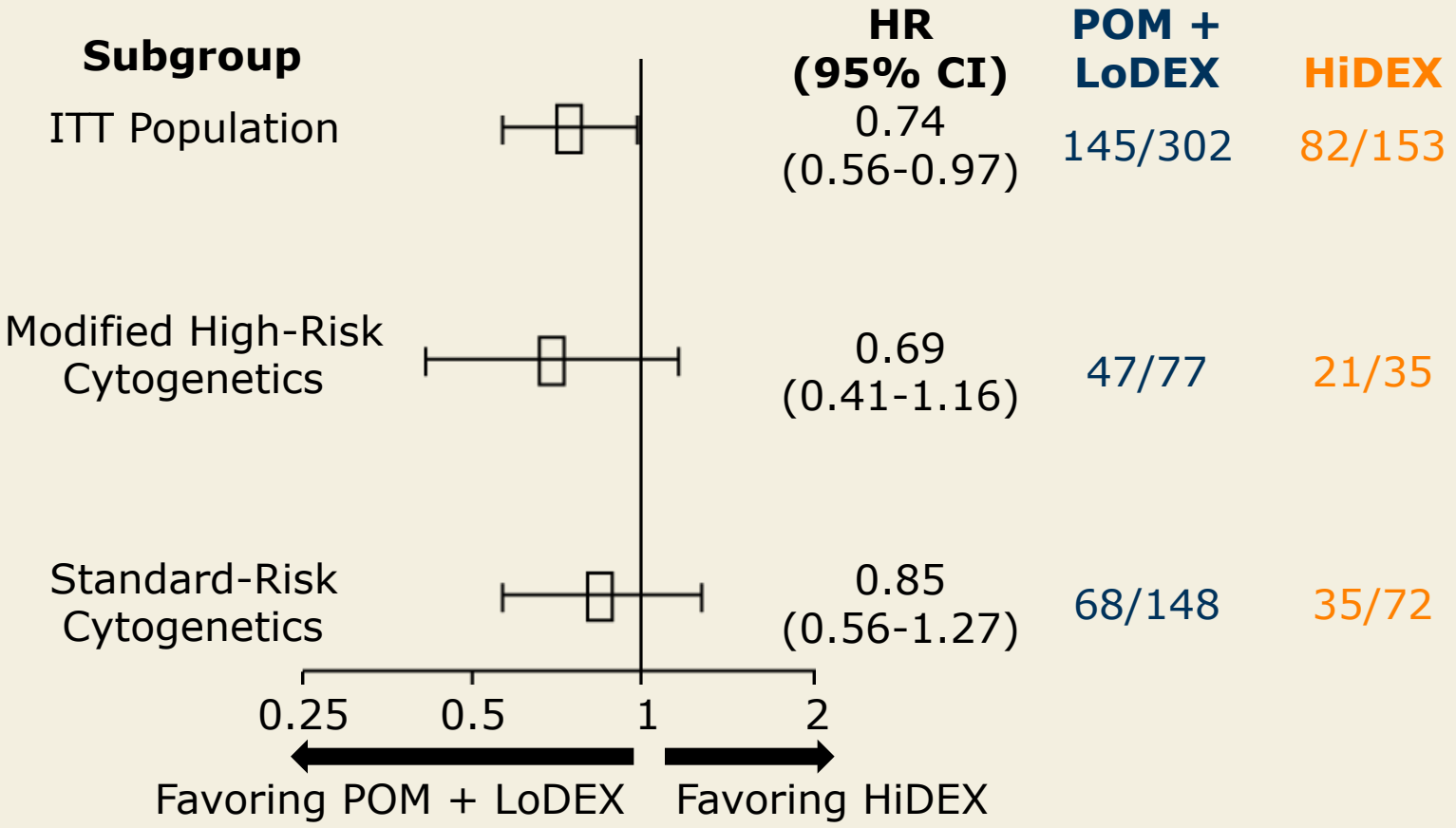
HR = 0.46
P < 0.001

- 43% of patients on the HiDex arm subsequently received POM.

With permission from Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

Overall Survival (OS) by Cytogenetic Risk Category

HR by Subgroup



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Response Rates by Cytogenetic Risk Category

Response	Modified high risk		Standard risk	
	POM + LoDex (n = 77)	HiDex (n = 35)	POM + LoDex (n = 148)	HiDex (n = 72)
ORR (≥PR)	23%	6%	34%	7%
≥MR	30%	11%	44%	15%

ORR = overall response rate; PR = partial response; MR = minimal response

- Regardless of cytogenetic risk category, ORR was significantly improved with POM + LoDex versus HiDex ($p < 0.001$)

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

Grade 3/4 Adverse Events in ≥10% of Patients

Event	Modified high risk		Standard risk	
	POM + LoDex (n = 76)	HiDex (n = 35)	POM + LoDex (n = 147)	HiDex (n = 70)
Neutropenia	54%	31%	50%	14%
FN	9%	0%	12%	0%
Anemia	46%	46%	31%	33%
Thrombocytopenia	28%	43%	24%	19%
Infections	28%	26%	38%	20%
DVT/PE	0%	0%	2%	0%
PN	3%	0%	1%	3%
Discontinuations	7%	9%	10%	8%

FN = febrile neutropenia; DVT/PE = deep vein thrombosis/pulmonary embolism

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

Author Conclusions

- Regardless of the cytogenetic risk category, treatment with POM + LoDex significantly prolonged PFS compared to HiDex.
- Treatment with POM + LoDex improved overall survival compared to HiDex, independent of cytogenetic status.
- The overall response rate was similar between cytogenetic groups.
- Consistent with previous reports, treatment with POM + LoDex was generally well tolerated, with manageable adverse events.
- POM + LoDex could be considered as a treatment option for patients with MM who have exhausted Btz and Len treatment options, regardless of cytogenetic status.

Goldschmidt H et al. *Proc ASCO* 2013;Abstract 8528.

Investigator Commentary:

Analysis of the MM-003 Trial of POM + LoDex versus HiDex in Advanced RRMM with or without Moderate Renal Impairment

The efficacy of POM and Len may be superimposable. The appropriate dosing is the issue for POM, so one should follow the dosing recommendations. I would administer POM to a patient with RRMM experiencing renal impairment. A creatinine-clearance cutoff of 60 mL/min does not significantly change clinical outcomes. We need to investigate dose reduction in patients with clearance of less than 30 mL/min. I would carefully check hematologic toxicities and would probably reduce the dose of POM if those were too high. However, data to support this approach are not presently available.

Analysis of the MM-003 Trial According to Cytogenetic Status

High-risk MM conveys worse prognosis. The observed benefit with POM for patients with advanced RRMM with high-risk cytogenetics is comparable to that with Btz. In fact, I don't believe a drug exists that is able to overcome high-risk disease. It is possible to rescue some patients with intermediate-risk disease with an intense regimen such as CyBorD or Btz.

