5 Minute JournalClub

POST-ASH Issue 5, 2013

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

CME Information

LEARNING OBJECTIVES

- Consider the benefits and risks of the investigational agent MLN9708 for patients with previously untreated multiple myeloma.
- Evaluate the efficacy and safety of carfilzomib with or without immunomodulatory drugs for newly diagnosed or relapsed/refractory multiple myeloma.
- Assess emerging clinical trial data on the novel combination of bendamustine, bortezomib and dexamethasone in relapsed/refractory multiple myeloma.
- Determine the maximum tolerated dose of pomalidomide in combination with bortezomib and low-dose dexamethasone for relapsed or relapsed/refractory multiple myeloma.
- Compare and contrast the effects of bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide to those of bortezomib/melphalan/prednisone on the overall survival of patients with relapsed/refractory multiple myeloma.

CME Information (Continued)

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2013/5/CME.

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:

Kenneth C Anderson, MD
Kraft Family Professor of Medicine
Harvard Medical School
Director, Jerome Lipper Multiple Myeloma Center
Director, LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Boston, Massachusetts

CME Information (Continued)

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Onyx Pharmaceuticals Inc, Sanofi; *Other Remunerated Activities:* Acetylon Pharmaceuticals Inc.

A Keith Stewart, MBChB
Dean for Research, Mayo Clinic in Arizona
Consultant, Division of Hematology/Oncology
Vasek and Anna Maria Polak Professorship in Cancer Research
Scottsdale, Arizona

Advisory Committee: Amgen Inc, Celgene Corporation; *Consulting Agreements:* Celgene Corporation, Millennium: The Takeda Oncology Company; *Contracted Research:* Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

5 MinuteJournalClub

POST-ASH Issue 5, 2013

New proteasome inhibitor-based combination regimens in multiple myeloma

Dr Ken Anderson's memorable Karnofsky Award presentation at ASCO 2011 provided an intriguing overview of how profoundly the clinical face of multiple myeloma (MM) has changed in the postchemotherapy era, and the recent approval of 2 new agents is additional evidence of how quickly things are moving forward. In a previous issue of this series we focused on immunomodulatory drugs, including the recently (February 8) FDA-approved pomalidomide (Pom) for relapsed/refractory disease, and in this issue we look at the other key class of agents that has revolutionized the treatment of MM, proteasome inhibitors, which were the focus of Dr Anderson's lecture and much of his clinical and laboratory research at Dana-Farber.

In retrospect, it seems intuitive to block the mechanism by which proteins are processed and excreted in cells that are noteworthy for protein overproduction — specifically immunoglobulins — but while the translational science behind these molecules is fascinating, perhaps more important is the bottom line in terms of patient impact. In a recent *JCO* editorial Drs Sagar Lonial and Jonathan

Kaufman make a compelling argument that in stark contrast to, for example, metastatic breast cancer, where sequential single agents are used, in MM combination regimens, although not usually curative, seem to yield better long-term outcomes. As bortezomib (BTZ) is a standard part of 2 of the most commonly used pretransplant induction regimens — RVD and CyBorD — and carfilzomib is now available for general use, it is easy to see how crucial these agents have become. Even more, at ASH we saw many interesting papers looking at various new proteasome inhibitor-based combinations that may one day soon be a part of the next generation of MM care.

1. Carfilzomib (CFZ)

This first-in-class irreversible proteasome inhibitor was approved last July for relapsed/refractory disease, but even before then there was considerable interest in testing it up front. At ASH 2011 Dr Andrzej Jakubowiak presented impressive Phase I findings with "CRd" in which the proteasome inhibitor was CFZ rather than BTZ, and this year an NCI team added to the database by reporting **a Phase II trial of 15 patients**. Once again this combo was found to have a profound antimyeloma effect (14 responses) with acceptable tolerability and no reported Grade ≥3 peripheral neuropathy (PN).

Similarly, Dr Antonio Palumbo presented results from **a Phase II trial evaluating another CFZ combination** (CFZ/cyclophosphamide/low-dose dexamethasone [dex], or CCd) as up-front therapy in 58 patients over age 65 or ineligible for transplant. Study participants received 9 cycles of CCd followed by

CFZ maintenance until progression. Of note, responses were seen in all patients, including those with adverse cytogenetics, and the progression-free survival at 1 year was 88%. Again, no Grade ≥3 PN was reported.

Finally, in the relapsed/refractory setting, **yet another CFZ triplet — CFZ/Pom/low-dose dex — showed encouraging activity**, with 15 of 30 patients responding, including many who had received extensive prior treatment and/or had adverse cytogenetics.

2. Ixazomib

Formerly MLN9708, this boron acid-based proteasome inhibitor in clinical trial development is similar to BTZ but not only seems to cause less PN but is also orally administered, opening up the enticing possibility of an all-oral RVD-like induction regimen. At ASH we saw **updated data from a Phase I/II study** of ixazomib/lenalidomide/low-dose dex in 64 patients with previously untreated MM. Importantly, 92% responded and only 2 developed Grade 3 PN (3%), helping to significantly increase enthusiasm for ongoing Phase III efforts evaluating this combination versus lenalidomide/low-dose dex in previously untreated patients.

3. More on bortezomib

Bendamustine has a similar structure to alkylating agents and is thought to perhaps have synergistic activity with BTZ. For that reason, **a Phase II study looked at a CyBorD-like** regimen in which bendamustine was substituted for

cyclophosphamide. Although significant activity was observed, including responses in 48 of 71 patients (68%), it is unclear whether this regimen will be used in US practice until further data emerge.

As usual Dr Paul Richardson was quite busy at ASH, and among his oral presentations was a **Phase I study evaluating BTZ/Pom/low-dose dex** in patients with relapsed/refractory MM. While data from only 15 patients were reported, the results suggest that BTZ in combination with POM is well tolerated and highly active, further justifying the ongoing Phase III clinical trial examining this strategy.

While we are all familiar with triplet regimens, many have wondered whether 4-drug combos might provide even greater benefit, and to that end, at ASH Dr Palumbo provided **updated results from his Phase III study** of BTZ/melphalan/prednisone/thalidomide (VMPT) with VT maintenance versus VMP alone in patients who were not transplant candidates. Previous reports showed that the quartet plus maintenance provided significantly longer disease control, and in Atlanta we came to learn that it also resulted in an overall survival advantage (HR 0.7). Of interest, patients (particularly those older than 75 years of age) in the VMPT-VT arm more commonly had to discontinue therapy or reduce the BTZ dose, suggesting that less intense therapy might be preferable, but Dr Anderson believes that subcutaneous weekly BTZ may allow more patients to be treated with this approach.

Next on this series… You've heard of "R squared" (lenalidomide/rituximab). How about "R squared/CHOP"? Check out our coverage of 2 major papers on this regimen in diffuse large B-cell lymphoma and other related ASH lymphoma papers.

Neil Love, MD
Research To Practice
Miami, Florida

Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma (MM) Patients

Korde N et al.

Proc ASH 2012;Abstract 732.

Background

- Carfilzomib (CFZ) is an irreversible proteasome inhibitor with potent antimyeloma effects and a significantly decreased incidence of peripheral neuropathy compared to bortezomib (*Onco Targets Ther* 2012;5:237).
- A Phase I/II study of CFZ in combination with lenalidomide (LEN) and low-dose dexamethasone (CRd) as front-line treatment for MM showed that the regimen was well tolerated with exceptional response rates (*Blood* 2012;120:1801).
- Therefore, this single-stage Phase II trial of front-line CRd followed by 1 year of LEN maintenance for transplant-eligible patients with MM defaulting to "delayed" ASCT was initiated.
- **Study objective:** Evaluate the efficacy and safety of the CRd regimen in patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2012;Abstract 732.

Phase II Study Eligibility and Endpoints (Abstract Only)

- **Eligibility:**
  - Newly diagnosed, untreated MM
  - Transplant-eligible and ineligible patients
- **Primary endpoint:** Incidence of Grade ≥3 neuropathy
- **Secondary objectives:**
  - Response rate
  - Profiling CFZ activity to biological endpoints
  - Impact of minimal residual disease (MRD) studies on clinical outcomes

Korde N et al. *Proc ASH* 2012;Abstract 732.

Phase II Study Methods (Abstract Only)

- Treatment consists of eight 28-d cycles of:
  - CFZ, 20/36 mg/m^2 IV (d1, 2, 8, 9, 15, 16)
  - LEN, 25 mg PO (d1-21)
  - Dexamethasone, 20/10 mg IV/oral (d1, 2, 8, 9, 15, 16, 22, 23)
- Transplant-eligible patients default to “delayed” ASCT per protocol by harvesting/cryopreserving stem cells after 4 cycles of CRd, followed by treatment continuation for cycles 5-8
- After 8 cycles of CRd, patients with ≥stable disease receive cycles 9-20 of LEN maintenance (10 mg; d1-21)
- Bone marrow samples collected at baseline, cycle 1/d2, CR/end of cycle 8 and CR/end of cycle 20
- Molecular responses are assessed by MRD studies using flow cytometry, PCR and FDG PET-CT on achievement of CR/end of cycle 8 (during cycles 1–8) and CR/end of cycle 20 (during cycles 9–20)

Korde N et al. *Proc ASH* 2012;Abstract 732.

Best Response After a Median of 4 CRd Cycles (Abstract Only)

Response	n = 15
ORR	93%
VGPR	5 (33%)
sCR + nCR	6 (40%)
PR	3 (20%)
SD	1 (6%)

- Median time from initiation of CRd to sCR: 5 cycles
- 4 patients with sCR had no evidence of immunophenotypic abnormal plasma cells by flow cytometry during MRD assessment
- PET-CT results for 3 of 4 patients who achieved sCR showed a substantial decrease in maximum standardized uptake value (SUV) avid lytic lesion from baseline (average SUV decline: 76%)
- All patients maintained their best response and have no evidence of clinical disease progression

Korde N et al. *Proc ASH* 2012;Abstract 732.

Select Grade ≥3 Adverse Events (Abstract Only)

Grade ≥3 AE	(n = 15)
Hematologic	
Lymphopenia	10 (66%)
Thrombocytopenia	1 (6%)
Nonhematologic	
Hypophosphatemia	3 (20%)
ALT increase	2 (13%)
Congestive heart failure	2 (13%)
Fatigue	1 (6%)
Rash	1 (6%)

- No patients with Grade ≥3 neuropathy

Korde N et al. *Proc ASH* 2012;Abstract 732.

Author Conclusions

- Using an approach that merges functional imaging with molecular responses beyond traditional clinical biomarkers, this study showed that CRd followed by LEN maintenance and delayed ASCT is a highly potent and tolerable combination regimen for patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2012;Abstract 732.

Investigator Commentary: Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide and Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma

This study evaluating CFZ in combination with lenalidomide and dexamethasone in the up-front setting reported a high response rate and an impressive complete remission rate. These results are probably the best reported in myeloma to date and were previously only achievable with stem cell transplantation. The fact that these results can be obtained without a transplant offers high hope for patients. One would hope to be able to use this regimen if CFZ receives approval for use in the front-line setting.

Interview with A Keith Stewart, MBChB, January 9, 2013

The results from this study demonstrated that the overall response rate to CFZ, lenalidomide and dexamethasone is nearly universal and the extent of the response is also high. The authors evaluated responses using the most stringent criteria that have been used in myeloma. The results highlight that when CFZ is combined with lenalidomide and dexamethasone, the frequency and the extent of the response are exceptional.

Interview with Kenneth C Anderson, MD, January 22, 2013

Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma (MM) Patients

Palumbo A et al.

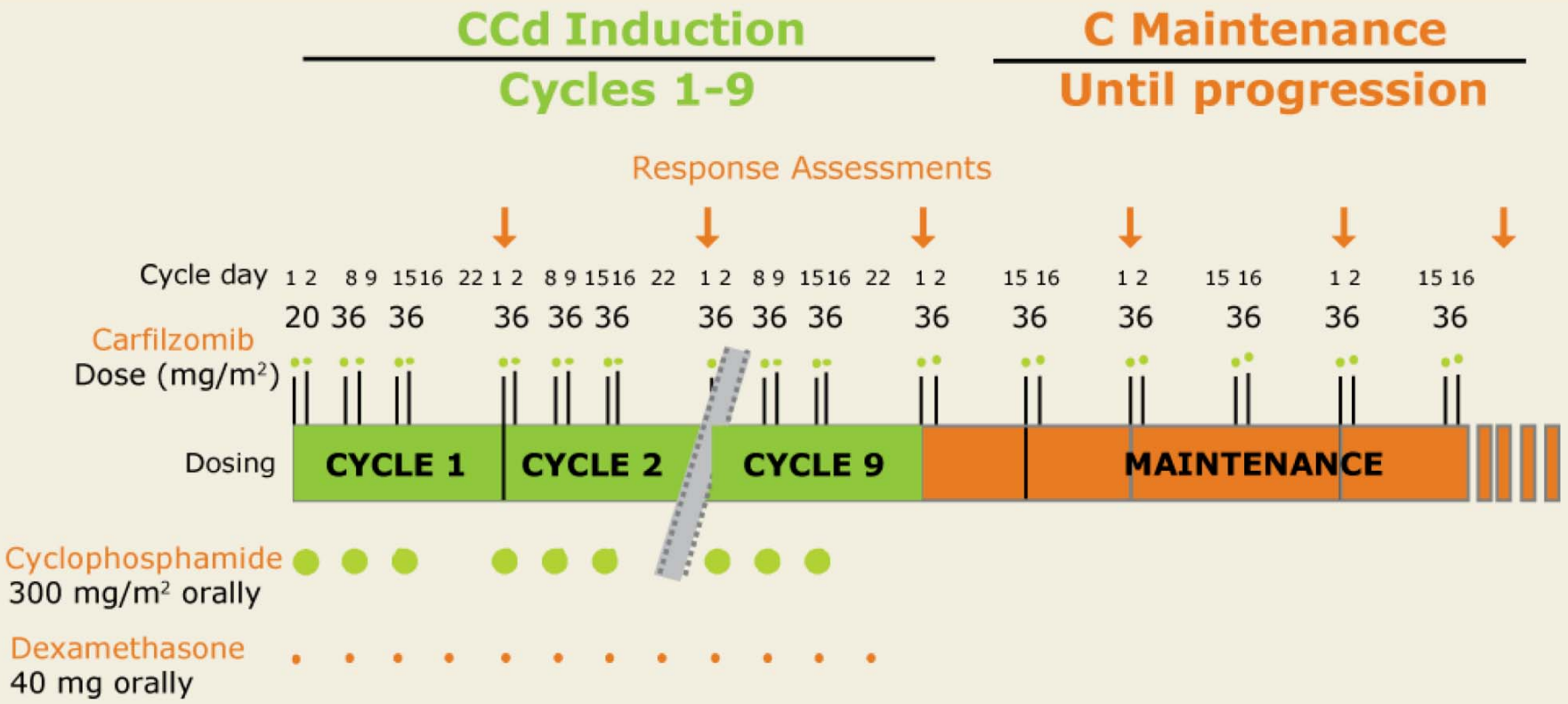
Proc ASH 2012;Abstract 730.

