5 Minute JournalClub

POST-ASH Issue 5, 2014

For more visit ResearchToPractice.com/5MJCASH2014

Research To Practice®

CME Information

LEARNING OBJECTIVES

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with MM.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including anti-CD38 antibodies and AKT, BTK, KSP and novel proteasome inhibitors — under evaluation for newly diagnosed and relapsed/refractory MM and WM and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appraise recent clinical research findings on the efficacy and safety of novel proteasome inhibitor- and/or BTK inhibitor-based therapeutic strategies for WM, and consider this information for the treatment of patients.

CME Information (Continued)

CREDIT DESIGNATION STATEMENT
Research To Practice designates this enduring material for a maximum of 2.5 *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/5MJCASH2014/5/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:

CME Information (Continued)

Rafael Fonseca, MD
Getz Family Professor of Cancer
Chair, Department of Internal Medicine
Mayo Clinic Arizona
Scottsdale, Arizona

Consulting Agreements: Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc; *Contracted Research:* Amgen Inc, Celgene Corporation.

Sagar Lonial, MD
Professor
Vice Chair of Clinical Affairs
Director of Translational Research, B-Cell Malignancy Program
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Advisory Committee and Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Sanofi.

5 MinuteJournalClub

POST-ASH Issue 5, 2014

Rafael Fonseca, MD

One might view current clinical research in multiple myeloma (MM) as being in a consolidation phase after the introduction of proteasome inhibitors, immunomodulatory drugs and bisphosphonates brought forth a huge wave of progress. This idea is reflected in many of the new MM reports presented in New Orleans, where we were treated to intriguing data attempting not only to help optimize the impact of our current tools but also to uncover novel agents that will launch a new era with even better outcomes. For this second MM issue of our ASH review series, Dr Rafael Fonseca comments on a handful of papers that help take the next step in what will hopefully be another quantum leap forward in this fascinating corner of oncology.

- **More on up-front carfilzomib/lenalidomide/ dexamethasone (dex) (CRd)**

MM is only one of a number of tumor types in oncology today for which there is considerable interest in moving newly approved agents up earlier in the course of the disease. In this regard, we have already seen preliminary data from Andrzej

Jakubowiak, and at ASH **the NCI presented** another major single-arm study evaluating induction CRd followed by maintenance therapy — in this case lenalidomide. As in the work presented by Dr Jakubowiak, in this study patients received long-term maintenance and transplant was optional, and with the extraordinary risk-benefit value of this regimen (near complete response [CR] or better in 73% of the 43 patients, 100% minimal residual disease negativity assessed by flow cytometry among 27 patients with near CR or stringent CR and no Grade 3 or 4 neuropathy), Dr Fonseca can foresee a time when treatment will be individualized based on depth of response, with transplant avoided in some patients and survival extended significantly. However, in terms of current practice, like most MM investigators Dr Fonseca believes that while preliminary data on this and similar regimens are very encouraging, carfilzomib should not be used up front outside of a trial setting and recommends that patients interested in this approach be referred to the major Intergroup study comparing CRd to RVD.

- **Carfilzomib/cyclophosphamide/dex (CCd) up front in elderly patients**

In the same vein as the previous study, another ASH data set reported on recent efforts to incorporate carfilzomib into popular and currently employed bortezomib-based up-front regimens. **This Phase II trial** looked at CCd (similar to CyBorD) induction in 55 evaluable patients aged 65 and over with newly diagnosed MM. The bottom line is that despite significant activity (47% near CR or better) and relatively good tolerability (14% of patients discontinued treatment because of toxicity, which is considerably fewer than in prior studies for elderly patients), Dr Fonseca — a major proponent of CyBorD — urges us all to hold off on CCd outside a clinical trial.

- **Pomalidomide (POM)/carfilzomib/dex in relapsed/refractory (RR) disease**

Combining the 2 new kids on the block, POM and carfilzomib, always seemed like a natural next step, and at ASH we saw encouraging data with this appealing regimen. **A multicenter Phase I/II effort** for patients with heavily pretreated lenalidomide-refractory MM (a median of 5 prior treatments) resulted in a 70% overall response rate among 79 evaluable patients and a manageable toxicity profile. Even more, this report demonstrates that the regimen is not only a viable option in very advanced disease but also an approach that is of great interest in up-front trials.

In a related manner, ASH also featured **2 data sets** providing updates from trials evaluating POM with low-dose dex in RR disease. Dr Fonseca's take-away from these presentations is that while patients with extensive prior treatment and adverse cytogenetic profiles often benefit from this therapy, myelosuppression in these individuals must be managed carefully with dose adjustments and growth factors.