Interview with Antonio Palumbo, MD, August 12, 2013

Phase I/II Study of Elotuzumab plus Lenalidomide/Dexamethasone in Relapsed/Refractory Multiple Myeloma: Updated Phase II Results and Phase I/II Long Term Safety[1]

Phase (Ph) I/II Study of Elotuzumab plus Lenalidomide/Dexamethasone (LEN/DEX) in Relapsed/Refractory Multiple Myeloma (RR MM): Updated Ph II Results and Ph I/II Long Term Safety[2]

[1] **Lonial S et al.**
Proc ASCO 2013;Abstract 8542.

[2] **Facon T et al.**
Proc EHA 2013;Abstract P764.

Background

- Elotuzumab (Elo) is a humanized monoclonal antibody that is currently under investigation for the treatment of multiple myeloma (MM).
- It targets CS1, a protein that is highly expressed on the surface of MM cells, and enhances antibody-dependent cellular cytotoxicity in myeloma cells.
- Previously, the Phase I part of this study showed that the combination of Elo with lenalidomide (Len) and low-dose dexamethasone (LoDex) was well tolerated with encouraging efficacy in relapsed or refractory MM (*JCO* 2012;30:1953).
- **Study objective**: To report updated efficacy and safety results of the Phase I/II study of Elo/Len/LoDex for patients with relapsed or refractory MM.

Lonial S et al. *Proc ASCO* 2013;Abstract 8542; Facon T et al. *Proc EHA* 2013;Abstract P764.

Phase II Trial Design

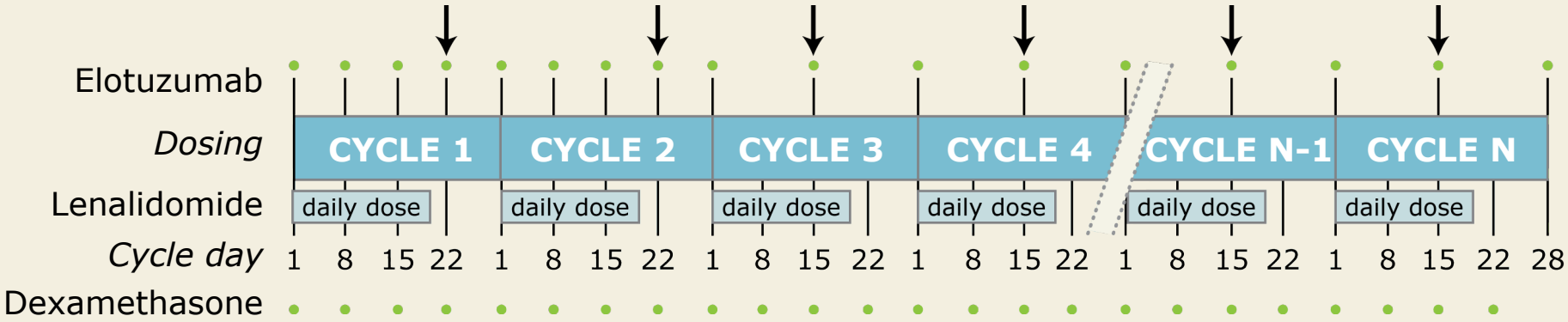
Eligibility (n = 73)

Relapsed/refractory MM
1-3 prior lines of therapy
No prior Len
No thalidomide, bortezomib or cortico-steroids within ≤2 weeks of entry

R

10 mg/kg Elo (IV)
+ Len/LoDex
(n = 36)

20 mg/kg Elo (IV)
+ Len/LoDex
(n = 37)



- Patients were stratified by prior lines of therapy (1 vs 2 or 3) and prior thalidomide or thalidomide analogs prior to randomization.

Lonial S et al. *Proc ASCO* 2013;Abstract 8542; Facon T et al. *Proc EHA* 2013;Abstract P764.

Phase II: Best Response

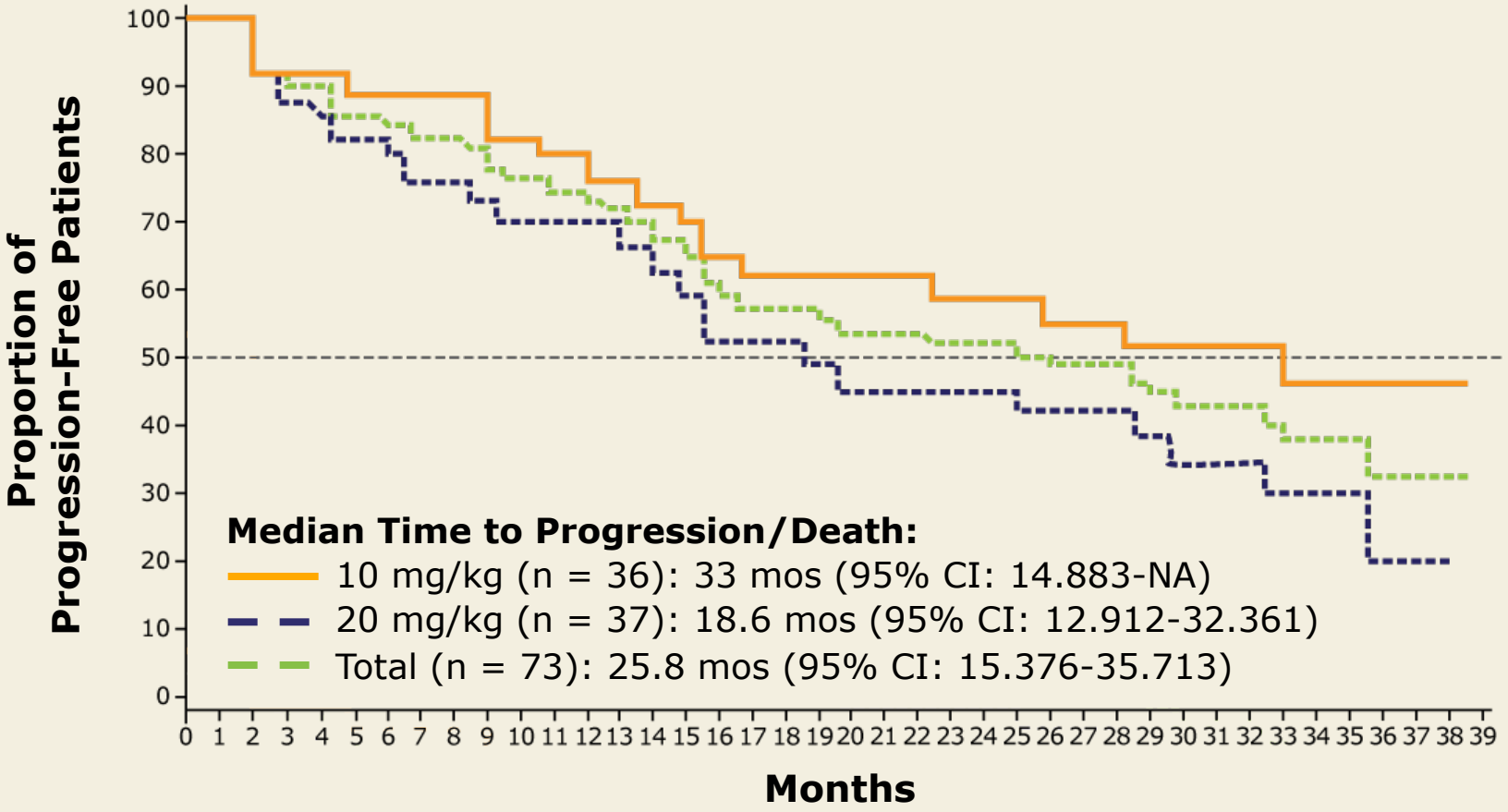
Response rate	Elo 10 mg/kg (n = 36)	Elo 20 mg/kg (n = 37)	Total (n = 73)
Objective response rate (ORR)	92%	76%	84%
Partial response (PR)	28%	27%	27%
VGPR	50%	38%	44%
CR/sCR	14%	11%	12%
<PR	8%	24%	16%

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

- Overall median time to first response: 1 month
- Overall median time to best response: 2.6 months
- Median duration of objective response: 17.8 months

Lonial S et al. *Proc ASCO* 2013;Abstract 8542; Facon T et al. *Proc EHA* 2013;Abstract P764.