Background

- Carfilzomib is a novel, irreversible proteasome inhibitor that was recently FDA approved for the treatment of multiple myeloma (MM) progressing after ≥2 prior therapies.
- Even though regimens such as melphalan/prednisone/thalidomide (MPT) and bortezomib/melphalan/prednisone (VMP) are clinically effective therapies for elderly patients with MM, the toxicity profile and discontinuation rate are significantly higher than comparable regimens for younger patients (*Blood* 2011;118:1239; *N Engl J Med* 2008;359:906).
- **Study objective:** To evaluate the efficacy and safety of combination therapy with carfilzomib, cyclophosphamide and dexamethasone (CCd) patients with newly diagnosed, symptomatic MM who are ≥65 years or ineligible for autologous stem cell transplantation.

Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Phase II Trial Design

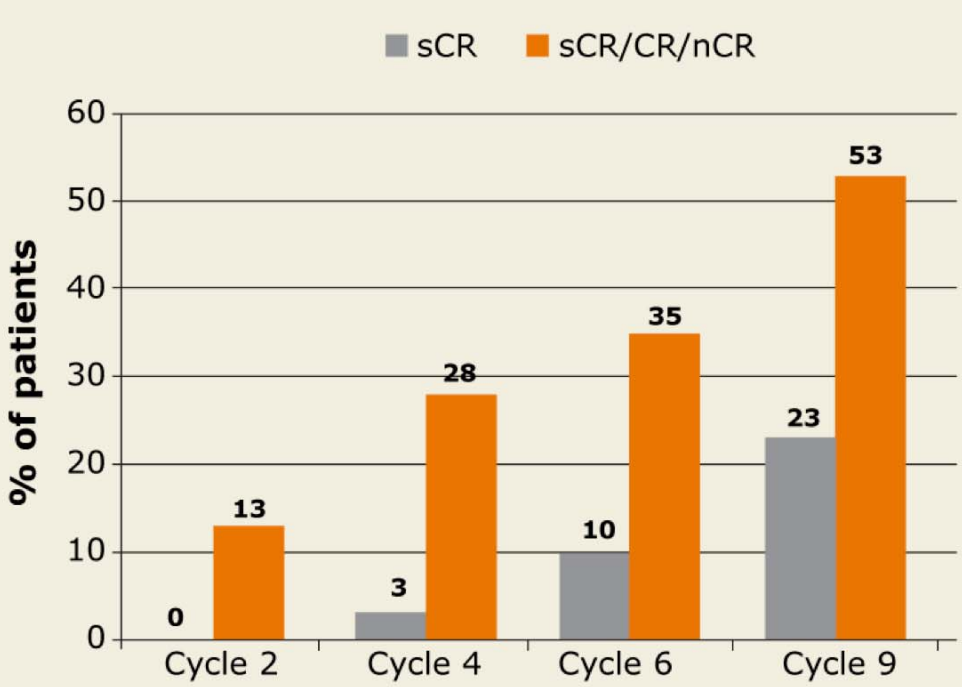


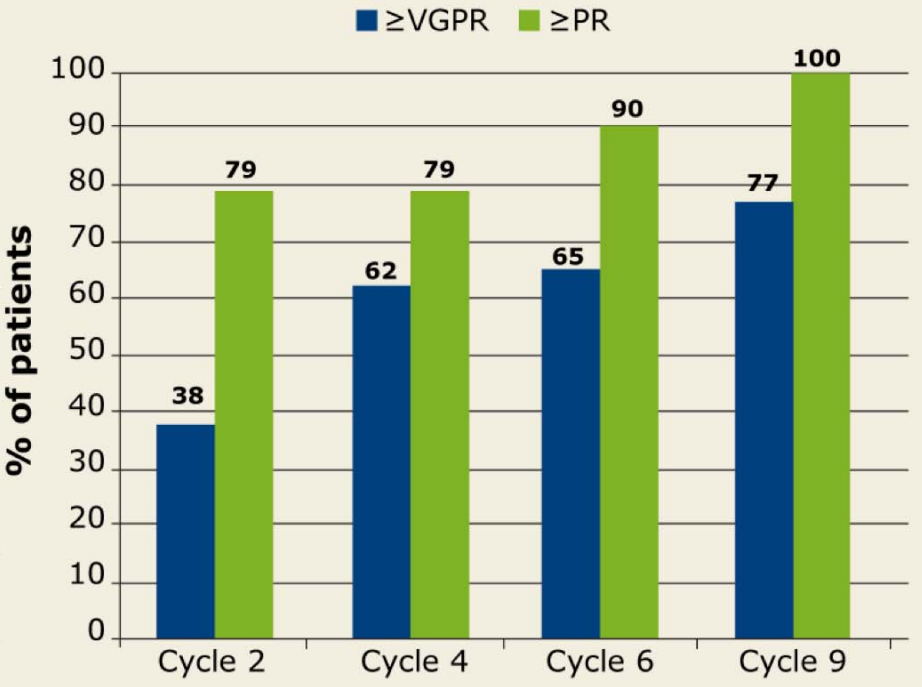
Primary objectives:

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

Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Response Rates by Treatment Duration (n = 58)

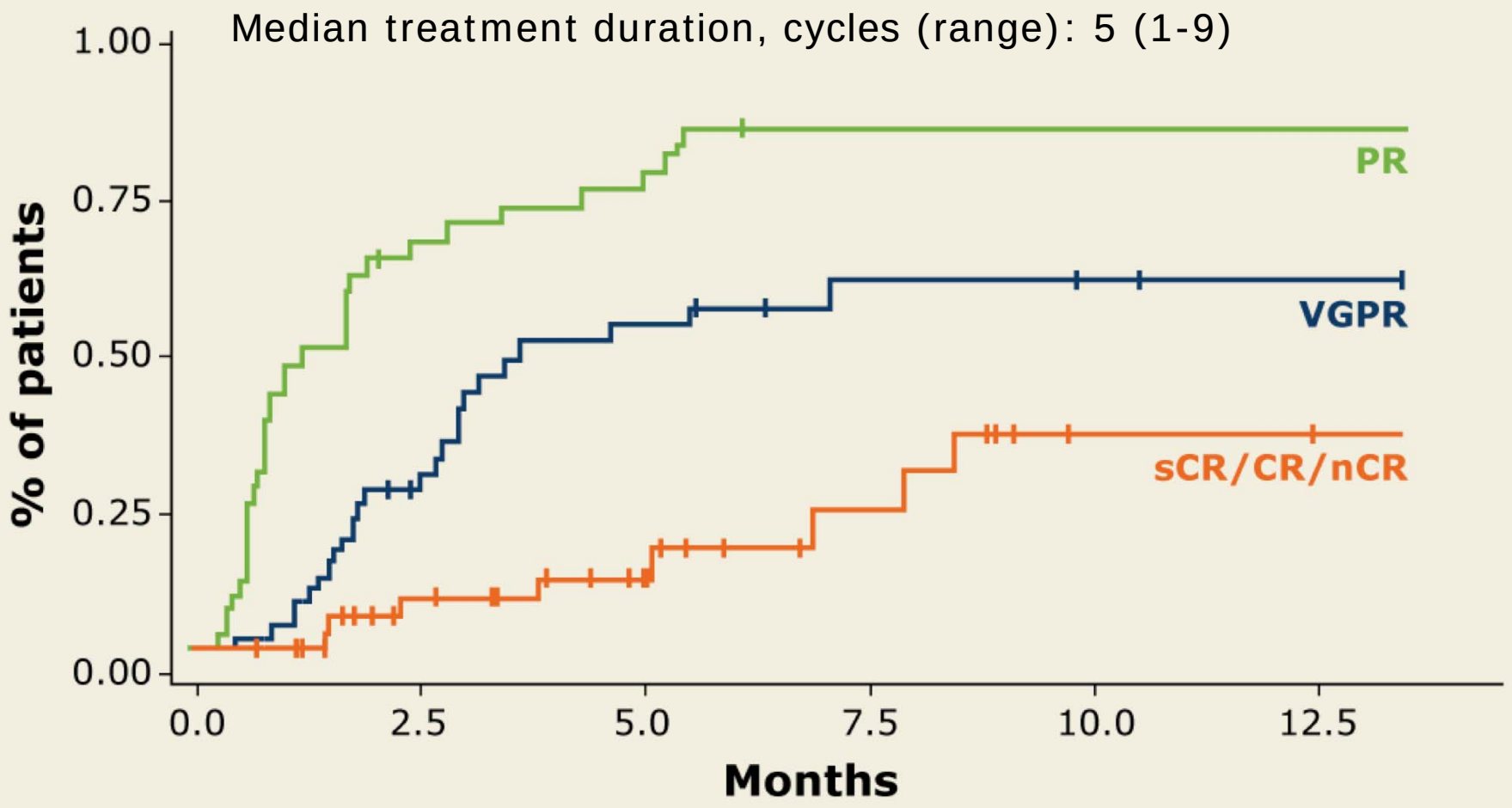




CR = complete response; sCR = stringent CR; nCR = near CR; VGPR = very good PR

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 730.

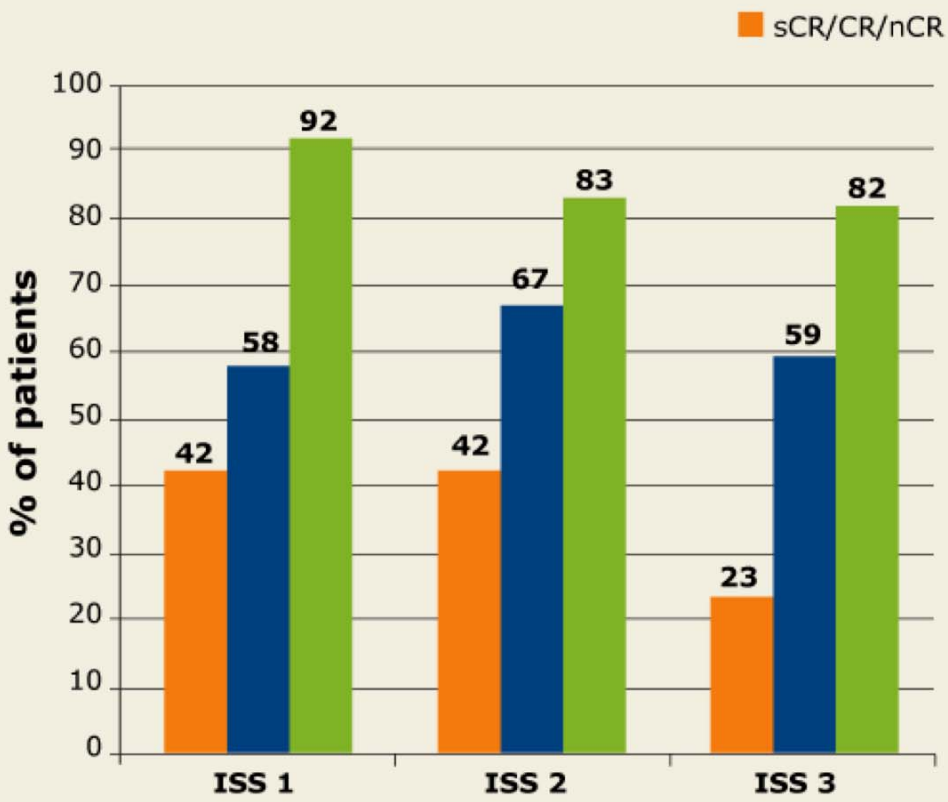
Time to Response (n = 58)