- **An all-oral "RVD"**

For the past several years we have profiled the early development of the oral proteasome inhibitors ixazomib and oprozomib, and at ASH **Paul Richardson presented more data** from his Phase I/II study looking at ixazomib/ lenalidomide/dex in previously untreated MM. This study, which evaluated twice-weekly ixazomib, revealed activity (94% response rate among 62 patients) similar to what is typically seen with RVD but slightly more peripheral

neuropathy (PN) (Grade 3 in 5% of 64 patients) than has been observed in trials using weekly administration of this fascinating agent. Not surprisingly, Dr Fonseca is eagerly and optimistically awaiting the results of ongoing Phase III trials.

- **Cool new compounds**

For the immediate future most myeloma investigators like Dr Fonseca believe monoclonal antibodies represent the most likely path to dramatically catapult survival in this disease, and there is great hope that a rituximab-like agent may be identified. The 2 compounds we have heard the most about up to now are the anti-CD38 antibody daratumumab, which has garnered FDA breakthrough therapy status, and elotuzumab, which is directed against human CS1 (a cell surface antigen glycoprotein that is highly expressed on MM cells) and appears to result in an R-squared-like synergy with lenalidomide.

However, for a disease diagnosed in "only" about 20,000 individuals a year in the United States, a stunning amount of active drug development is under way in MM, and at ASH we were provided with a preview of some of the agents and strategies we may be hearing a lot more about in the next few years:

– SAR650984

Similar to daratumumab, **this anti-CD38 antibody** was shown to have significant single-agent efficacy in patients with relapsed MM (31% response rate among 13 patients receiving the 10-mg/kg dose every 2 weeks) and minimal toxicity other than manageable infusion reactions. Dr Fonseca stated that "this is probably one of most important molecules for future MM therapy."

– Filanesib

A report from a **Phase II trial** of this selective inhibitor of kinesin spindle protein alone or in combination with dex demonstrated a 15% response rate among 55 evaluable patients receiving the combination and manageable toxicity. What seems most exciting about this data set is that activity was absent in patients with high serum levels of α-1 acid glycoprotein (which binds the drug, making it unavailable), potentially opening the door for a predictive biomarker.

– Afuresertib

AKT is a critical signaling node in MM, and this **single-arm Phase IB trial** evaluated the potent AKT inhibitor afuresertib in combination with dex and bortezomib in 81 patients with relapsed or refractory disease. The overall response rate was 65% and the clinical benefit rate was 73% among 37 patients in the safety expansion cohort. The results are favorable enough to justify further study, but of particular interest was the demonstration of consistent increases in the levels of the phosphorylated form of the drug target in MM cells.

• Bonus feature: Two compelling data sets in Waldenström's macroglobulinemia (WM)

WM is unusual in oncology in that investigators focused on both lymphomas and plasma cell disorders are involved in clinical research and patient care. Most importantly, borrowing from progress in both of these fields, the outlook for the 1,500 US patients diagnosed annually continues to improve as reflected in the following data sets:

– Carfilzomib

The lack of PN with carfilzomib, even in indirect comparison to weekly subcutaneous bortezomib, is particularly appealing in WM, in which PN is part of the disease biology. As such, this agent was **evaluated in a Phase II study** combining it with rituximab and dex for 31 patients with symptomatic WM. As reported at ASH, this combination resulted in a best overall response rate of 81% and significant IgM declines along with improved marrow profiles and hemoglobin levels. Even more important, PN of Grade 2 or higher was not reported, leading the authors to conclude that the regimen represents a "neuropathy-sparing approach" for the treatment of WM. In relation to these findings, Dr Fonseca verbalized his concern that the rarity of this disease has led to a dearth of FDA-approved therapies, making it a considerable challenge to obtain reimbursement for novel agents with proven patient benefit.

– Ibrutinib

Now approved for mantle-cell lymphoma and chronic lymphocytic leukemia, perhaps it should not be that big of a surprise that ibrutinib is effective in WM, especially since a somatic mutation (MYD88 L265P) that appears to support malignant growth through Bruton tyrosine kinase is present in more than 90% of these patients. Indeed, in this **exciting Phase II study** 51 of 63 patients (81%) had best overall responses — which were usually rapid, often with rising hematocrit and reductions in serum IgM — strongly suggesting that this agent is destined to have a critical role in the care of these patients.

Next up, we focus on papers in Hodgkin lymphoma and the rapidly emerging role of the antibody-drug conjugate brentuximab vedotin.

Neil Love, MD
Research To Practice
Miami, Florida

Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Extended Dosing (CRD-R) Induces High Rates of MRD Negativity in Newly Diagnosed Multiple Myeloma (MM) Patients

Korde N et al.

Proc ASH 2013;Abstract 538.

Background

- Recent emerging evidence indicates a potential role for flow cytometry, functional imaging and PCR-based assays as possible methods to detect residual disease.
  - As therapies improve, there are increasing needs for characterization of deep responses with more sensitive technology and of long-term disease remissions.
- Carfilzomib (Cfz) is an irreversible proteasome inhibitor with potent anti-multiple myeloma (MM) effects resulting in deep clinical responses and durable remissions as well as decreased peripheral neuropathy compared to bortezomib.
- **Study objective:** To determine the incidence of Grade ≥3 neuropathy and the efficacy of Cfz, lenalidomide (Ln) and dexamethasone (CRd) → 2 years of Ln maintenance in patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2013;Abstract 538.