Phase II: Progression-Free Survival



- Median follow-up: 10 mg/kg cohort = 20.8 mo, 20 mg/kg cohort = 17.1 mo
- Patient follow-up is ongoing

With permission from Lonial S et al. *Proc ASCO* 2013;Abstract 8542.

Phase I/II: Select Grade 3/4 Adverse Events in ≥5% of Patients

Event	Elo 10 mg/kg		Elo 20 mg/kg	
	≤18 mo (n = 39)	>18 mo (n = 20)	≤18 mo (n = 59)	>18 mo (n = 31)
Neutropenia	21%	5%	22%	3%
Thrombocytopenia	21%	5%	17%	0%
Lymphopenia	26%	5%	9%	0%
Anemia	13%	5%	12%	0%
Fatigue	8%	5%	9%	0%
Diarrhea	10%	10%	5%	0%
Hypokalemia	8%	5%	5%	3%
Pneumonia	8%	0%	5%	7%

Lonial S et al. *Proc ASCO* 2013;Abstract 8542; Facon T et al. *Proc EHA* 2013;Abstract P764.

Author Conclusions

- The combination of Elo with Len/LoDex was well tolerated for all evaluated doses.
  - Adverse events occurring after 18 months of therapy were consistent with the safety profile observed with this combination. No new safety signals were identified.
- Elo/Len/LoDex was effective in the treatment of relapsed/refractory MM.
  - ORR at 10 mg/kg of Elo was 92% and 84% in the total population.
- Two Phase III trials of Elo at 10 mg/kg in combination with Len/LoDex are ongoing:
  - ELOQUENT-1 for previously untreated MM (NCT01335399)
  - ELOQUENT-2 for relapsed/refractory MM (NCT01239797)
- Several trials of Elo in combination with other agents are ongoing in various settings for patients with MM.

Lonial S et al. *Proc ASCO* 2013;Abstract 8542; Facon T et al. *Proc EHA* 2013;Abstract P764.

Investigator Commentary: Updated Results of the Phase I/II Trial of Elo/Len/LoDex in Relapsed/Refractory MM

Single-agent elotuzumab does not have any activity. It demonstrated activity when combined with lenalidomide. This study had relatively few patients, and the results may change with a larger population. If the Phase III study confirms the results of this Phase II trial, elotuzumab will be validated as a beneficial agent. It has a novel mechanism of action, and it belongs to a new class of agents. This is a major plus.

The toxicity profile is similar to that of rituximab. It is a well-tolerated agent. It is not associated with any unusual toxicities. Strikingly, it demonstrated a progression-free survival (PFS) of more than 2 years in this patient population. If you consider that Len/Dex is approved in the same setting but is associated with a PFS of about 12 to 15 months, the PFS results observed with elotuzumab in this study are dramatic. Also, the objective response rate was >90% with 10 mg/kg of elotuzumab. These are impressive results. Hopefully, these data will be confirmed in a Phase III study.

Interview with Antonio Palumbo, MD, August 12, 2013

Daratumumab, a CD38 Monoclonal Antibody in Patients with Multiple Myeloma — Data from the Dose-Escalation Part of the FIH Study[1]

Daratumumab, a CD38 Monoclonal Antibody Study in Advanced Multiple Myeloma — An Open-Label, Dose Escalation Followed by Open-Label Extension in a Single-Arm Phase I/II Study[2]

Lokhorst HM et al.

[1] *Proc ASCO* 2013;Abstract 8512.

[2] *Proc EHA* 2013;Abstract S576.

Background

- Daratumumab is a human CD38 monoclonal antibody with broad-spectrum killing activity.
- It effectively mediates killing of CD38-expressing tumor cells via complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis.
- Daratumumab has shown promising activity in the treatment of relapsed or refractory multiple myeloma (MM) (*Proc EHA* 2012; Abstract 1143).
- This investigational agent has received breakthrough designation by the FDA for relapsed and refractory MM.
- **Study Objective:** Present efficacy and safety results from a dose-escalation study (part 1) of daratumumab in patients with relapsed or relapsed and refractory MM.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Phase I/II Study Design

- Relapsed or relapsed and refractory MM
- ≥2 prior lines of therapy
- Ineligible for ASCT

PART 1

Dose-escalation cohorts

Open label, weekly IV infusion, 8 weeks
Dose escalation: 3 + 3 scheme*
0.005 → 0.05 → 0.1 → 0.5 → 1.0 → 2.0 → 4.0 → 8.0 → 16.0 → 24.0 mg/kg