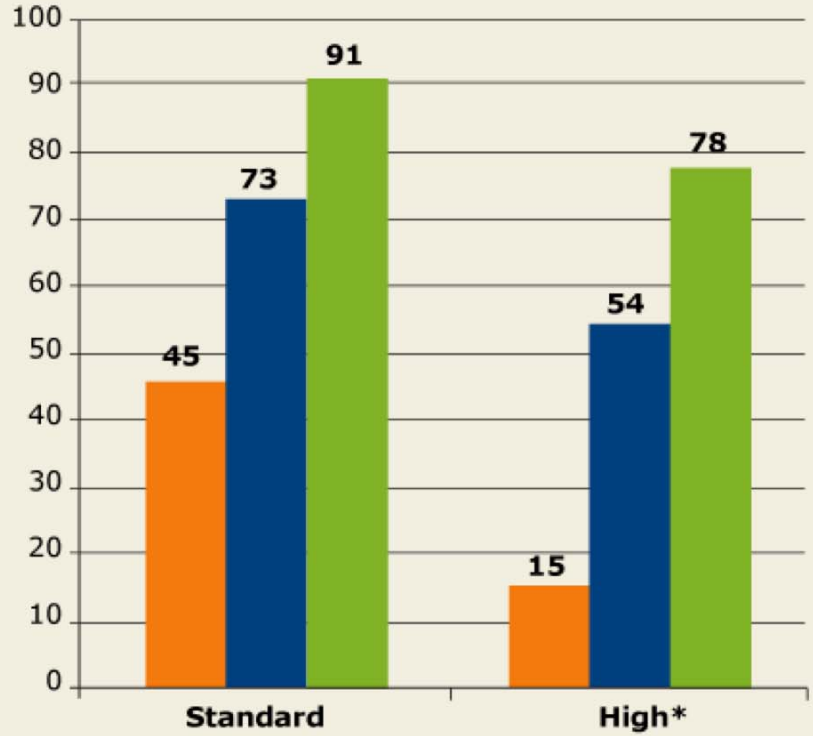
With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Subgroup Analysis of Best Response Rates

By ISS Staging (n = 58)



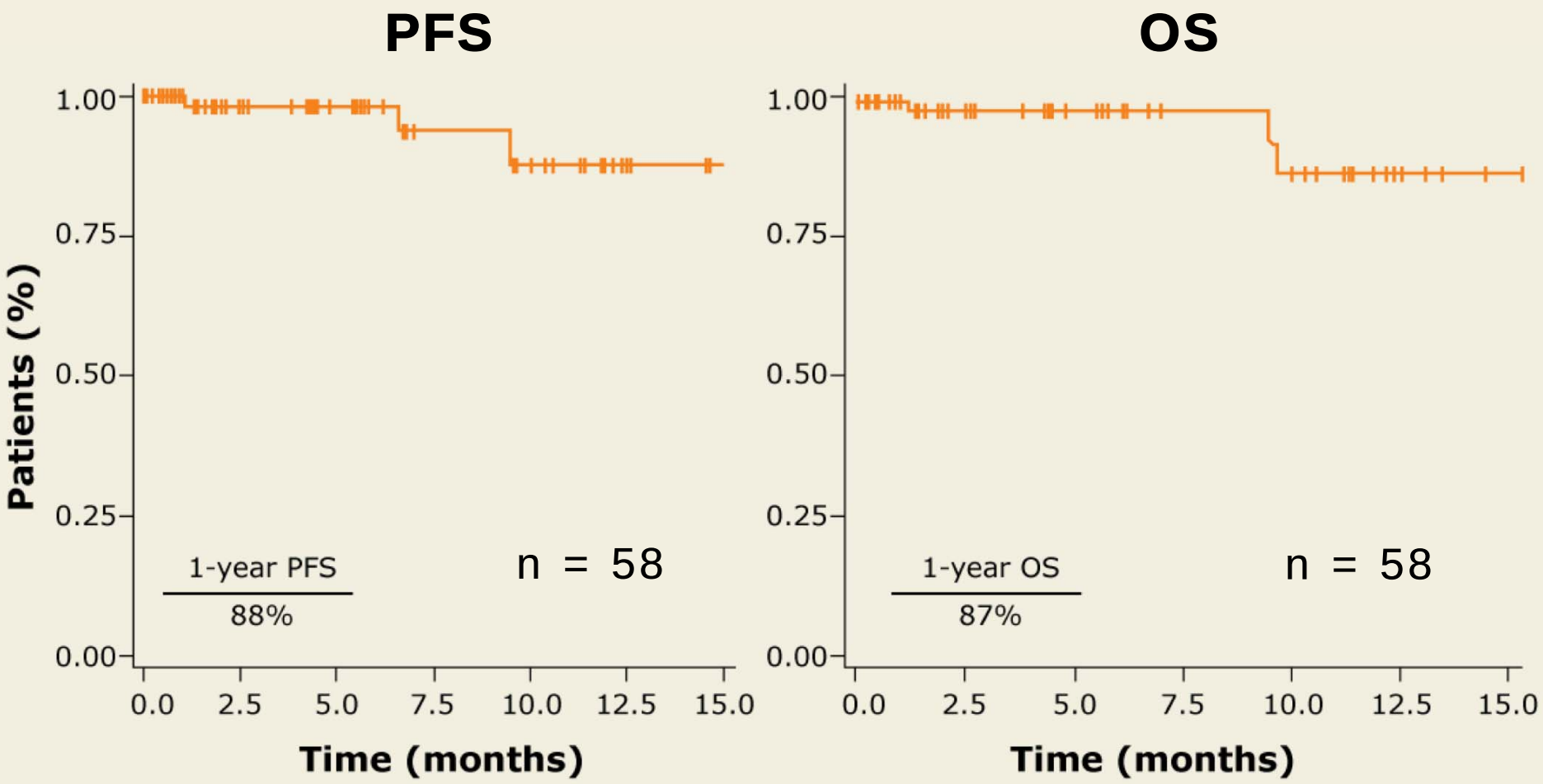
By Cytogenetic Risk (n = 51)



* Defined as presence of t(4;14), t(14;16) or del(17p)

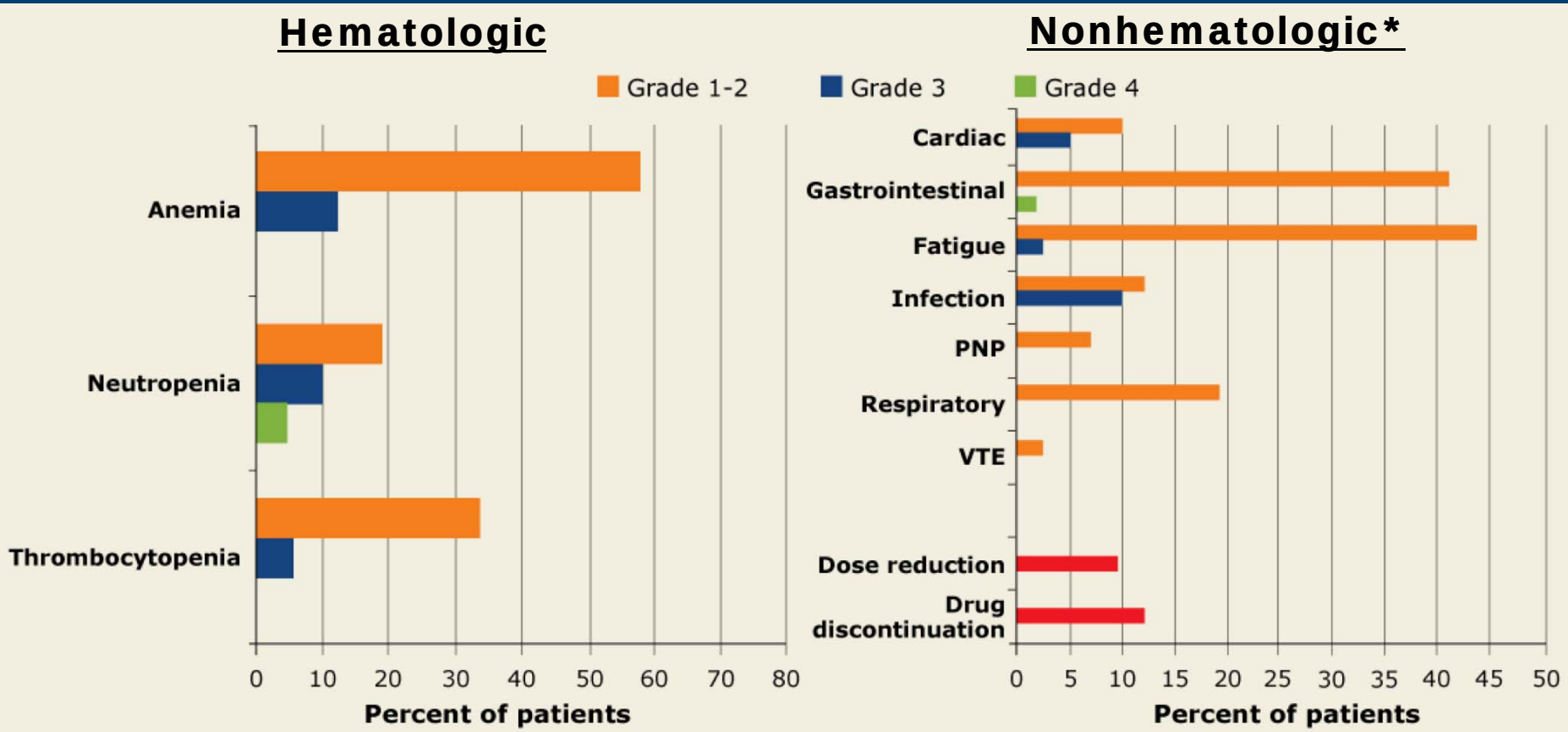
With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Progression-Free Survival (PFS) and Overall Survival (OS)



With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Adverse Events (AEs) of All Grades (n = 58)



* No difference between patients younger or older than 75 years

- Grade 3 cardiac AEs: Acute MI, atrial fibrillation; Grade 3 infections: Pneumonia and bronchitis; Grade 4 GI AEs: Ileum perforation

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Author Conclusions

- In comparison to other regimens, CCd showed encouraging activity in elderly patients with newly diagnosed MM.
  - ≥VGPR: CCd (77%), MPT (36%), VMP (41%)
  - nCR/CR/sCR: CCd (53%), MPT (27%), VMP (30%)
  - sCR: CCd (23%), MPT (not reported), VMP (not reported)
- The CCd combination was well tolerated.
  - Platelets: CCd (5%), MPT (3%), VMP (37%)
  - Peripheral neuropathy: CCd (0%), MPT (6%), VMP (14%)
  - Venous thromboembolism: CCd (0%), MPT (9%), VMP (1%)
  - Discontinuation: CCd (12%), MPT (35%), VMP (33%)

Palumbo A et al. *Proc ASH* 2012;Abstract 730.

Investigator Commentary: CCd for Elderly Patients with Newly Diagnosed MM

For elderly patients with newly diagnosed MM, melphalan and prednisone have been combined with novel therapies like lenalidomide or bortezomib. These combinations have prolonged PFS and OS compared to melphalan/prednisone alone in randomized trials. Palumbo and colleagues similarly combined carfilzomib, a novel proteasome inhibitor, with cyclophosphamide and dexamethasone, followed by carfilzomib maintenance. The response rate increased to ≥PR of 100%, ≥VGPR of 77% and CR/sCR/nCR of 53% with sCR of 23% after 9 cycles of therapy. Although the follow-up period was short, 1-year PFS and OS were 88% and 87%, respectively.

These data suggest that, like bortezomib, the incorporation of carfilzomib into the initial treatment of elderly patients with newly diagnosed MM can achieve high rates and extent of response, with a favorable side-effect profile. Also, it was possible to escalate the carfilzomib dose to 36 mg/m^2 while maintaining a favorable therapeutic index. It is exciting that the CCd regimen was effective even in patients with high-risk cytogenetics, although follow-up was short and early relapses may still occur. This study suggests that carfilzomib in combination with melphalan/prednisone may have utility as first-line therapy for elderly patients with MM and warrants further testing. This is one of the first studies to examine the efficacy and tolerability of carfilzomib maintenance in this setting.

Interview with Kenneth C Anderson, MD, March 3, 2013

A Multi-Center Phase I/II Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory Multiple Myeloma

Shah JJ et al.

Proc ASH 2012;Abstract 74.

Background

- Carfilzomib, an irreversible proteasome inhibitor (PI), and pomalidomide, an immunomodulatory drug (IMiD), are novel agents that have each demonstrated single-agent activity in relapsed/refractory multiple myeloma (MM).
- Preclinical evidence supports the combination of PIs with IMiDs to overcome drug resistance and improve response rates (*Blood* 2002;99:4525).
- In addition, early data with carfilzomib and lenalidomide (Len)/dexamethasone yielded encouraging high response rates in relapsed or refractory MM (*Proc ASH* 2009;Abstract 304).
- **Study objective:** To determine the maximum tolerated dose (MTD), efficacy and safety of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) for patients with relapsed or refractory MM.