CRd in Newly Diagnosed MM

	Jakubowiak et al study* (Phase I/II, n = 53)	Current study (Phase II, n = 45)
Combination therapy	CRd (Phase II Cfz 20/36 mg/m^2) 8 cycles	CRd (Cfz 20/36 mg/m^2) 8 cycles
Extended dosing	CRd (Cfz every other week) 16 cycles, off-protocol Ln at last tolerated dose d1-21 after 16 cycles	Ln 10 mg d1-21, 24 cycles
Transplant	≥PR stem cell collection, HDM optional	Stem cell collection
Correlatives	Flow cytometry — MRD	Flow cytometry — MRD, PET-CT, proteasome assays, GEP, whole-genome sequencing

* Jakubowiak A et al. *Blood* 2012;120(9):1801-8.

GEP = gene expression profiling

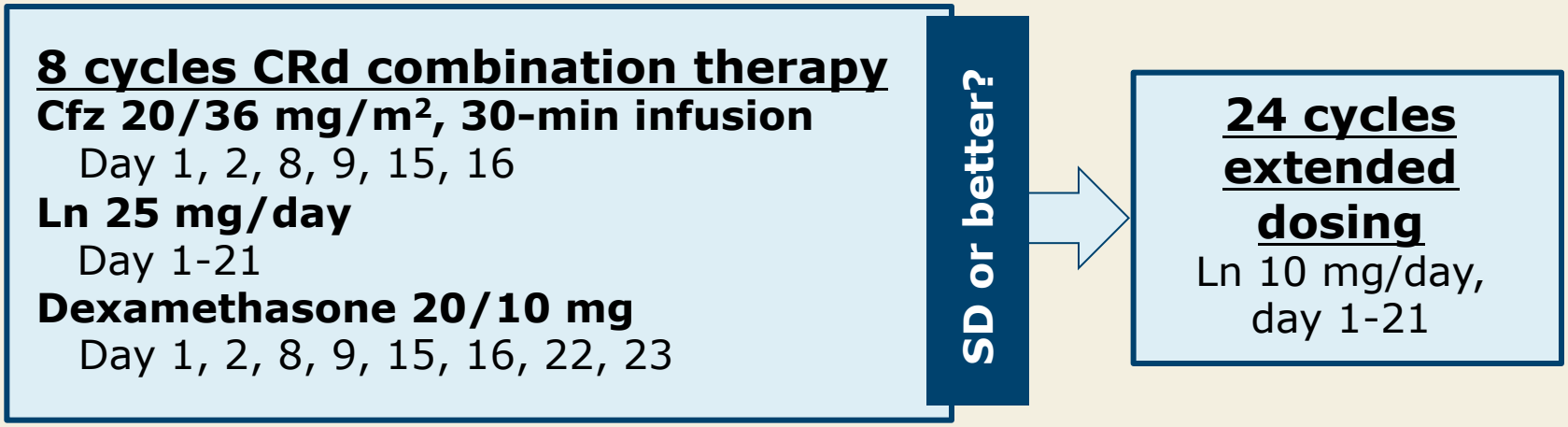
Korde N et al. *Proc ASH* 2013;Abstract 538.

Study Objectives and Enrollment

- **Primary study objective:**
  - Incidence of Grade ≥3 neuropathy
- **Secondary study objectives:**
  - Correlatives: GEP, biomarkers, proteasomes, flow cytometry, PCR, FDG PET-CT
  - Clinical: Response rate, progression-free survival (PFS), overall survival and duration of response
- **Target enrollment (n = 45):**
  - Phase II study, 2-stage design:
    - Stage I: Patients 1-20 — If 4 or more develop Grade ≥3 neuropathy, then study stops
    - Stage II: Patients 21-45

Korde N et al. *Proc ASH* 2013;Abstract 538.

Phase II Study Design



- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <75 years of age
- Cycle 1, day 1, 2: Cfz dose is 20 mg/m^2
- Cycles 1-4: Dexamethasone dose is 20 mg; cycles 5-8: Dexamethasone dose is 10 mg

SD = stable disease

Korde N et al. *Proc ASH* 2013;Abstract 538.

Patient Characteristics

Variable	
Patients enrolled	45
Patients completed 2 cycles (evaluable)	43
Median age, y (range)	60 (40-88)
Male sex, n (%)	26/43 (60)
Isotype, n (%) IgG IgA Kappa Lambda	 28 (65) 10 (23) 4 (9) 1 (2)
Median cycles of CRd → Ln received (range)	12 cycles (2-25)
Median follow-up in months (range)	12 months (2-26)
Patients completed 8 cycles of CRd	29

Korde N et al. *Proc ASH* 2013;Abstract 538.