PART 2

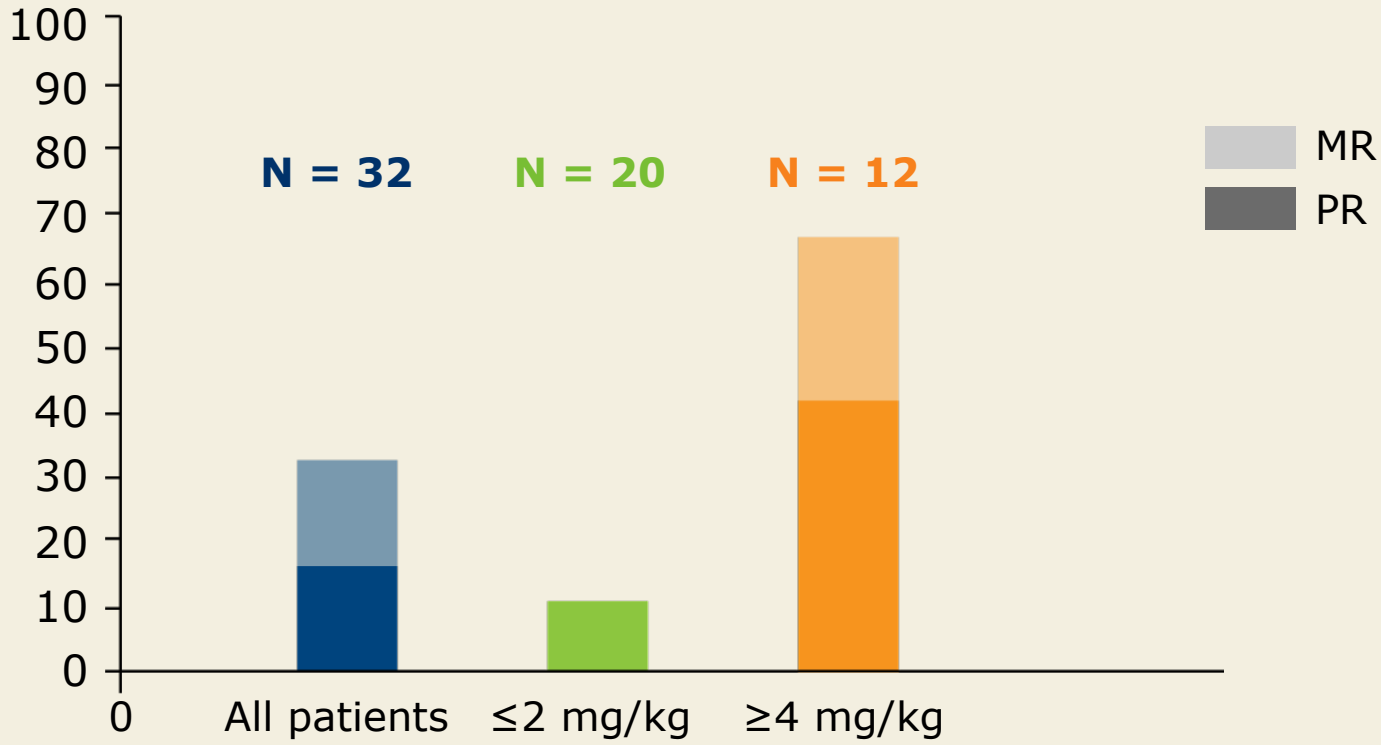
Expansion cohorts

Ongoing
Several cohorts and dose schedules are being tested

* Start with predose at 10% of the full dose, maximum 10 mg; 3 weeks delay after first full dose

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

IMWG Response to Daratumumab



- Of all patients, 10 (31%) achieved a clinical response:
  5 patients (15.5%) achieved a partial response (PR) and 5 patients (15.5%) achieved a minor response (MR).
- In the ≥4 mg/kg cohort, 8 patients (67%) achieved a clinical response:
  5 patients (42%) achieved a PR and 3 patients (25%) achieved an MR.

With permission from Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

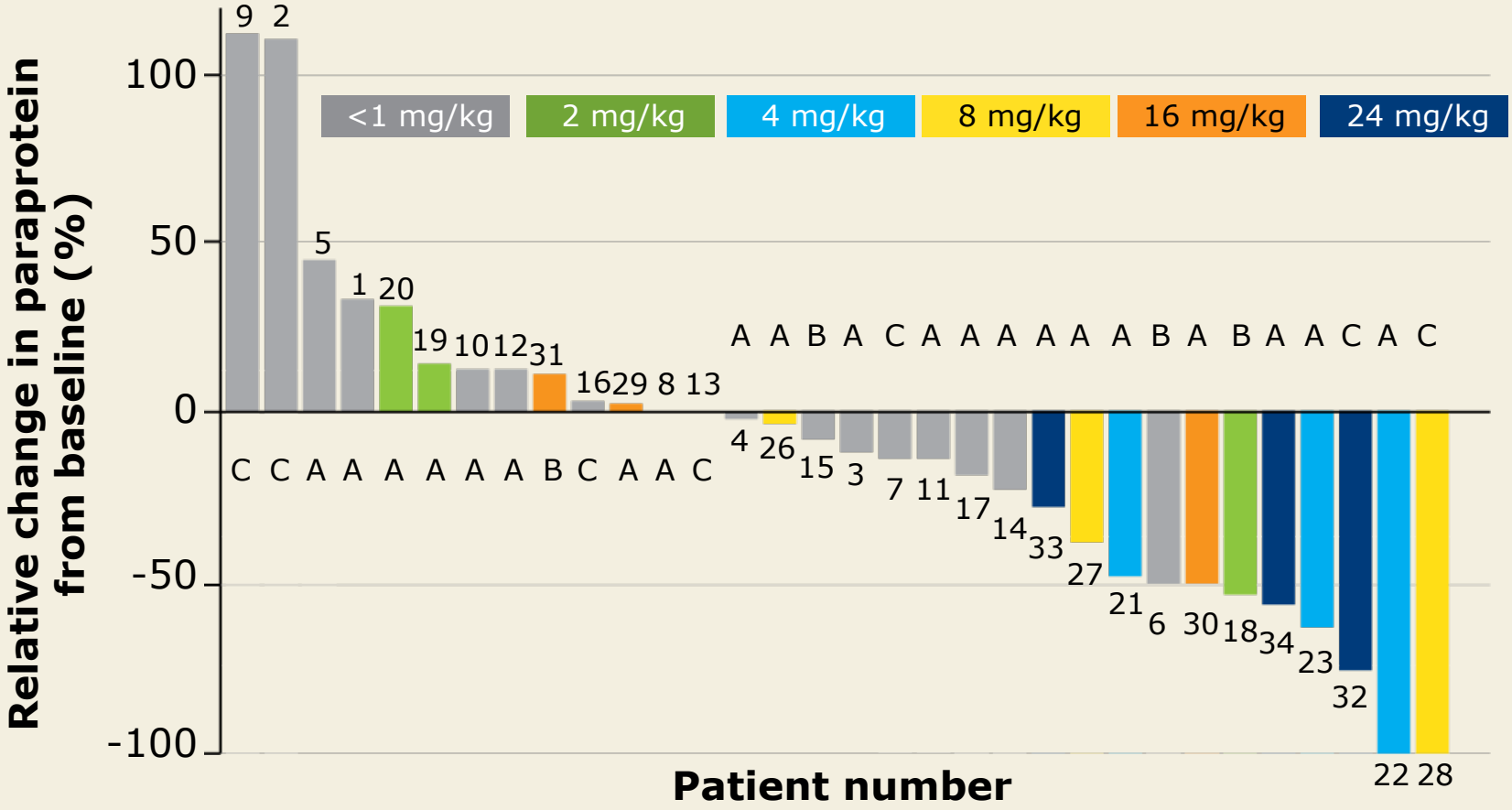
Summary of Response

Cohort mg/kg (n)	Max reduction in M component (%)		Max reduction in difference between involved and uninvolved FLC (%)	Max reduction in plasma cells in bone marrow biopsy (%) [Baseline value, %]	Response according to IMWG[†]
	Serum	Urine			
4 (3)	49 100 64	* 87 *	* 96 *	80 [12.5] 89 [23] 97 [19]	MR PR PR
8 (3)	4 39 *	* * *	* * *	-29 [14] 93 [7.5] —	SD MR NE
16 (3)	-3 50 *	* * -12	-12 88 55	— 100 [31.5] 100 [2]	PD PR SD
24 (3)	* 29 68[‡]	* * 93	80[‡] * 94	51 [18.5] 17 [3.0] 91 [17.0]	PR MR PR

* No measurable disease/normal at baseline; [†] Evaluation based on maximum reduction in M component or FLC; [‡] Follow-up still ongoing
FLC = free light chain; SD = stable disease; NE = not evaluable; — = data not available

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Maximal Change in Paraprotein