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

3 + 3 Phase I Dose-Escalation Study

- All patients had Len-refractory MM that was relapsed/refractory to their most recent therapy
- Carfilzomib dose on d1, 2 of cycle 1 for all cohorts was 20 mg/m^2
- For all cohorts, dexamethasone dose was reduced to 20 mg after cycle 4

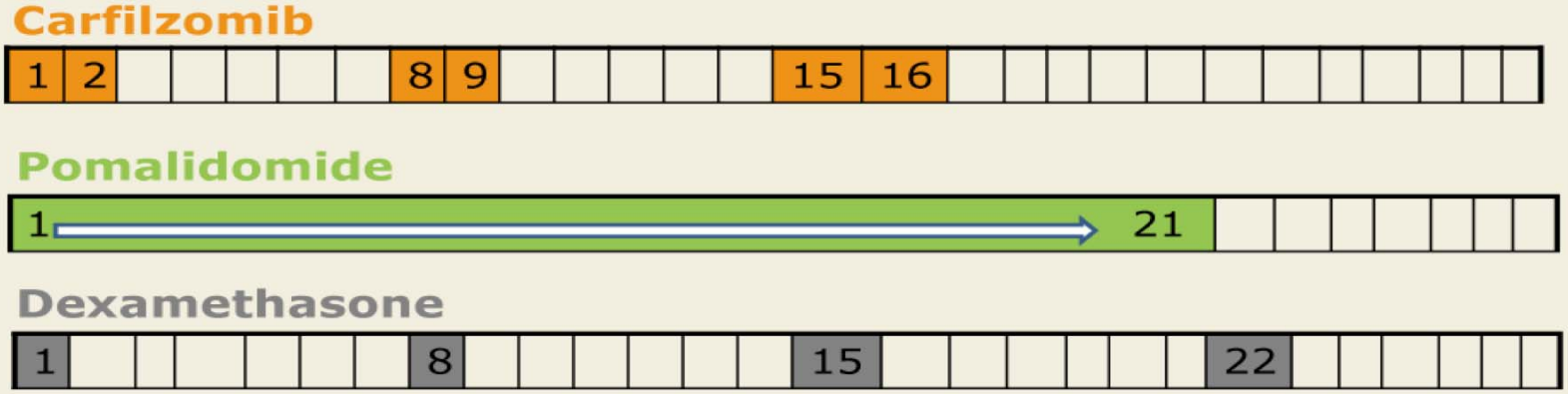
Cohort (n = 12)	Carfilzomib	Pomalidomide	Dexamethasone
Cohort 1	27 mg/m^2	3 mg	40 mg
Cohort 1 (MTD)	27 mg/m^2	4 mg	40 mg
Cohort 2	36 mg/m^2	4 mg	40 mg
Cohort 3	45 mg/m^2	4 mg	40 mg
Cohort 4	56 mg/m^2	4 mg	40 mg

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Study Schema

- 12 patients enrolled in Phase I and 20 additional patients enrolled at MTD (n = 32)
- 97% of patients had MM that was also refractory to bortezomib

Treatment cycles 1-6: 28-day cycles



- Cycles ≥7: Maintenance cycles with carfilzomib dosed on d1, 2, 15, 16; pomalidomide/dexamethasone unchanged

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Response Rates

Response	n = 30
Overall response rate	50%
Very good partial response (VGPR)	13%
Partial response (PR)	37%
Minimal response (MR)	17%
Stable disease (SD)	23%
Progressive disease (PD)	10%

Clinical benefit rate (≥MR): 67%

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Response Rates According to Cytogenetic Risk Status*

n (%)	High (n = 5)	Intermediate (n = 6)	Standard (n = 18)	Total (n = 29)
VGPR	0 (0%)	0 (0%)	4 (22%)	4 (14%)
PR	4 (80%)	2 (33%)	6 (33%)	12 (41%)
MR	1 (20%)	1 (17%)	3 (17%)	5 (17%)
SD	0 (0%)	2 (33%)	3 (17%)	5 (17%)
PD	0 (0%)	1 (17%)	2 (11%)	3 (10%)

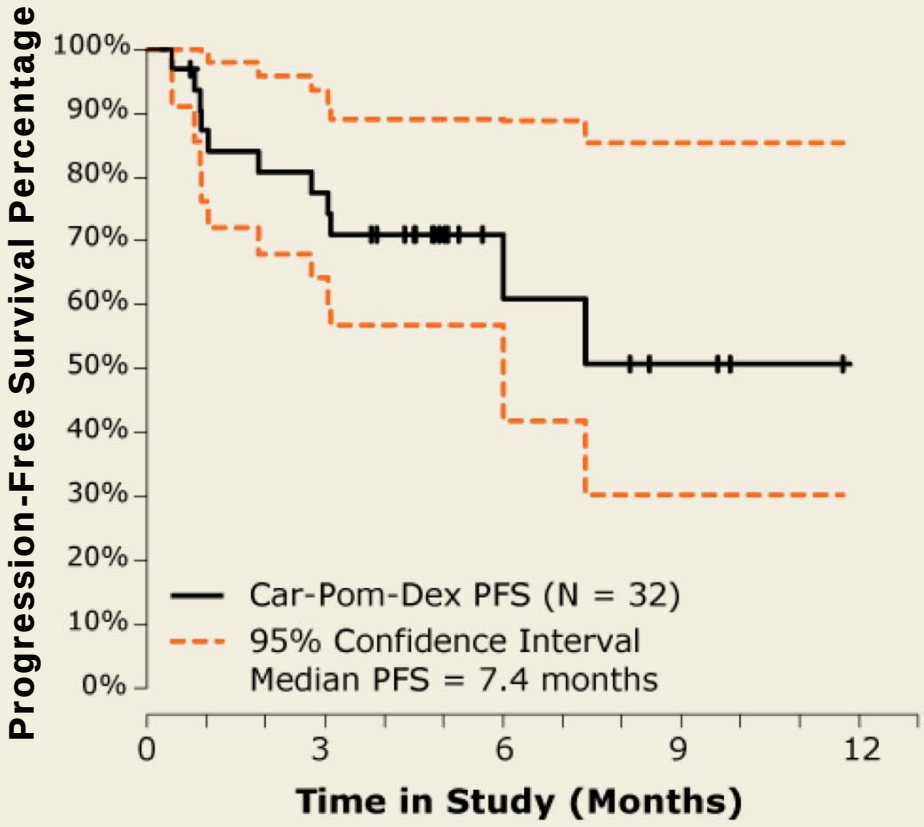
* According to mSMART risk classification: high risk, 17p-positive/t(14;16); intermediate risk, t(4;14)-positive/hypodiploid; standard risk, hyperdiploid/t(11;14); FISH/cytogenetic data missing for 1 patient

Responses were preserved in patients with high-risk FISH/cytogenetics.

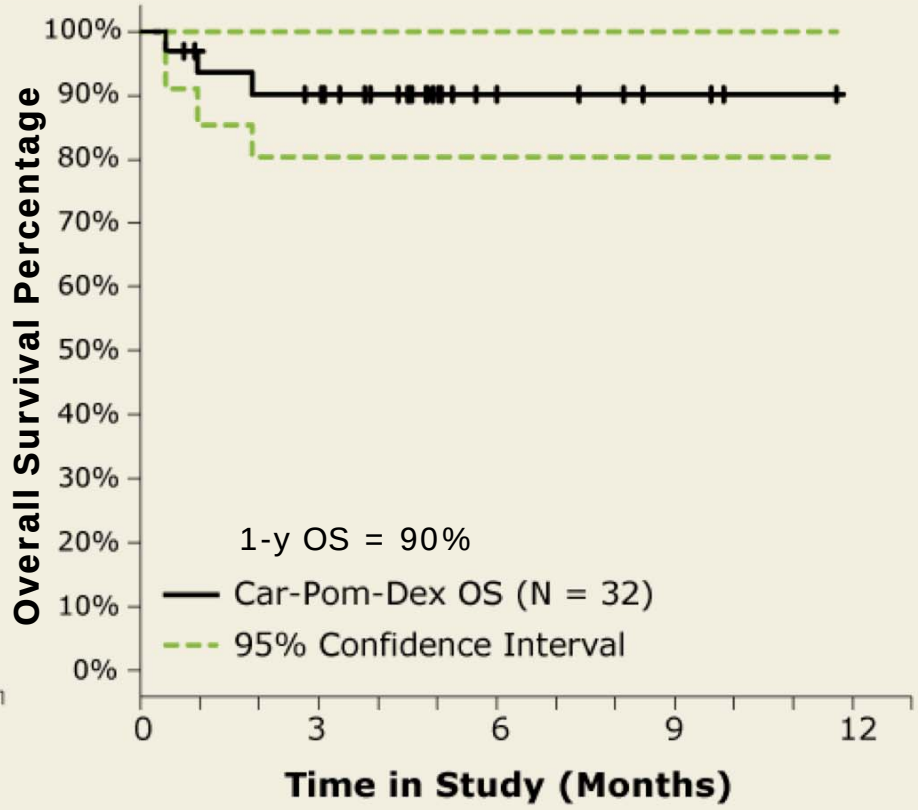
Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Survival Outcomes (All Patients)

Progression-free survival (PFS)



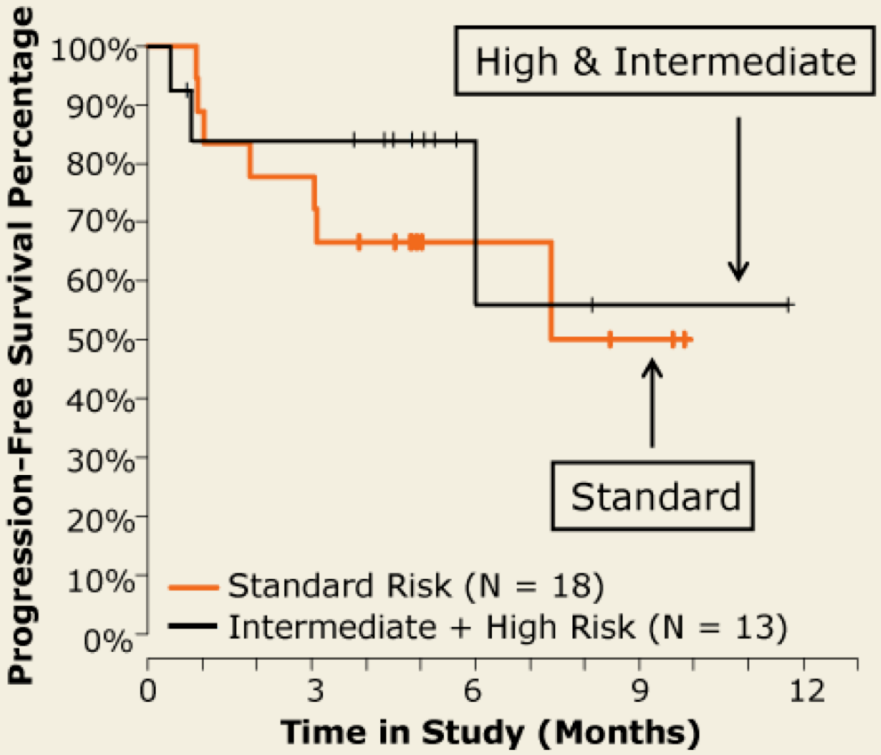
Overall survival (OS)



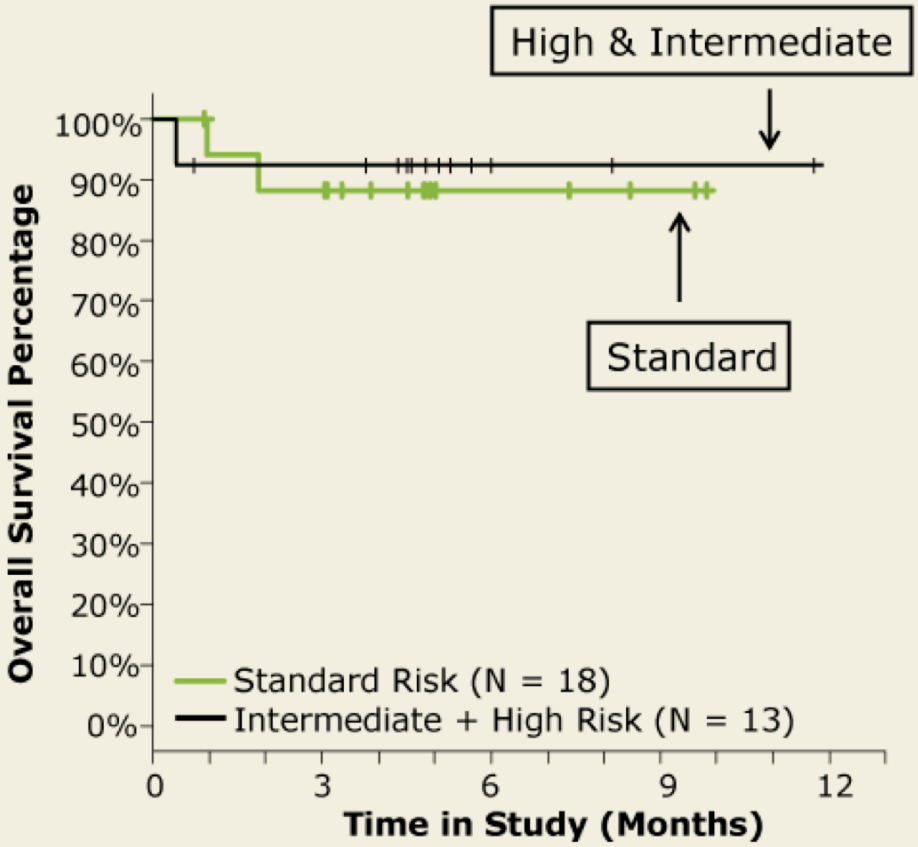
With permission from Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Survival According to Cytogenetic Risk Status

Progression-free survival (PFS)



Overall survival (OS)



Responses and survival were sustained and durable independent of risk status.