Response Rates

Response	2 cycles	8 cycles	Best response*
ORR (≥PR)	98%	97%	98%
≥VGPR	51%	91%	88%
nCR/CR/sCR	16%	73%	67%
CR/sCR	7%	42%	51%
VGPR	35%	18%	21%
PR	47%	6%	9%
SD	2%	3%	2%

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

* Median 12 cycles of CRd → Ln maintenance

Korde N et al. *Proc ASH* 2013;Abstract 538.

Time to CR/sCR and PFS

Time to CR/sCR	
CR/sCR, n/N (%)	22/43 (51%)
Patients reaching CR/sCR with ≥8 cycles of CRd, n/N (%)	5/22 (23%)
Median time to CR/sCR, months (range)	5 (2-18)
PFS at 12 months	**97%**

- 4 patients have come off study treatment, 3 due to progression and 1 due to personal reasons. All other patients remain on study treatment.

Korde N et al. *Proc ASH* 2013;Abstract 538.

Select Grade 3/4 Adverse Events (AEs)

Nonhematologic AEs	(n = 43)
Electrolyte disturbances	21%
LFT elevation	12%
Skin (rash, pruritus, eye)	12%
Constitutional (fatigue, presyncope, dehydration, adrenal insufficiency)	12%
Lung (dyspnea, respiratory failure)	9%
Cardiac (hypertension, heart failure)	9%
Infection (pneumonia, enterocolitis, febrile neutropenia)	9%
VTE	7%

- None of the 43 evaluable patients developed Grade ≥3 neuropathy

Korde N et al. *Proc ASH* 2013;Abstract 538.

Select Grade 3/4 AEs (Continued)

Hematologic AEs	(n = 43)
Lymphopenia	65%
Anemia	28%
Neutropenia	21%
Thrombocytopenia	19%

- **Dose reductions**:
  - 4 decreased Cfz (dyspnea, renal injury)
  - 11 decreased dexamethasone (fatigue, anxiety, dyspnea)
  - 12 decreased Ln (rash, fatigue, renal adjustment, cytopenias and LFT increase)

Korde N et al. *Proc ASH* 2013;Abstract 538.

Author Conclusions

- Treatment with CRd → Ln maintenance did not result in any incidence of Grade 3/4 neuropathy in patients with newly diagnosed MM.
  - Limited severe toxicities
- Treatment resulted in high response rates as well as deep and rapid responses.
  - ORR (PR or better) = 98%
  - nCR/CR/sCR = 67%
  - Median time to sCR = 5 months (range: 2-18)
- PFS rate at 12 months is 97%.
- CRd → Ln maintenance is an effective and tolerable therapy for older patients (data not shown).
- Among 27 patients with nCR/sCR assessed by flow cytometry, all were MRD negative (data not shown).

Korde N et al. *Proc ASH* 2013;Abstract 538.

Investigator Commentary: Phase II Clinical and Correlative Study of CRd → Lenalidomide — Extended Dosing Induces High Rates of MRD Negativity in Newly Diagnosed MM

In addition to the quality of the data, the correlative science associated with this elegant study taught us more than would a standard Phase II clinical trial. Consistent with what was reported in a recent paper from Andrzej Jakubowiak (*Blood* 2012;120(9):1801), this was a highly active regimen. The current study attempted to focus predominantly on particularly deep responses. Patients who were able to go through 8 cycles of therapy and were assessed for response at that point achieved a nCR, CR or sCR rate of 73%, which is impressive. These results help set the stage for what the majority of people in the field are considering: As your first intention, getting a deep response with induction therapy seems to be an important goal.

(Continued)

This potentially sets the patient up for even better outcomes after transplant. I say "potentially" because this study has raised the question, is there a future in which transplant is not part of treatment for myeloma? The majority of patients on this study who achieved nCR/sCR also had MRD-negative disease. That certainly provides a context in which to ask this question as we move into the future. The treatment of myeloma must still be based on clinical parameters, but perhaps it's time that we incorporate some of these biomarkers earlier on to better gauge what kind of progress we're making as we treat the disease.

Interview with Rafael Fonseca, MD, February 14, 2014

A Phase II Study with Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma

Bringhen S et al.