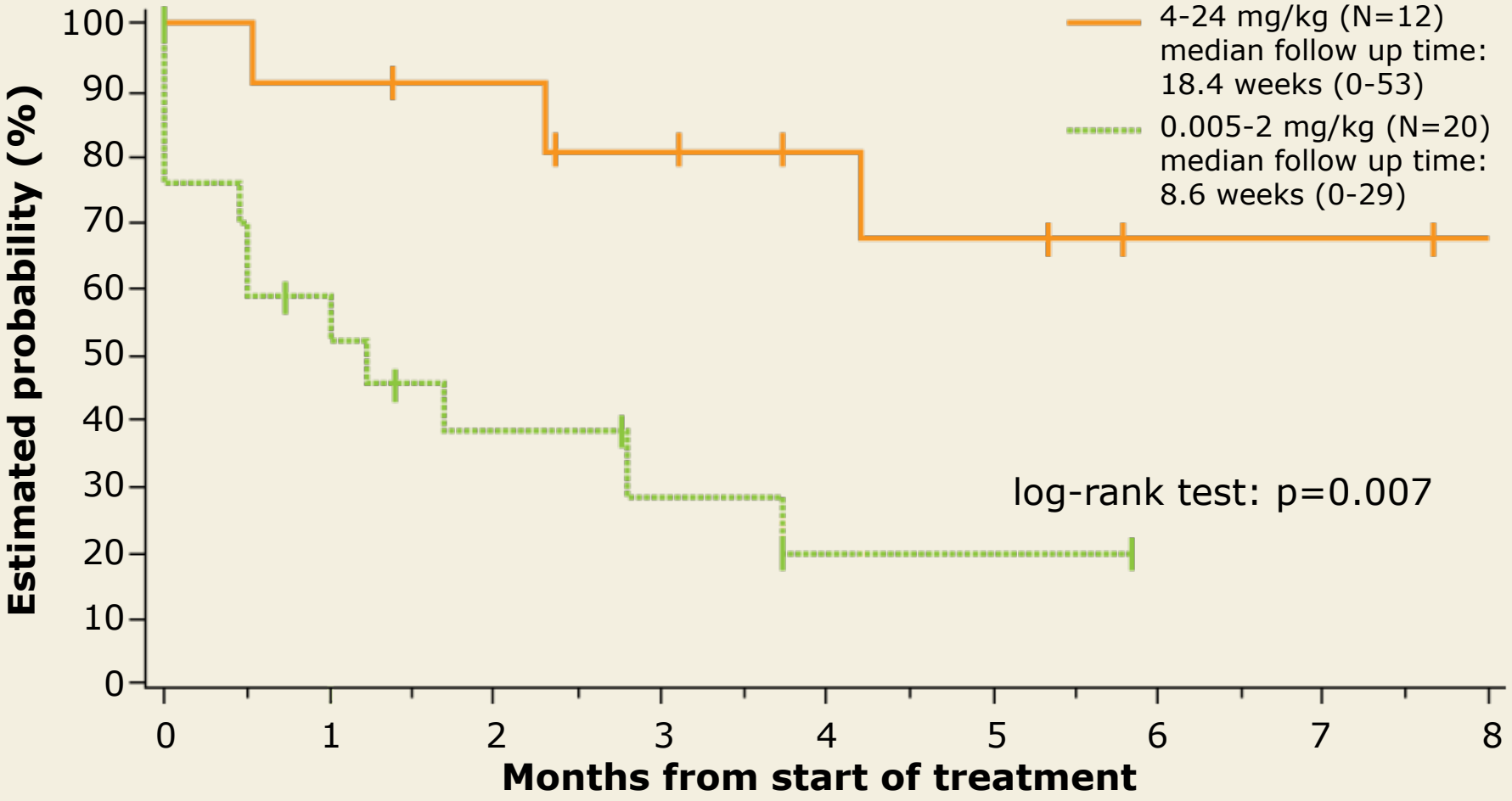


A = serum M-component; B = urine M-component; C = Free Light Chains

- 47% of patients treated with 8 weeks of daratumumab at doses of ≤24 mg/kg showed a reduction in paraprotein.

With permission from Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Progression-Free Survival



- Median PFS in the ≥4mg/kg dose groups has not been reached.

With permission from Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Drug-Related Adverse Events

Adverse event (n = 32)	Patients, %	Grade
Bronchospasm	6%	2, 3
Anemia	3%	3
Thrombocytopenia	3%	4
Aspartate aminotransferase >5.2 times the upper limit of normal	3%	2, 3
Cytokine release syndrome	3%	2

- The most common adverse events reported were infusion-related events (IREs), which occurred mainly during the first full infusion.
- 44% of patients across all dose groups experienced IREs of Grade 1 to 3, of which 2 were Grade 3.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Author Conclusions

- Daratumumab has a favorable safety profile as monotherapy for patients with relapsed or relapsed and refractory MM.
- 47% (15/32) of patients with heavily pretreated MM who received 8 weeks of daratumumab at doses of ≤24 mg/kg showed a reduction in paraprotein.
- 31% (10/32) of patients who received doses of ≤24 mg/kg achieved a clinical response.
- 67% (8/12) of patients who received doses of ≥4 mg/kg achieved a clinical response.
- Biochemical response was accompanied by clearance of myeloma cells from the bone marrow.
- At higher dose levels, plasma concentrations were close to those predicted (data not shown).

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Author Conclusions (Continued)

- Overall, increased daratumumab exposure correlated with longer PFS.
- Future studies:
  - An 8-mg/kg weekly schedule is currently being explored.
  - Higher doses and different schedules will also be investigated.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Investigator Commentary: Phase I/II Study of Daratumumab in Relapsed or Refractory MM

CD38 is as important in MM as CD20 is in lymphoma. So the usual question is whether daratumumab will demonstrate efficacy in MM that is equivalent to that seen with rituximab in lymphoma. From this perspective, great expectations surround daratumumab. Presently, several companies are trying to develop new anti-CD38 antibodies.

In this Phase I/II study, about 40% of patients achieved partial responses with daratumumab at a dose of ≥4 mg/kg. This appears to be the therapeutic dose. The median progression-free survival (PFS) was not reached after 8 courses of daratumumab. This was not a study of treatment until disease progression. This Phase I study involved the administration of single-agent daratumumab for only 8 weeks, and therefore the PFS results are interesting. This study also demonstated major reductions in bone marrow plasma cells with daratumumab monotherapy.

Interview with Antonio Palumbo, MD, August 12, 2013

Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Relapsed/Refractory Multiple Myeloma: Results from a Phase I Study After Full Enrollment

Kumar SK et al.