With permission from Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Hematologic Adverse Events (n = 32)

Adverse event (AE)	All grades	Grade 3	Grade 4
Anemia	63%	34%	3%
Thrombocytopenia	56%	22%	6%
Neutropenia	84%	41%	16%
Febrile neutropenia	6%	6%	0%

- Low incidence of febrile neutropenia
- Hematologic toxicites were reversible and manageable
- No Grade 3 or 4 peripheral neuropathy; serious AEs: pneumonia (n = 3), pulmonary embolus (n = 1), congestive heart failure (n = 1)

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Author Conclusions

- The MTD was carfilzomib at 20/27 mg/m^2, pomalidomide at 4 mg and dexamethasone at 40 mg in relapsed/refractory MM.
- Car-Pom-d was well tolerated with no unexpected toxicities:
  - Limited Grade 3 and 4 nonhematologic AEs were observed, and no Grade 3 or 4 peripheral neuropathy was observed (data not shown).
- Combination therapy with Car-Pom-d was highly active in this patient population with heavily pretreated relapsed or refractory MM.
- Car-Pom-d produced encouraging preserved response rates and survival outcomes independent of FISH/cytogenetic risk status.
- Enrollment is ongoing in a Phase II trial within the Academic Myeloma Consortium (NCT01464034).

Shah JJ et al. *Proc ASH* 2012;Abstract 74.

Investigator Commentary: A Phase I/II Trial of Carfilzomib, Pomalidomide and Dexamethasone for Relapsed or Refractory MM

Pomalidomide (Pom) was recently granted accelerated FDA approval for the treatment of MM in patients whose disease has progressed during or after treatment with bortezomib and an IMiD. In that setting, carfilzomib achieved a response rate (RR) of about 20% to 24% with a duration of response of 8 months and an OS of 15 months. After the accelerated approval of carfilzomib, it has gone forward to be used with Len/dexamethasone (dex) in relapsed MM with an RR of about 55%. This provided the basis for the ongoing ASPIRE trial evaluating carfilzomib/Len/dex versus Len/dex in relapsed MM.

This was a dose-escalation Phase I trial of Pom/carfilzomib, and the MTD was actually the first dose — carfilzomib at 20-27 mg/m^2, Pom at 4 mg and dex at 40 mg. Both Pom and carfilzomib were so potent that there was no opportunity to escalate either one when combined. The RRs were higher, as one might have predicted, and at the MTD this combination was well tolerated. This study further confirms the exciting ability to combine an IMiD with a PI. Pom and carfilzomib are second-generation, more potent drugs in their classes. Even in MM that is refractory to Len and bortezomib, the combination achieved an RR of about 50% regardless of adverse cytogenetics.

Interview with Kenneth C Anderson, MD, January 22, 2013

Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma

Kumar SK et al.

Proc ASH 2012;Abstract 332.

Background

- The high response rates seen with the bortezomib, lenalidomide and dexamethasone regimen highlight the feasibility of combining a proteasome inhibitor with an immunomodulatory agent and a steroid for untreated multiple myeloma (MM) (*Blood* 2012;119(19):4375).
- MLN9708 is an investigational, oral, reversible proteasome inhibitor with promising antimyeloma effects and a favorable toxicity profile with low rates of peripheral neuropathy (*Proc ASCO* 2012;Abstract 8034; *Proc ASCO* 2012;Abstract 8017).
- **Objective:** Present updated results of the Phase I/II study evaluating the efficacy and safety of weekly MLN9708 in combination with lenalidomide and dexamethasone in patients with previously untreated MM.

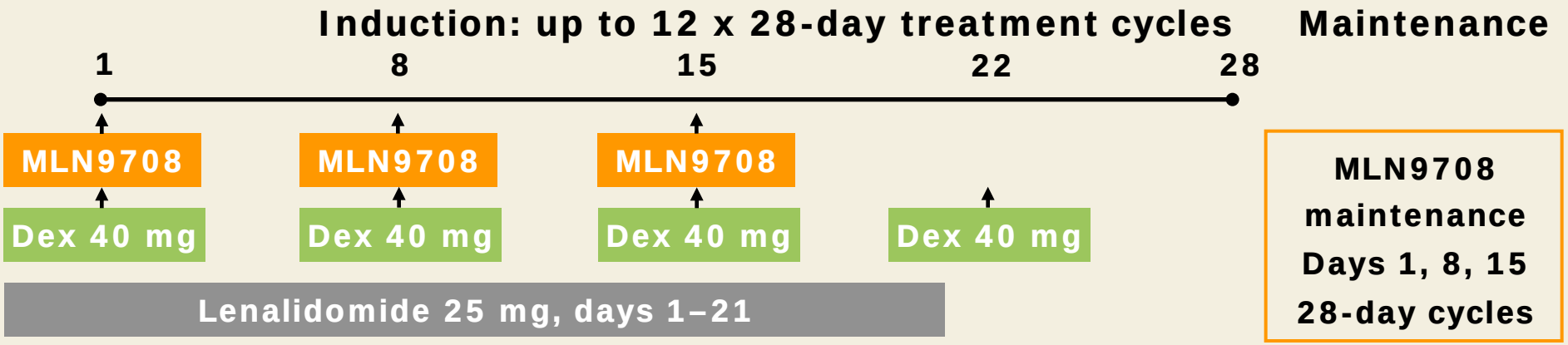
Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Eligibility and Key Objectives

- **Eligibility:**
  - Previously untreated MM and measurable disease
  - No Grade ≥2 peripheral neuropathy or prior/concurrent deep vein thrombosis/pulmonary embolism
- **Phase I objectives:** Safety, tolerability, maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)
- **Phase II objectives:**
  - Primary: Combined complete and very good partial response (CR + VGPR) rate, safety and tolerability
  - Secondary: Overall response rate (ORR), time to response, duration of response and progression-free survival
  - Exploratory: ORR in patients with high-risk cytogenetics and minimal residual disease (MRD) status in patients achieving CR

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Phase I/II Study Design



- Phase I (n = 15): 4 MLN9708 dose-escalation cohorts from 1.68 to 3.95 mg/m^2, based on dose-limiting toxicities (DLTs) in cycle 1
- Phase II (n = 53):
  - 3 patients from the dose-escalation cohort, 50 patients from Phase II
  - MLN9708 at the RP2D of 4.0 mg
- Mandatory thromboprophylaxis with aspirin or low molecular weight heparin

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Preliminary Response Data

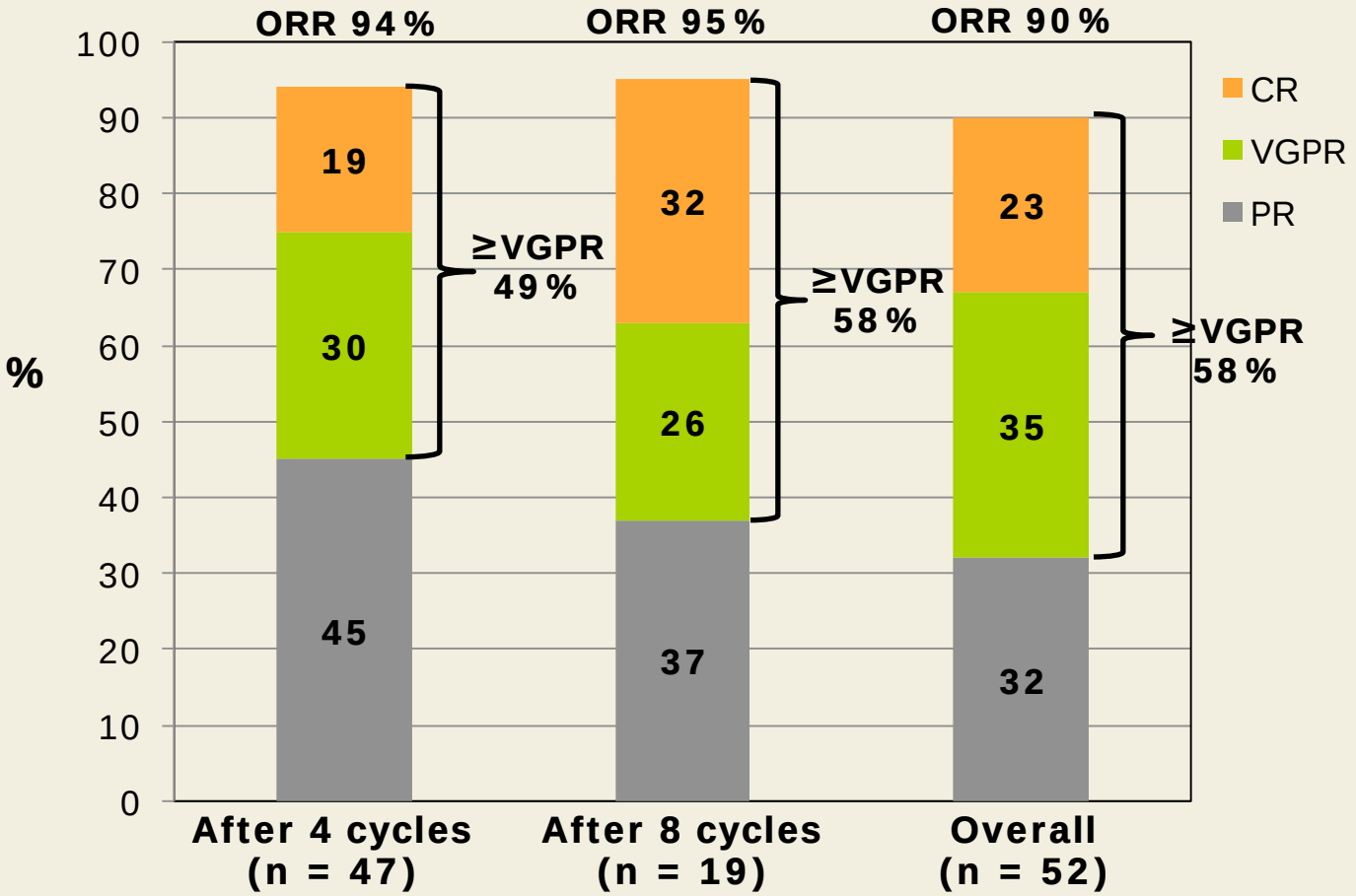
	Phase I (n = 15)	RP2D (n = 52)	Total (n = 64)
ORR	100%	90%	92%
≥VGPR	53%	58%	55%
CR + nCR*	33%	29%	28%
CR	33%	23%	23%

* Required bone marrow confirmation per protocol

- 64 of 65 patients were evaluable for response
- Median number of cycles of MLN9708 received in Phase I and RP2D was 6 and 7, respectively
- Median time to first response (≥PR) was 1 cycle
- Median duration of response not reached
- Similar responses seen in patients with favorable and unfavorable cytogenetics

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

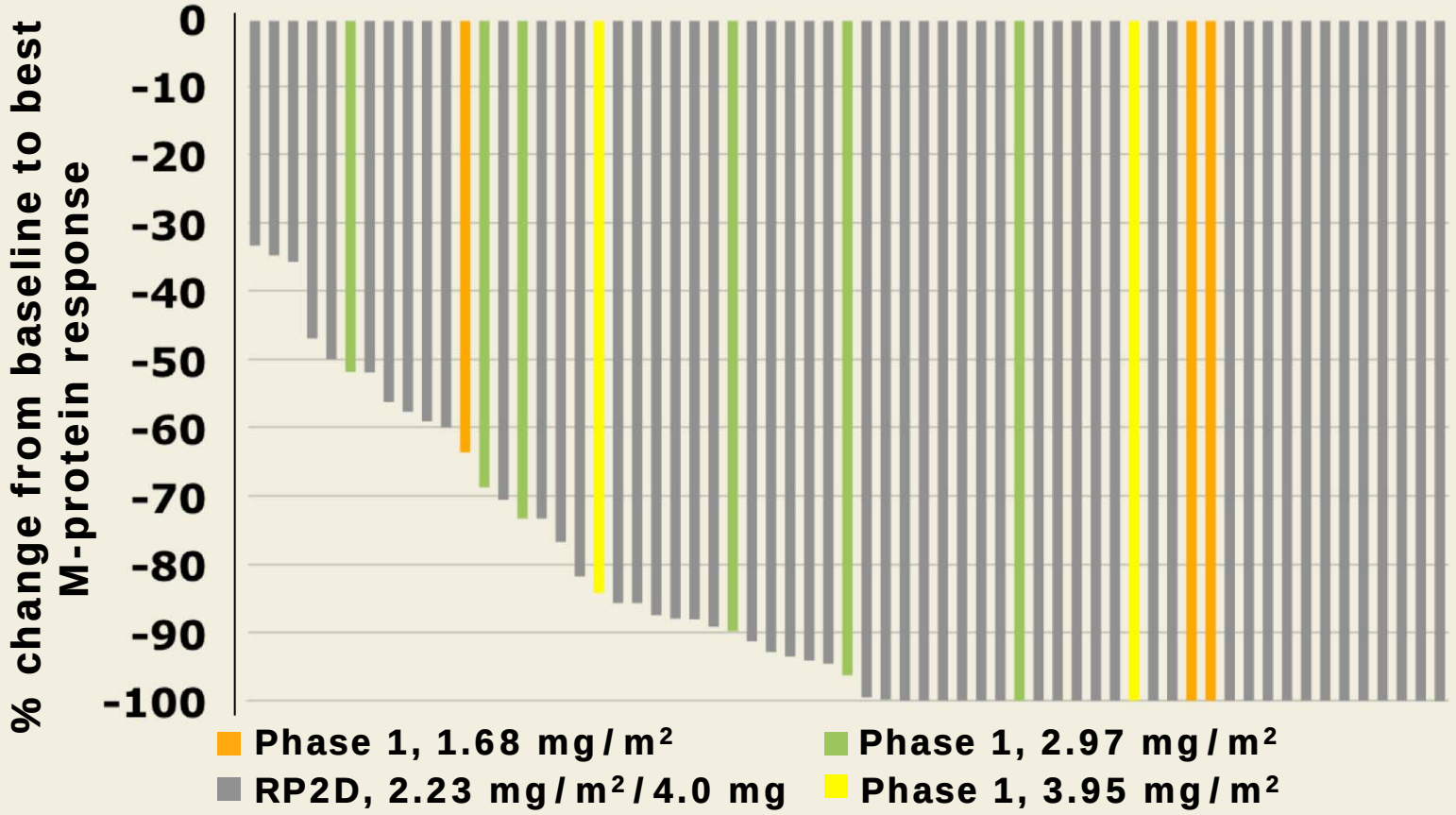
Preliminary Response Over Course of Treatment at RP2D



- Patients treated at RP2D (2.23 mg/m^2 or 4.0 mg fixed dose)
- 3 response-evaluable patients completed 12 cycles: CR (n = 2), VGPR (n = 1)

With permission from Kumar SK et al. *Proc ASH* 2012;Abstract 332.