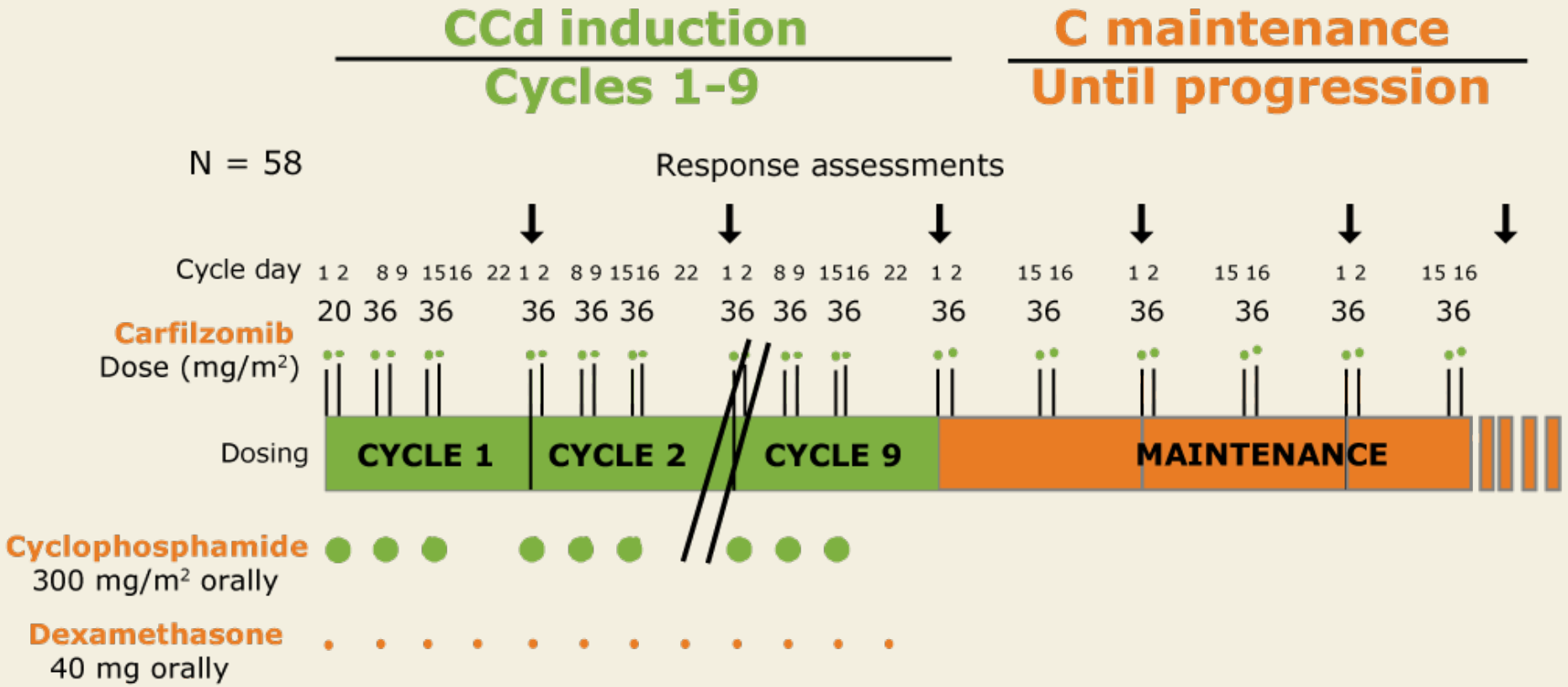
Proc ASH 2013;Abstract 685.

Background

- Current therapies for elderly patients with newly diagnosed multiple myeloma (NDMM) induce about a 30% near-complete response/complete response (nCR/CR) rate, with a discontinuation rate of 35% due to adverse events.
- Carfilzomib, an irreversible proteasome inhibitor, has significant activity and favorable toxicity in MM.
- Initial Phase II study results with a combination of carfilzomib with cyclophosphamide and dexamethasone (CCd) showed encouraging activity in elderly patients with NDMM (*Proc EHA* 2013;Abstract S578).
- **Study objective:** To present updated study results on the efficacy and safety of the CCd regimen in patients with symptomatic NDMM who are ≥65 years old or younger patients who are ineligible for autologous stem cell transplantation.

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

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 ASH* 2013;Abstract 685.

Response (≥nCR) Rate by Treatment Duration

Induction phase	**n = 55**
At 1 month	4%
At 3 months	12%
At 6 months	30%
At 9 months	47%
Maintenance phase	**n = 43**
At 3 months	49%
At 6 months	50%
At 9 months	56%

- Median treatment duration: 15 months
- Median maintenance duration: 9 months

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

Stringent Complete Response (sCR) Rate by Treatment Duration

Induction phase	**n = 55**
At 4 months	2%
At 6 months	9%
At 9 months	23%
Maintenance phase	**n = 43**
At 3 months	24%
At 6 months	25%
At 9 months	37%

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

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

Clinical variable	
2-year PFS rate	76%
2-year OS rate	87%

- Long-term outcomes were affected by quality of response:
  - 100% of patients achieving a sCR were alive and in remission at 2 years
  - 74% of patients achieving ≥PR were alive and in remission at 2 years

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

Adverse Events Summary: Induction

- The more frequent Grade 1 and 2 adverse events were anemia, thrombocytopenia, gastrointestinal toxicity and fatigue or fever.
- Grade 4 neutropenia occurred in 7% of patients.
- The more frequent nonhematologic Grade 3 and 4 adverse events were infections and cardiac and gastrointestinal toxicities.
- Peripheral neuropathy occurred in 9% of patients and was limited in severity to Grades 1 and 2.
- Patients requiring carfilzomib dose reduction: 21%
- Patients requiring early discontinuation of treatment due to toxicity: 14%

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

Adverse Events Summary: Maintenance

- The more frequent Grade 1 and 2 adverse events were anemia, gastrointestinal toxicity and fatigue or fever.
- Grade 3 and 4 adverse events were rare, recorded in <5% of patients.