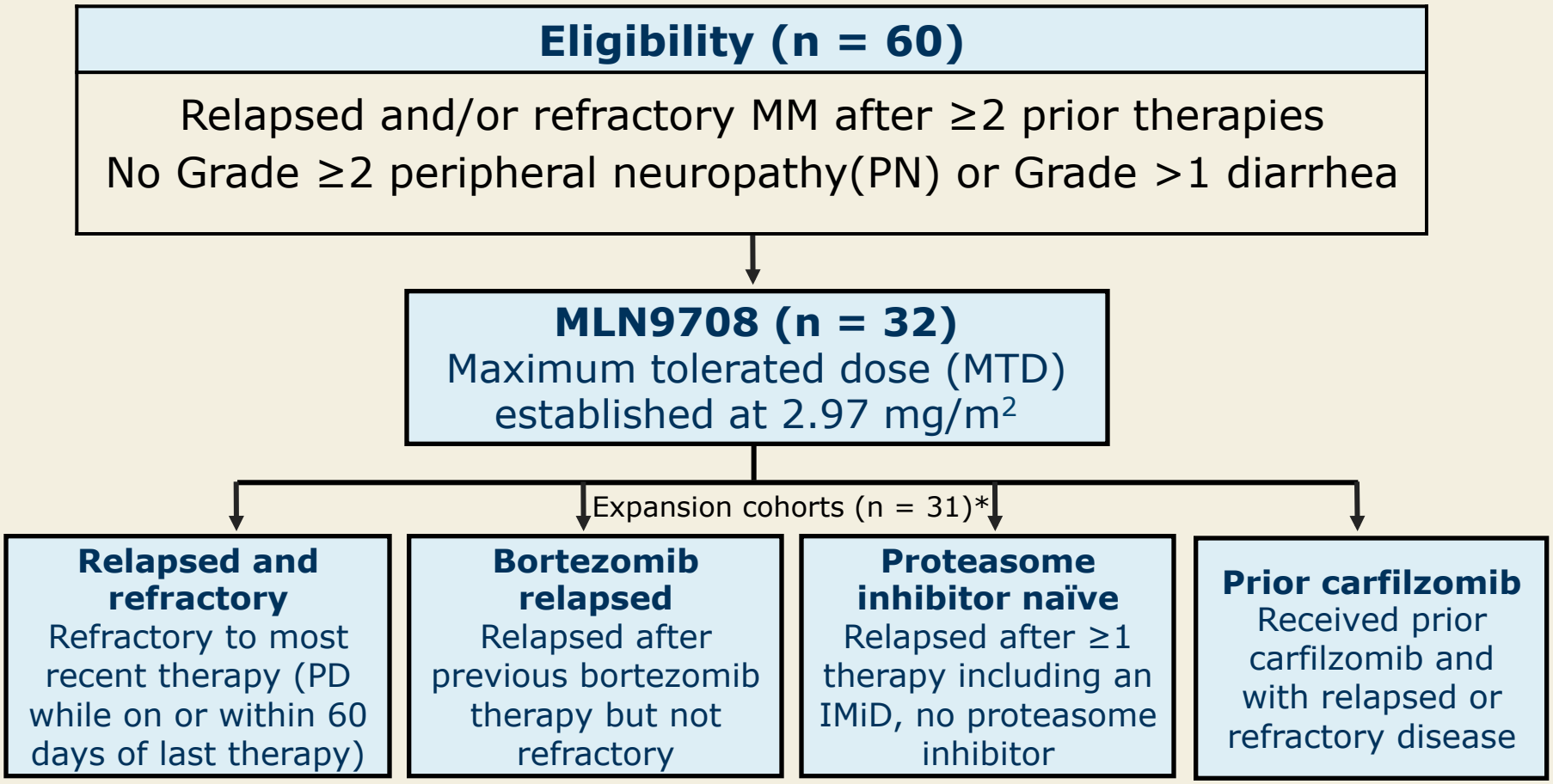
Proc ASCO 2013;Abstract 8514.

Background

- Proteasome inhibition is one of the most effective antimyeloma strategies, as shown by the efficacy of bortezomib (*N Engl J Med* 2005;352:2487-98).
- MLN9708 (ixazomib) is a potent, investigational, orally bioavailable, reversible inhibitor of the 20S proteasome.
- MLN9708 is the first oral proteasome inhibitor to enter clinical investigation in multiple myeloma (MM).
- **Study objectives:** To determine the maximum tolerated dose, safety, activity and pharmacokinetics of weekly MLN9708 treatment for patients with relapsed and/or refractory MM.