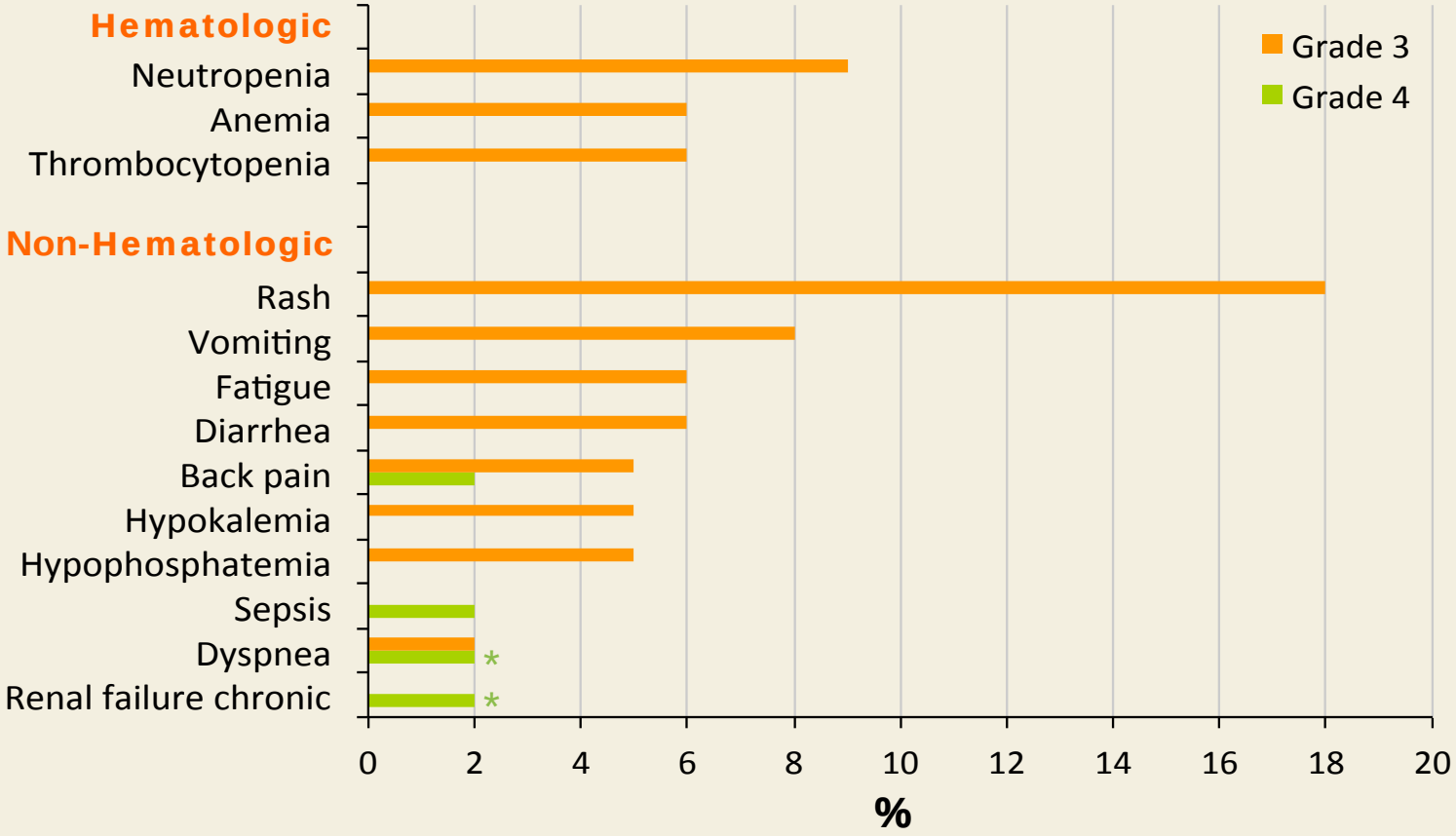
Best Percent Change in M-Protein from Baseline in Response-Evaluable Patients



- 48% of patients achieved a 100% reduction in M-protein
- Reductions were seen at multiple dose levels

With permission from Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Select Grade 3 (≥5%) and Grade 4 Adverse Events (N = 65)



* Occurred in the same patient

- 1 patient treated at RP2D (4.0 mg) died on study, possibly treatment related

With permission from Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Peripheral Neuropathy (PN)

- Treatment-emergent PN: 21 (32%) patients; 2 patients had PN at baseline
- PN was Grade 1 in the majority of patients: 13 (20%)
- Grade 2 PN reported in 6 (9%) patients
- Grade 3 PN reported in 2 (3%) patients
  - Both patients off study
  - PN has resolved in 1 and reduced to Grade 1 in the other

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Author Conclusions

- The all-oral combination of weekly MLN9708, lenalidomide and dexamethasone appears to be generally well tolerated with limited PN.
- The primary endpoint of the study was met, suggesting antitumor activity at the RP2D.
  - 92% of patients had achieved ≥PR, including a ≥VGPR rate of 55% and a CR rate of 23% at a median drug exposure of 6 months.
  - Responses increased with number of cycles and deepened over time.
  - 88% of patients achieving CR who were evaluable for MRD status were confirmed as MRD-negative (data not shown).
- A Phase III trial of MLN9708 with lenalidomide/dexamethasone for relapsed and/or refractory MM is currently enrolling (NCT01564537), and a Phase III trial of MLN9708 with lenalidomide/dexamethasone in previously untreated MM is being planned.

Kumar SK et al. *Proc ASH* 2012;Abstract 332.

Investigator Commentary: Phase I/II Study of MLN9708 with Lenalidomide and Dexamethasone in Untreated MM

MLN9708 is similar to bortezomib in terms of its structure and predicted activity. This study demonstrated an impressive 90% response rate with a complete remission rate higher than 20%. These results are slightly better than lenalidomide/dexamethasone and approach the type of results seen with bortezomib/lenalidomide and dexamethasone in the same patient population. The advantages of MLN9708 are that it is an oral inhibitor, as opposed to subcutaneous or intravenous bortezomib, it elicits high response rates and it does not have significant toxicity, with a low rate of neuropathy. If we had a completely oral regimen that we could offer patients, this regimen could be a game changer.

Interview with A Keith Stewart, MBChB, January 9, 2013

The idea of combining a proteasome inhibitor with an immunomodulatory drug is exciting. This study of MLN9708 with lenalidomide/ dexamethasone showed almost universal responses and good tolerability. I believe if the results continue to be promising, we are likely to have an all-oral regimen to treat multiple myeloma in the future.

Interview with Kenneth C Anderson, MD, January 22, 2013

Treatment with Bendamustine-Bortezomib-Dexamethasone in Relapsed/Refractory Multiple Myeloma Shows Significant Activity and Is Well Tolerated

Ludwig H et al.

Proc ASH 2012;Abstract 943.

Background

- The clinical activity of bendamustine (BEN) as a single agent and in combination therapy, coupled with its potential lack of cross-resistance with several other agents, make it an attractive therapy for newly diagnosed and refractory hematologic malignancies.
- Its structural and mechanistic features differentiate it from other alkylating agents, providing increased stability and potency in DNA crosslinking and subsequent cytotoxicity.
- Several studies have suggested that bendamustine may exert synergistic activity when combined with bortezomib (BTZ) (*Proc ASH* 2007;Abstract 4851; *Proc ASCO* 2012;Abstract 8014).
- **Study objective:** To evaluate the efficacy and safety of BEN in combination with BTZ and dexamethasone (Dex) for patients with relapsed or refractory multiple myeloma (MM).

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Phase II Trial Design

Eligibility (n = 79)

Relapsed/refractory MM after ASCT or standard chemotherapy

From 1 to 6 prior therapy lines

Platelets: ≥100 x 10^9/L

No BEN/BTZ within previous 6 months

→

BEN + BTZ + Dex (n = 79)

BEN: 70 mg/m^2 (IV), d1, 4

BTZ: 1.3 mg/m^2 (IV), d1, 4, 8, 11

Dex: 20 mg, d1, 4, 8, 11

q4wk for up to 8 cycles

ASCT = autologous stem cell transplant

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

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Response Rates

Response	n = 71*
ORR	67.6%
sCR/CR/nCR	21.2%
Very good partial response (VGPR)	15.5%
Partial response (PR)	31.0%
Minimal response (MR)	16.9%
Stable disease (SD)	15.5%

CR = complete response; sCR = stringent CR; nCR = near complete response
* Eight patients who completed <2 treatment cycles were excluded from analysis.

- Of patients previously exposed to BTZ or lenalidomide (Len) and completing ≥2 cycles,
  - Those who experienced CR to PR: 28/45 (BTZ); 23/39 (Len)
  - Those who experienced CR to MR: 37/45 (BTZ); 30/39 (Len)

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Survival Outcomes

Intent-to-treat population	**n = 79**	
Median PFS	9.7 months	
Median OS	Not yet reached (NYR)	
Two-year OS	60%	
By prior lines of therapy	**1 to 2 (n = 46)**	**3 to 6 (n = 25)**
Median PFS*	12 months	7.8 months
Median OS†	NYR	20.6 months

* $p = 0.069$; † $p = 0.007$

- Median follow-up period was 13.7 months.
- No significant difference in median PFS and OS was observed when analysis was based on the time from the start of first treatment line (≤46 vs >46 months).

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

PFS and OS According to Prior Exposure to BTZ and/or Len

Outcome	No BTZ	BTZ	*p*-value
Median PFS	12 months	7.8 months	0.187
Median OS	NYR	NYR	0.800
	No Len	**Len**	***p*-value**
Median PFS	12.8 months	8 months	0.009
Median OS	NYR	20.6 months	0.006
	No BTZ or Len	**BTZ and Len**	***p*-value**
Median PFS	12.8 months	7 months	0.001
Median OS	NYR	20.6 months	0.034

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

PFS and OS According to Cytogenetic Risk

Outcome	Cytogenetic risk		*p*-value
	Standard	High	
Median PFS	9.7 months	9.4 months	0.662
Median OS	NYR	20.6 months	0.12

- Multivariate analysis of prognostic parameters demonstrated a significant difference in PFS when analyzed according to age (<65 versus ≥65 years), $p = 0.011$.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Select Adverse Events (AEs)

AE (n = 79)	Grade 1 or 2	Grade 3	Grade 4
Anemia	—	15%	3%
Leucopenia	—	16%	1%
Thrombocytopenia	—	32%	6%
Polyneuropathy	49%	5%	1%
Infection/sepsis	43%	16%	4%
Insomnia/fatigue	40%	3%	—
Nausea/emesis	33%	1%	—
Diarrhea	22%	8%	—

- Grade 5 infection/sepsis (n = 2); Grade 4 exanthema (n = 1)
- Peripheral neuropathy (PN) increased over time from cycle 2 to 8; Grade 3 or 4 PN was highest at the end of cycle 8, observed by investigators in <10% of pts.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Author Conclusions

- This study demonstrated an ORR of 67.6% and a sCR/CR of 21.2% in the evaluable patient population.
  - The rate of sCR/CR and VGPR was significantly lower for patients previously exposed to 3 or more lines of therapy (data not shown).
- In the intent-to-treat population, the median PFS was 9.7 months and the median OS has not yet been reached.
  - No significant difference was observed in PFS and OS between patients with and without high-risk cytogenetics.
  - PFS and OS were significantly shorter with BTZ and/or Len pretreatment.
- PN increased over time, and patient self-rated symptoms were significantly higher than investigator ratings.
- The BEN/BTZ/Dex treatment regimen was well tolerated.
- This regimen is a valuable choice for second- and further-line therapy.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

Investigator Commentary: Phase II Study of Bendamustine in Combination with Bortezomib and Dexamethasone for Relapsed or Refractory MM

Ludwig and colleagues evaluated bendamustine 70 mg/m^2 on days 1 and 4, bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 and dexamethasone 20 mg on days 1, 4, 8 and 11 every 4 weeks for a planned 8 cycles in 79 patients with relapsed or refractory MM. For 71 evaluable patients the overall response rate was approximately 67%, with 21% sCR/CR/nCR, 15.5% VGPR, 31% PR, 16.9% MR and 15.5% SD. Responses were seen in patients with heavily pretreated MM and those with adverse cytogenetics. The overall median PFS was 9.7 months. Previous exposure to lenalidomide was associated with a lower response rate and shorter time to disease progression.

This study demonstrated that the bendamustine/bortezomib/dexamethasone regimen is active in relapsed or refractory MM. Although this combination is active in patients with heavily pretreated MM, its side-effect profile may limit its repeated or chronic use. Moreover, 2 other novel agents, carfilzomib and pomalidomide, are active and are now FDA approved for the treatment of this patient population.