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

Author Conclusions

- The combination of CCd is effective, with 47% of patients achieving at least a nCR and 23% of patients achieving a sCR.
- Although a direct comparison between different trials should be viewed with caution, these data compared favorably with the current best standard treatment for elderly patients after diagnosis.
- The CCd combination is well tolerated and Grade 3 to 4 events were rare.
- Longer follow-up is needed to better assess long-term outcomes.
- The carfilzomib dose of 36 mg/m^2 is well tolerated by elderly patients in this setting, and further dose increases could be evaluated in future trials.

Bringhen S et al. *Proc ASH* 2013;Abstract 685.

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

Part of the rationale for performing this study was that the rate of discontinuation when treating MM in the elderly is high because of toxicity. So it was of interest to determine whether the CCd regimen could be effective without garnering a high rate of discontinuation. The study focused on patients with NDMM who were elderly or those considered ineligible for stem cell transplant. A high response rate was reported with the CCd combination — 47% nCR or better after the induction phase and 56% after the maintenance phase. The 2-year PFS of 76% and 2-year OS of 87% were also favorable. Patients who achieved a stringent CR had a better OS rate than those who did not, although the difference was not significant.

The discontinuation rate was 14%, which is similar to what has been reported with lenalidomide/low-dose dexamethasone but lower than combinations that include melphalan.

(Continued)

Overall the regimen was well tolerated. We need to better understand the cardiac and respiratory toxicities associated with this combination.

Currently carfilzomib should be used only in the relapsed/refractory setting for MM. These studies are paving the way for this agent to be incorporated into front-line therapy.

Interview with Rafael Fonseca, MD, February 14, 2014

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 2013;Abstract 690.

Background

- In a pivotal Phase II study, carfilzomib (Car), a novel proteasome inhibitor (PI), demonstrated single-agent activity in relapsed/refractory multiple myeloma (RRMM) (*Blood* 2012;120:2817).
  - Car received FDA approval for this indication in July 2012.
- Pomalidomide (Pom), an immunomodulatory agent (IMiD), is active in RRMM (*Blood* 2014;[Epub ahead of print]).
  - Pom received FDA approval for RRMM in February 2013.
- Preclinical and clinical data demonstrate that the combination of PIs with IMiDs can overcome resistance and improve response rates (*Blood* 2013;122:3122).
- **Study objective:** To determine the efficacy and safety of Car in combination with Pom and dexamethasone (Car-Pom-d) in RRMM.

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

3 + 3 Phase I Dose-Escalation Study* (Cohort Design)

Cohort	Car	Pom	Dexamethasone
Cohort -1	27 mg/m^2	3 mg	40 mg
Cohort 1†	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

* Dose expansion at the maximum tolerated dose (MTD)

† Established as MTD

- All patients had lenalidomide (Len)-refractory MM
- Car 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

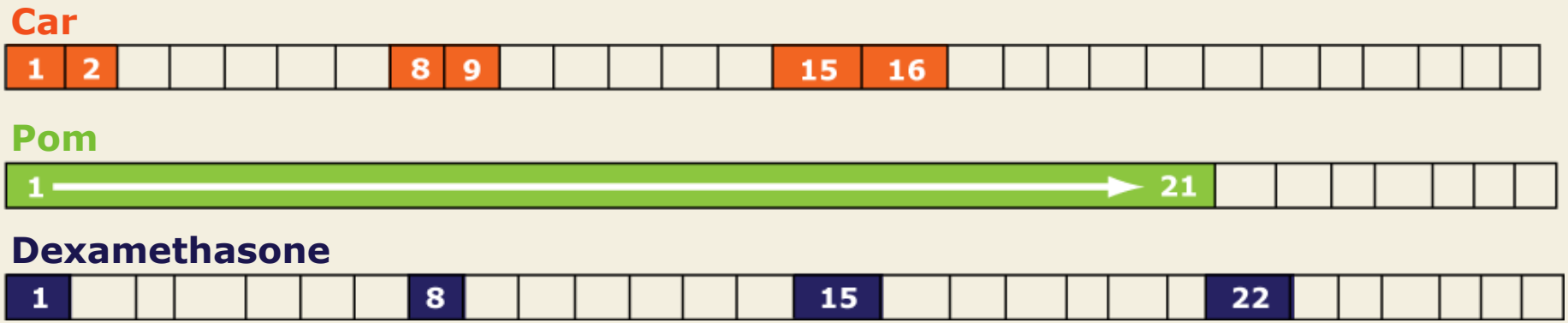
Shah JJ et al. *Proc ASH* 2012;Abstract 74; *Proc ASH* 2013;Abstract 690.