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Phase I Trial Design



* Includes 3 patients from MTD dose-escalation cohort

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

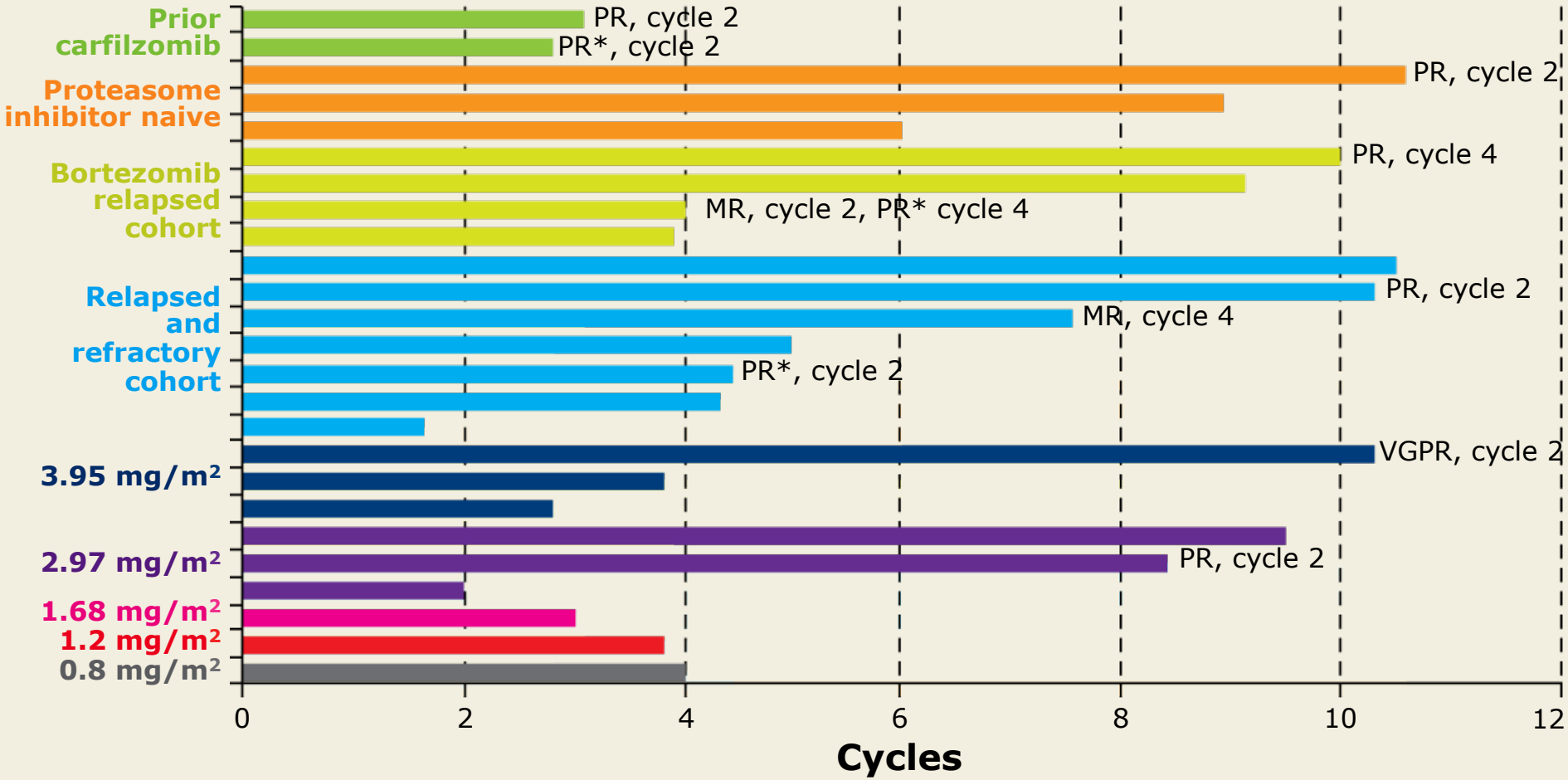
Best Responses

Response rate	All cohorts (n = 50)	Expansion cohort (n = 31)
ORR	9 (18%)	8 (26%)
VGPR	1 (2%)	0
Partial response	8 (16%)	8 (26%)
Minimal response	1 (2%)	1 (3%)
Stable disease	15 (30%)	NR

ORR = overall response rate; VGPR = very good partial response;
NR = not reported

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

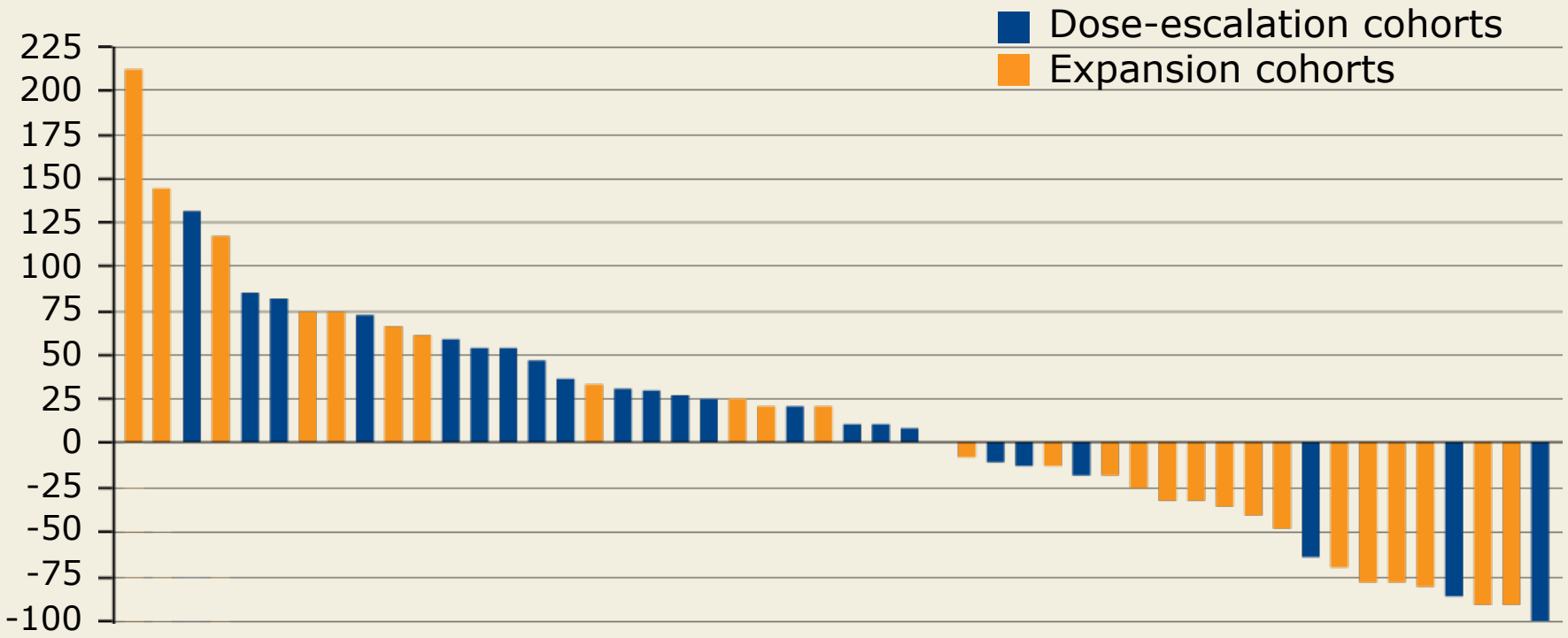
Duration of ≥Stable Disease with MLN9708



* Unconfirmed best response

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

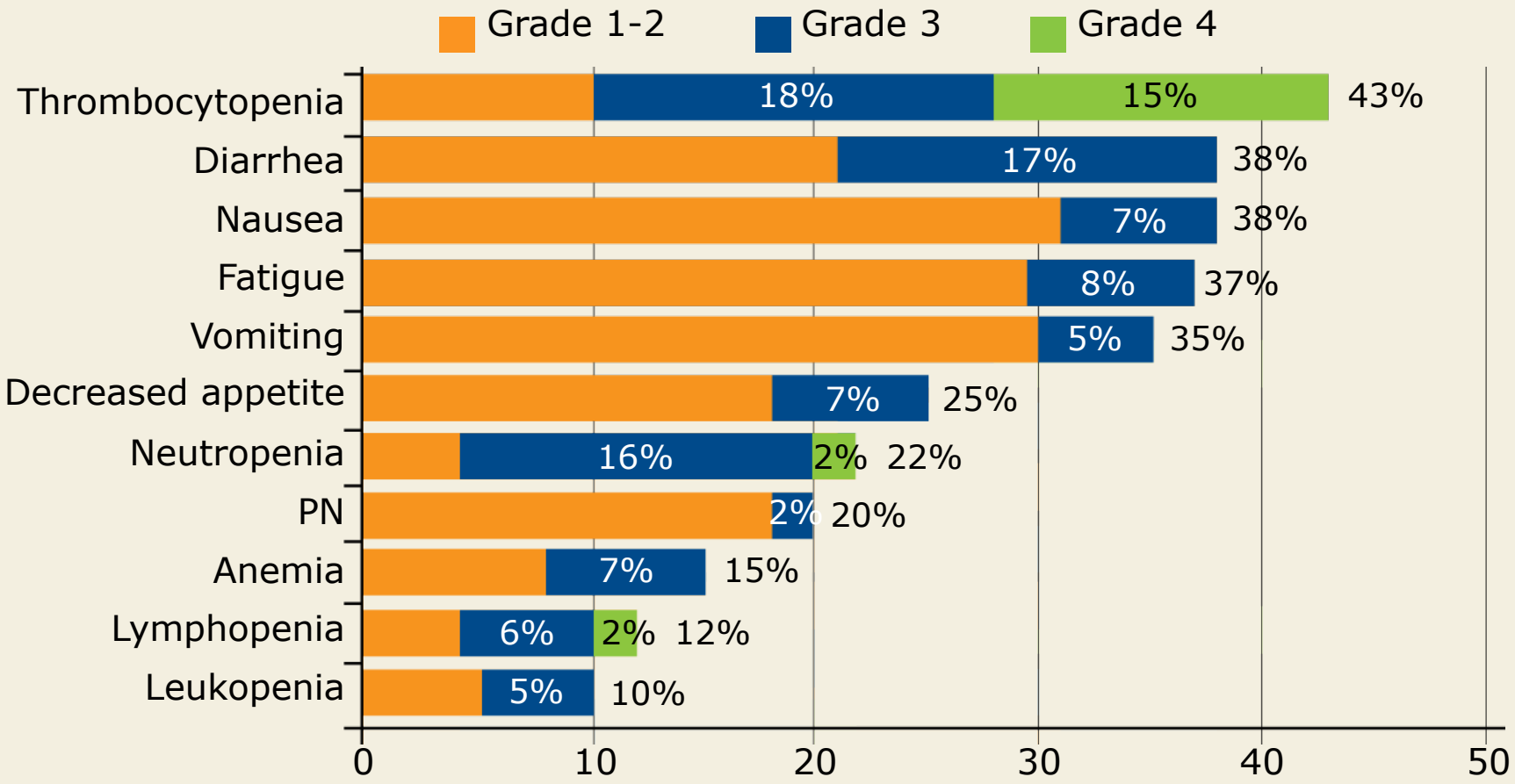
Patients' Best M-Protein Responses to Treatment with MLN9708