Interview with Kenneth C Anderson, MD, March 29, 2013

MM-005: A Phase 1, Multicenter, Open-Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose for the Combination of Pomalidomide, Bortezomib, and Low-Dose Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma

Richardson PG et al.

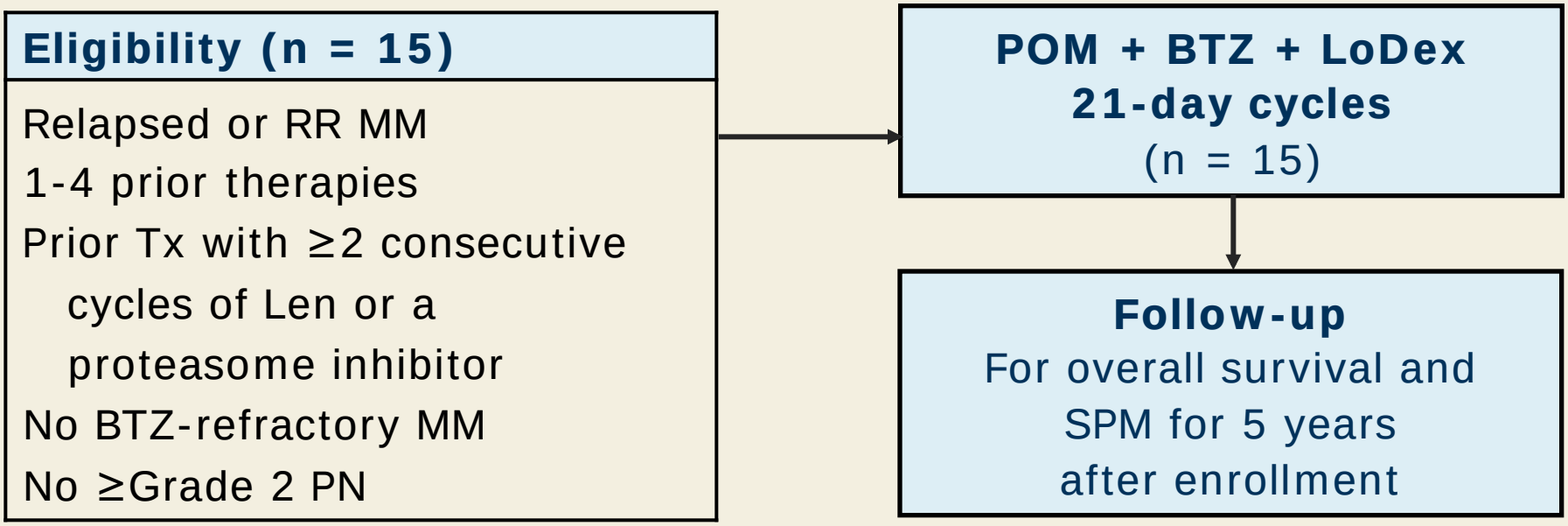
Proc ASH 2012;Abstract 727.

Background

- Pomalidomide (POM) is a distinct immunomodulatory agent with a mechanism of action involving antimyeloma activity, stromal cell-support inhibition and immune modulation.
- POM combined with low-dose dexamethasone (LoDex), demonstrated activity in relapsed/refractory (RR) multiple myeloma (MM) in patients who had previously received lenalidomide (Len) and/or bortezomib (BTZ) (*Proc ASCO* 2012;Abstract 8016).
- The combination of Len with BTZ (a proteasome inhibitor) and Dex demonstrated preclinical synergy with promising efficacy in the front-line and salvage settings in MM.
- **Study objective:** To determine the maximum tolerated dose (MTD) of POM in combination with BTZ and LoDEX for patients with relapsed or RR MM.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

MM-005: Phase I Trial Design



PN = peripheral neuropathy; SPM = second primary malignancy

- **Primary endpoint:** MTD
- **Secondary endpoints included:** Response (IMWG criteria), overall survival and safety
- Patients were evaluated every 21 ± 3 days; supportive care provided as needed.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

3 + 3 Design

Cohort	POM	BTZ	LoDex*
1 (n = 3)	1 mg/d	1 mg/m^2	20 mg
2 (n = 3)	2 mg/d	1 mg/m^2	20 mg
3 (n = 3)	3 mg/d	1 mg/m^2	20 mg
4 (n = 3)	4 mg/d	1 mg/m^2	20 mg
5 (n = 3)	4 mg/d	1.3 mg/m^2	20 mg
Expansion (n = 6)	MTD/maximum planned dose (MPD)		

* 10 mg for patients >75 years

- **POM:** d1-14
- **BTZ:** d1, 4, 8, 11 for cycles 1-8, then d1, 8 from cycle 9 onward
- **LoDex:** d1-2, 4-5, 8-9, 11-12 for cycles 1-8, then d1-2, 8-9 from cycle 9 onward
- **Required concomitant medications:** Aspirin or low-molecular-weight heparin for thromboprophylaxis and an antiviral prophylaxis agent

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Summary of Best Response

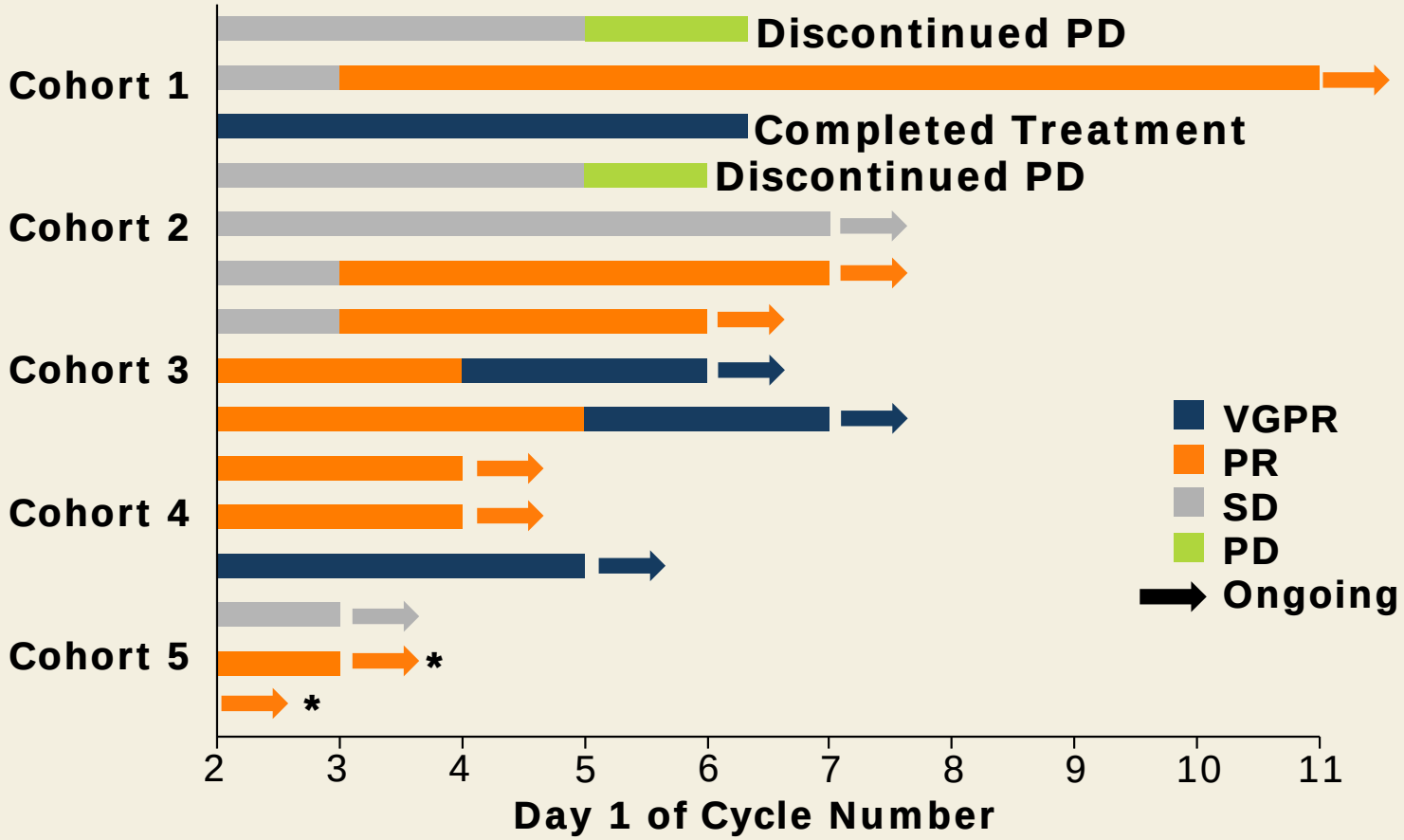
Cohort	VGPR (n)	PR (n)	SD (n)
1 (n = 3)	1	1	1
2 (n = 3)	0	1	2
3 (n = 3)	2	1	0
4 (n = 3)	1	2	0
5 (n = 3)	0	2	1
All patients	**ORR (≥PR)**	**VGPR**	**SD**
Cohorts 1-5 (n = 15)	73%	27%	27%

PR = partial response; VGPR = very good PR; SD = stable disease;
ORR = overall response rate

- Median time to response: 1 cycle (range 1-2)
- Most responses are currently ongoing

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Duration of Response



* Unconfirmed PR as of data cutoff

Total number of completed cycles: 59

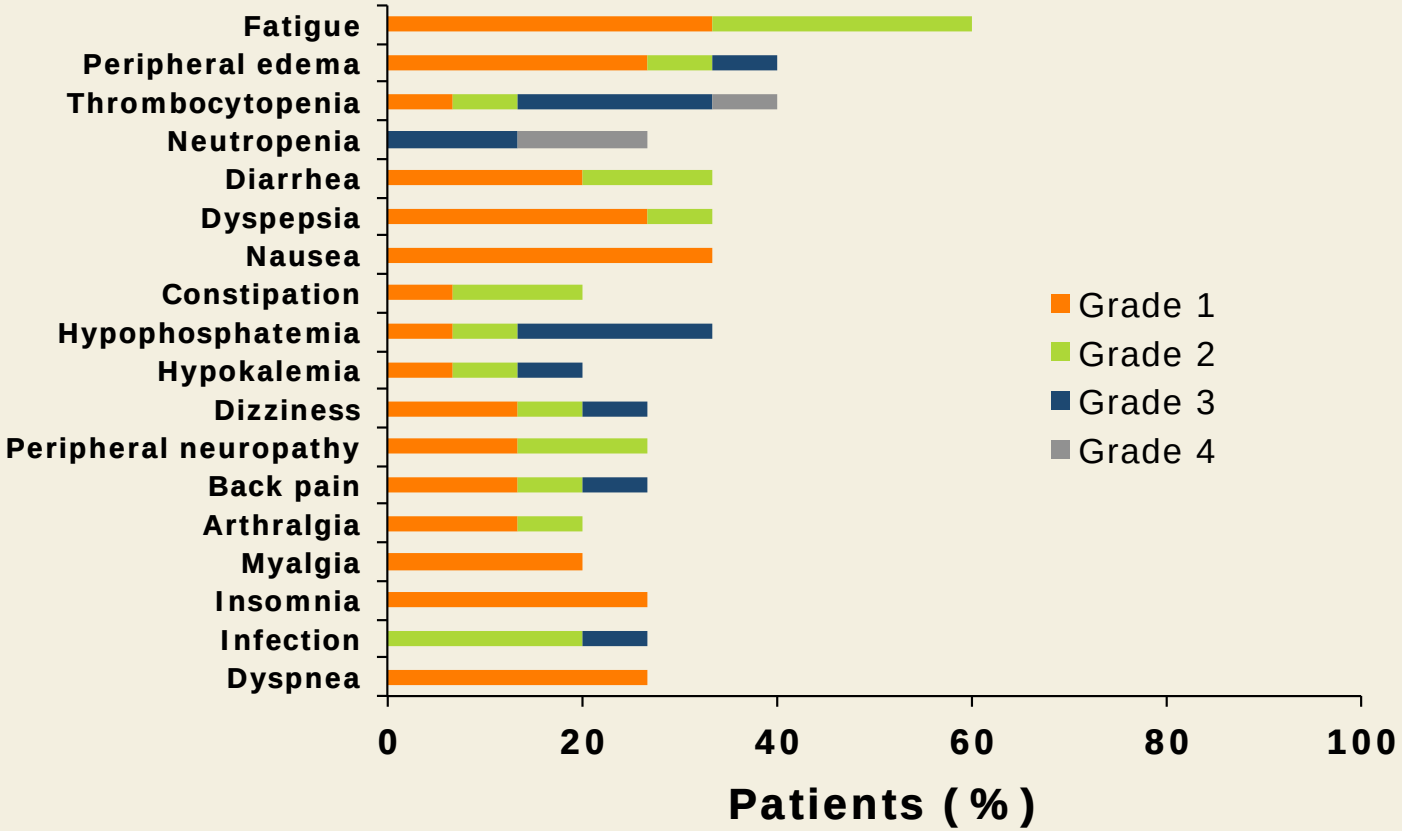
With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Summary of Trial Outcomes

- Total planned enrollment (n = 21)
  - Currently evaluable patients (n = 15)
- 12/15 patients on dose-escalation study remain on treatment
- No dose-limiting toxicities (DLTs) were observed at any dosage
- Confirmation of MTD is ongoing
- With appropriate dose adjustments, no patient discontinued all treatments
  - One patient discontinued BTZ due to persistent Grade 2 PN but continued to receive POM or LoDex, per protocol
- 5 patients have been added to the MTD/MPD expansion cohort, and none experienced DLTs at cycle 1
  - These patients were treated at the dosage administered to Cohort 5

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Select Adverse Events (≥20% of Patients)



- No Grade 3/4 PN observed
  - Grades 1 and 2 PN reported for 4 and 2 patients, respectively
- No DVT observed; no treatment discontinuation due to adverse events

With permission from Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Author Conclusions

- The combination of POM with BTZ/LoDex was well tolerated in patients with RR MM.
- POM/BTZ/Dex was active and produced responses in RR MM across all cohorts.
- The efficacy of POM/BTZ/Dex is encouraging with a favorable tolerability profile in the studied population, including those with RR MM harboring adverse cytogenetics (data not shown).
- The MPD identified in this trial will serve as the recommended dose for the recently activated Phase III MM-007 trial comparing POM/BTZ/Dex to BTZ/Dex.
- The observed activity of POM/BTZ/Dex provides a strong rationale for POM use in different therapeutic combinations.
- Phase I/II trials evaluating POM/steroids with other agents are ongoing in RR MM.