Ongoing Phase II Trial Design

Target accrual (n = 82)

Patients with RRMM
Prior Len with ≤25% response/progression during Tx or ≤60 d after completion of regimen containing Len at full dose or MTD for ≥2 cycles

Cycles 1-6: 28-day cycles



- Car on d1, 2 of cycle 1 was 20 mg/m^2, escalated to 27 mg/m^2 on d8 of cycle 1
- ≥Cycle 7: Maintenance cycles with Car on d1, 2, 15, 16; Pom/dexamethasone unchanged
- Concomitant medications included antiviral and defined anticoagulation therapies
- **Primary endpoint:** Overall response rate (ORR) and safety

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Response Rates

Best response	n = 79
ORR	55 (70%)
Very good partial response (VGPR)	21 (27%)
Partial response (PR)	34 (43%)
Minimal response (MR)	10 (13%)
Stable disease (SD)	13 (16%)
Progressive disease (PD)	1 (1%)

- Clinical benefit rate: 83%
- The median duration of response for patients with VGPR or PR: 17.7 months

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Responses by Cytogenetic Risk Status*

Best response	High risk (n = 18)	Intermediate risk (n = 19)	Standard risk (n = 38)
ORR	78%	53%	74%
VGPR	22%	26%	32%
PR	56%	26%	42%
MR	17%	21%	8%
SD	6%	26%	16%
PD	0%	0%	3%

* mSmart risk classification; 4 patients with incomplete cytogenetics data

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

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Survival Outcomes

All patients	**n = 79**
Median PFS	9.7 months
Median OS*	Not yet reached
Patients with del(17p)	**n = 14**
12-month PFS	57.9%
12-month OS	80%

PFS = progression-free survival; OS = overall survival

* Not yet reached at 18 months

- PFS and OS were sustained independent of risk status

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Select Adverse Events

N = 79	All grades	Grade 3	Grade 4
Neutropenia	34%	22%	8%
Anemia	32%	16%	1%
Thrombocytopenia	28%	8%	6%
Febrile neutropenia	4%	4%	0%
Fatigue	42%	4%	0%
Dyspnea	28%	1%	0%
Diarrhea	16%	3%	0%
Skin, rash, pruritus	13%	3%	0%
Pneumonia*	11%	8%	0%
Peripheral neuropathy	6%	1%	0%
Congestive heart failure	3%	3%	0%

* 1 treatment-related Grade 5 pneumonia and pulmonary embolism occurred

- Toxicities were generally reversible and manageable

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Author Conclusions

- The combination of Car-Pom-d is highly active in patients with heavily pretreated Len-refractory MM.
  - Patients had received a median of 5 prior lines of therapy.
  - 49% of patients had high- or intermediate-risk cytogenetics at baseline.
- Response rates, PFS and OS were preserved independent of the cytogenetic risk status.
- The Car-Pom-d regimen was well tolerated with no unexpected toxicities.
- Enrollment is nearly complete in the Phase II trial.
- Subsequent dose escalation of Car in a less heavily pretreated population of patients with 1 to 3 lines of prior therapy is planned.

Shah JJ et al. *Proc ASH* 2013;Abstract 690.

Investigator Commentary: Phase I/II Study of Car-Pom-d in Patients with RRMM

We're seeing patients who are seeking second opinions in our clinics after they have been exposed to all the active agents. A lot of empirical recommendations are being made, and I'm happy to know that we have some data in support of the treatment decisions. We have "community knowledge" that if an agent fails, its combination with another agent may result in responses. Multiple anecdotes exist for that. More often than not, the responses are short-lived and not all patients respond. This study is important because it enrolled patients with Len-refractory MM who have experienced progression on their most recent therapy. The patients on the Phase II study had Pom- and Car-naïve disease. The results demonstrated a VGPR rate of 27% and a PR rate of 43%, and 10 patients achieved MRs. The ORR was 70%, and the rate of ≥MR was 83%. These response rates are encouraging.

(Continued)

In addition, the toxicity profile of Car-Pom-d is manageable. This study provides objective data to support the idea of combining these agents for 2 reasons. First, these patients have exhausted some of the standard therapeutic options. Second, Pom is active in MM and it may be possible to move it further up front in the overall strategy for the treatment of MM. These results suggest that when no therapy is effective, Car-Pom-d is the next step.

Interview with Rafael Fonseca, MD, February 14, 2014

Final Analysis, Cytogenetics, Long-Term Treatment, and Long-Term Survival in MM-003, a Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEX) vs High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM)

A Multicenter Open Label Phase II Study of Pomalidomide and Dexamethasone in Progressive Relapsed or Refractory Multiple Myeloma with Deletion 17p and/or Translocation (4;14) Adverse Karyotypic Abnormalities — Interim Analysis

Dimopoulos MA et al.
Proc ASH 2013;Abstract 408.