- Among 50 response-evaluable patients, 15 (30%) had M-protein reductions of ≥25%
  - 9 (18%) had best M-protein reductions of ≥50%, including 3 of ≥90% and 1 immunofixation-negative

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

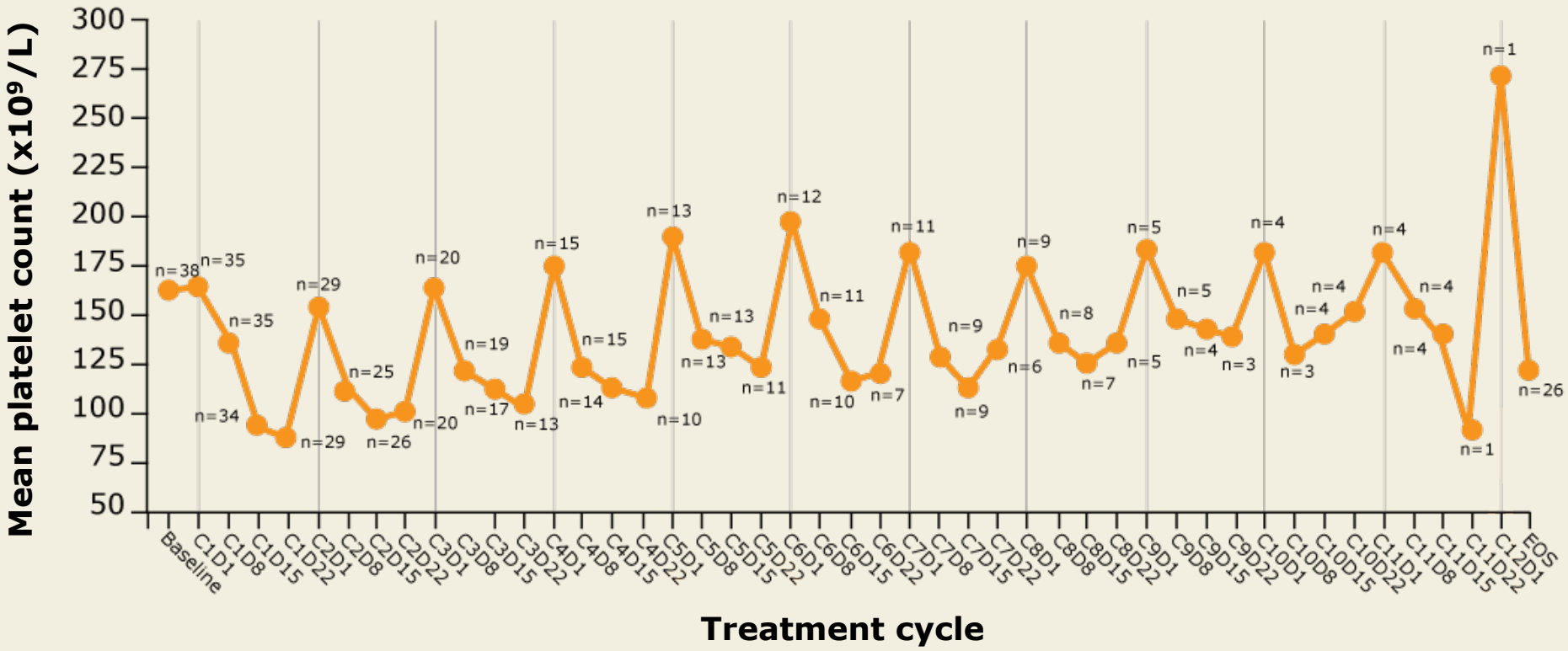
Drug-Related Adverse Events (AEs)*



* ≥20% any grade or ≥5% Grade ≥3

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Thrombocytopenia



- Thrombocytopenia appeared to be transient and cyclical:
  - Platelet count recovered toward baseline in the rest period at the end of each cycle.
- Only 8% of patients required platelet transfusions.

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Author Conclusions

- Single-agent oral MLN9708 MTD was established as 2.97 mg/m^2 on a weekly (days 1, 8 and 15 q28d) dosing schedule.
- Oral MLN9708 was generally well tolerated.
  - AEs consisted mostly of hematologic and gastrointestinal events and were generally manageable, with a low rate of discontinuations
  - Infrequent peripheral neuropathy
- Pharmacokinetic profile supports weekly oral dosing (data not shown).
- Phase I data suggest clinical activity in relapsed and/or refractory MM (median 4 prior lines of therapy).
  - ORR (≥PR) of 18%, plus 2% MR and 30% SD
  - Responses seen in patients with prior exposure to proteasome inhibitors, including bortezomib

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Investigator Commentary: Phase I Trial of MLN9708 (Ixazomib) in Relapsed/Refractory MM

Oral MLN9708 is a major improvement on intravenous or even subcutaneous bortezomib (Btz). This Phase I study of weekly MLN9708 as a single agent managed to achieve a nice administration schedule with limited toxicity. I believe we may have an opportunity to use oral MLN9708 in the elderly, frail patient population.

MLN9708-associated thrombocytopenia is similar to that observed with Btz. A slight increase in mainly Grade 1 and 2 diarrhea also seems to occur with MLN9708. The gastrointestinal toxicities are a concern. They appear to be slightly increased compared to those seen with Btz. On the other hand, as with carfilzomib, peripheral neuropathy (PN) seems to be less of an issue with MLN9708 than with Btz. In this study, the rate of Grade 1 and 2 PN was 18% and the rate of Grade 3 and 4 PN was 2%.

The efficacy of MLN9708, to some extent, seems to be comparable to that of Btz. With single-agent MLN9708, 30% of patients experienced a 25% or higher reduction in M-protein and 24% experienced reductions of 50% or more. From the efficacy and safety point of view, oral MLN9708 has a good chance of making it into clinical practice in my opinion.

Interview with Antonio Palumbo, MD, August 12, 2013