Richardson PG et al. *Proc ASH* 2012;Abstract 727.

Investigator Commentary: Phase I MM-005 Dose-Escalation Study of Combination Therapy with POM/BTZ/Dex for RR MM

In this study, POM was escalated from 1 to 4 mg/d and BTZ from 1 to 1.3 mg/m^2. No dose-limiting toxicities were observed at any dose level, and the combination of POM (4 mg) with BTZ (1.3 mg/m^2) and Dex (20 mg) is the regimen for further clinical evaluation. No Grade 3 or 4 peripheral neuropathy or deep vein thrombosis was observed, and none of the patients discontinued therapy. The ORR was 73%, with 27% VGPR and 27% stable disease.

POM received accelerated FDA approval based on a Phase II trial demonstrating an ORR of 34% and an overall survival of approximately 14 months. Preclinical studies demonstrated that the combination of the immunomodulatory drugs thalidomide or lenalidomide with proteasome inhibitors mediates synergistic myeloma cytotoxicity, and clinical trials demonstrated high overall and extent of response. This study suggests that the addition of BTZ to the next-generation and more potent immunomodulatory drug POM markedly enhances response and is well tolerated. It has provided the framework for an ongoing Phase III clinical trial of BTZ/Dex versus POM/BTZ/Dex for patients with relapsed or refractory MM.

Interview with Kenneth C Anderson, MD, March 29, 2013

Overall Survival Benefit for Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance with Bortezomib-Thalidomide (VMPT-VT) versus Bortezomib-Melphalan-Prednisone (VMP) in Newly Diagnosed Multiple Myeloma Patients

Palumbo A et al.

Proc ASH 2012;Abstract 200.

Background

- A Phase III trial demonstrated that VMPT followed by VT (VMPT-VT) was superior to VMP alone in patients with multiple myeloma (MM) who are ineligible for autologous stem cell transplant (ASCT) (*JCO* 2010;28(34):5101).
  - 3-year progression-free survival rate:

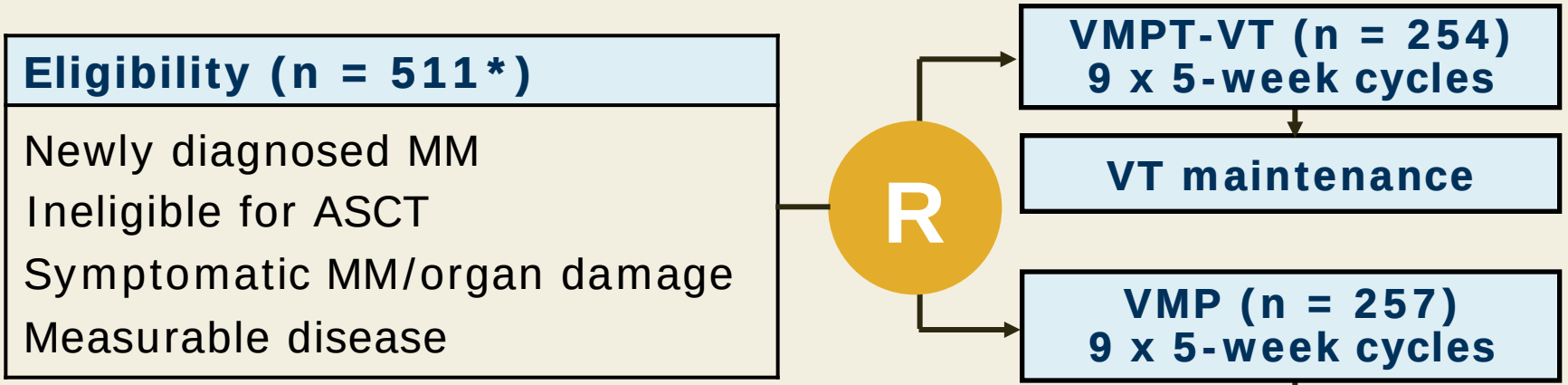
    56% (VMPT-VT), 41% (VMP); HR = 0.67; $p = 0.008$
  - 3-year overall survival rate:

    89% (VMPT-VT), 87% (VMP); HR = 0.92; $p = 0.77$
  - Overall response rate (ORR):

    89% (VMPT-VT), 81% (VMP); $p = 0.01$
- **Study objective:** To report updated analysis of OS benefit for patients with newly diagnosed MM treated with VMPT-VT versus VMP after 4 years of follow-up.

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Phase III Trial Design



* Induction schedules were amended after the inclusion of 139 patients.

V: Bortezomib 1.3 mg/m^2 IV d1, 8, 15, 22
M: Melphalan 9 mg/m^2 d1-4
P: Prednisone 60 mg/m^2 d1-4
T: Thalidomide 50 mg/d continuously

- 66 (VMP) and 73 (VMPT-VT) patients received twice-weekly V
- **Primary endpoint:** Progression-free survival (PFS)
- **Secondary endpoints included:** Overall survival (OS), time to next therapy (TTNT) and safety

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

PFS, TTNT and OS (All Patients)

Outcome	VMPT-VT	VMP	HR	*p*-value
Median PFS	35.3 mo	24.8 mo	0.58	<0.0001
Five-year PFS	29%	13%		
Median TTNT	46.6 mo	27.8 mo	0.52	<0.0001
Five-year TTNT	41%	19%		
Median OS	Not reached	60.6 mo	0.70	0.01
Five-year OS	61%	51%		

Median follow-up: 54 months

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

One-Year Landmark Analysis*

Outcome	VMPT-VT	VMP	HR	*p*-value
Median PFS	31.5 mo	17.8 mo	Not reported	Not reported
Four-year PFS	33%	16%		
Median OS	Not reached	54.2 mo	0.63	0.006
Four-year OS	67%	55%		

* Landmark analysis was performed with patients who completed induction.

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Landmark Analysis* of OS by Subgroup

Subgroup	VMPT-VT vs VMP	
	HR	*p*-value
Age <75 years	0.60	0.009
Age ≥75 years	0.76	0.36
ISS 1 to 2	0.66	0.05
ISS 3	0.64	0.22
Complete response	0.45	0.01
VGPR/PR	0.80	0.28

* Landmark analysis was performed with patients who completed induction.

- ISS = International Staging System; PR = partial response; VGPR = very good PR
- HR <1.0 favors VMPT-VT

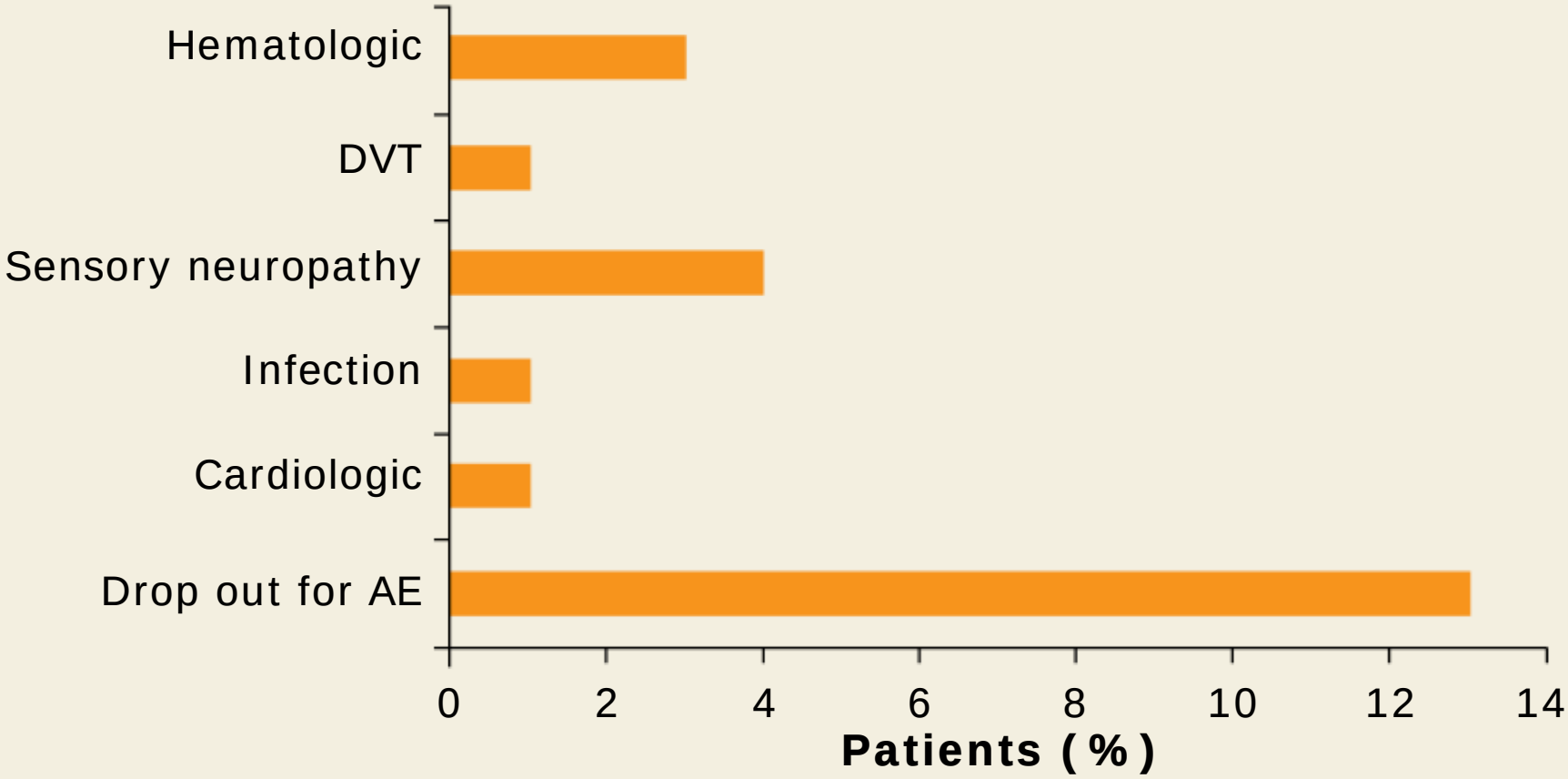
Palumbo A et al. *Proc ASH* 2012;Abstract 200.

OS After Relapse

	VMPT-VT	VMP	HR	*p*-value
Median OS	27.8 mo	27.3 mo	0.92	0.63
Three-year OS	47%	46%		

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Grade 3 or 4 Adverse Events (AEs) During VT Maintenance



Newly occurring or worsening Grade 3-4 adverse events

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Treatment Discontinuation Due to AEs

	VMPT → VT	VMP
Discontinuation rate, %		
65-75 years old	25	15
>75 years old	35	16
Bortezomib dose intensity, %		
65-75 years old	81	89
>75 years old	58	80

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Author Conclusions

- For patients with newly diagnosed MM who were ineligible for ASCT, treatment with VMPT-VT significantly prolonged 5-year PFS, TTNT and OS compared to VMP alone.
  - 5-year PFS: 29% vs 13%; $p < 0.0001$
  - 5-year TTNT: 41% vs 19%; $p < 0.0001$
  - 5-year OS: 61% vs 51%; $p = 0.01$
    - Prolonged OS was observed especially in patients <75 years old and in patients achieving CR after induction.
- No significant difference was observed between treatment arms in the 3-year OS rate after relapse:
  - 47% (VMPT-VT) vs 46% (VMP); $p = 0.63$

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

Investigator Commentary: Phase III Trial of VMPT-VT versus VMP Alone for Patients with Newly Diagnosed MM

In this study both PFS (35.3 vs 24.8 mo) and TTNT (46.6 vs 27.8 mo) were statistically significantly prolonged with the 4-drug and maintenance (VMPT-VT) regimen compared to VMP alone. Maintenance therapy decreased the risk of death by 30%, and OS was not reached in the VMPT-VT arm but was 60.6 months with VMP. OS from relapse was equivalent in both arms. Importantly, patients in the VMPT-VT arm more commonly had to discontinue therapy or reduce bortezomib dose, particularly patients older than 75 years.

This study demonstrated impressive 5-year PFS, TTNT and OS rates with VMPT-VT. However, the high discontinuation rate, especially among patients older than 75 years, suggests that less intensive therapies should be administered. Notably, this was the first study to show decreased neuropathy without compromising efficacy with the use of weekly bortezomib. Subcutaneous administration also reduces the neurotoxity of bortezomib. Therefore, VMPT-VT utilizing weekly and subcutaneous bortezomib may allow more patients to continue this regimen with high frequency and extent of response in addition to the prolonged PFS and OS observed in this study.

Interview with Kenneth C Anderson, MD, March 29, 2013