Leleu X et al.
Proc ASH 2013;Abstract 689.

Final Analysis, Cytogenetics, Long-Term Treatment, and Long-Term Survival in MM-003, a Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEX) vs High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM)

Dimopoulos MA et al.

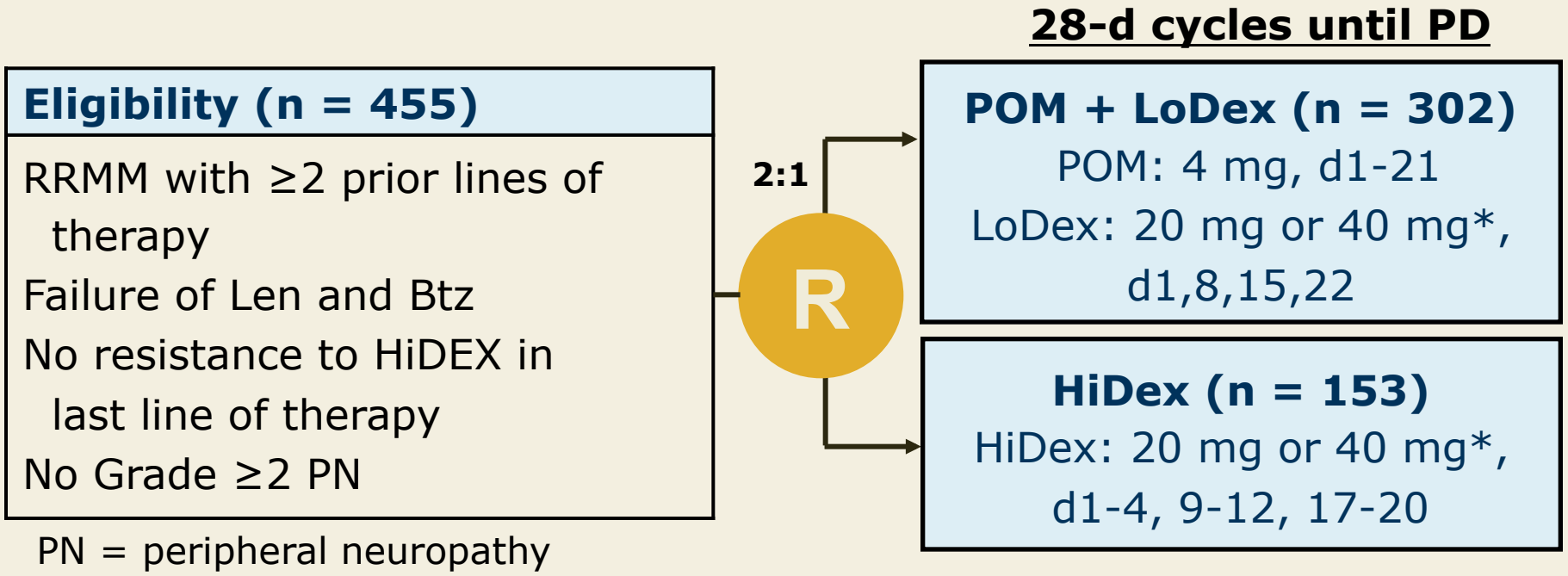
Proc ASH 2013;Abstract 408.

Background

- Patients with advanced RRMM have limited effective options.
- The presence of high-risk cytogenetics is predictive of a short overall survival benefit (*Blood* 2007;109:3489).
- Pomalidomide (POM) is an oral immunomodulatory agent with direct antimyeloma and stromal cell-support inhibitory effects.
- POM recently received FDA approval for the treatment of MM after ≥2 prior therapies, including lenalidomide (Len) and bortezomib (Btz), and after disease progression ≤60 days from completion of last therapy.
- Earlier results of the MM-003 Phase III trial demonstrated clinical efficacy and tolerability with POM + LoDex in patients with RRMM (*Proc EHA* 2013;Abstract S1151).
- **Study objective:** To determine the long-term efficacy of POM and LoDex versus HiDex for patients with RRMM in the MM-003 trial.

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Phase III MM-003 Trial Design



PN = peripheral neuropathy

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

- Thromboprophylaxis was required for all patients receiving POM and those at high risk of thromboembolic events
- **Primary endpoint:** Progression-free survival (PFS)

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

PFS and OS for Intention-to-Treat (ITT) Population

Outcome	POM + LoDEX (n = 302)	HiDEX (n = 153)	HR	*p*-value
Median PFS	4.0 months	1.9 months	0.50	<0.001
Median OS	13.1 months	8.1 months	0.72	0.009

HR = hazard ratio; OS = overall survival

- Median follow-up: 15.4 months
- 85 patients (56%) on the HiDEX arm received subsequent POM

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

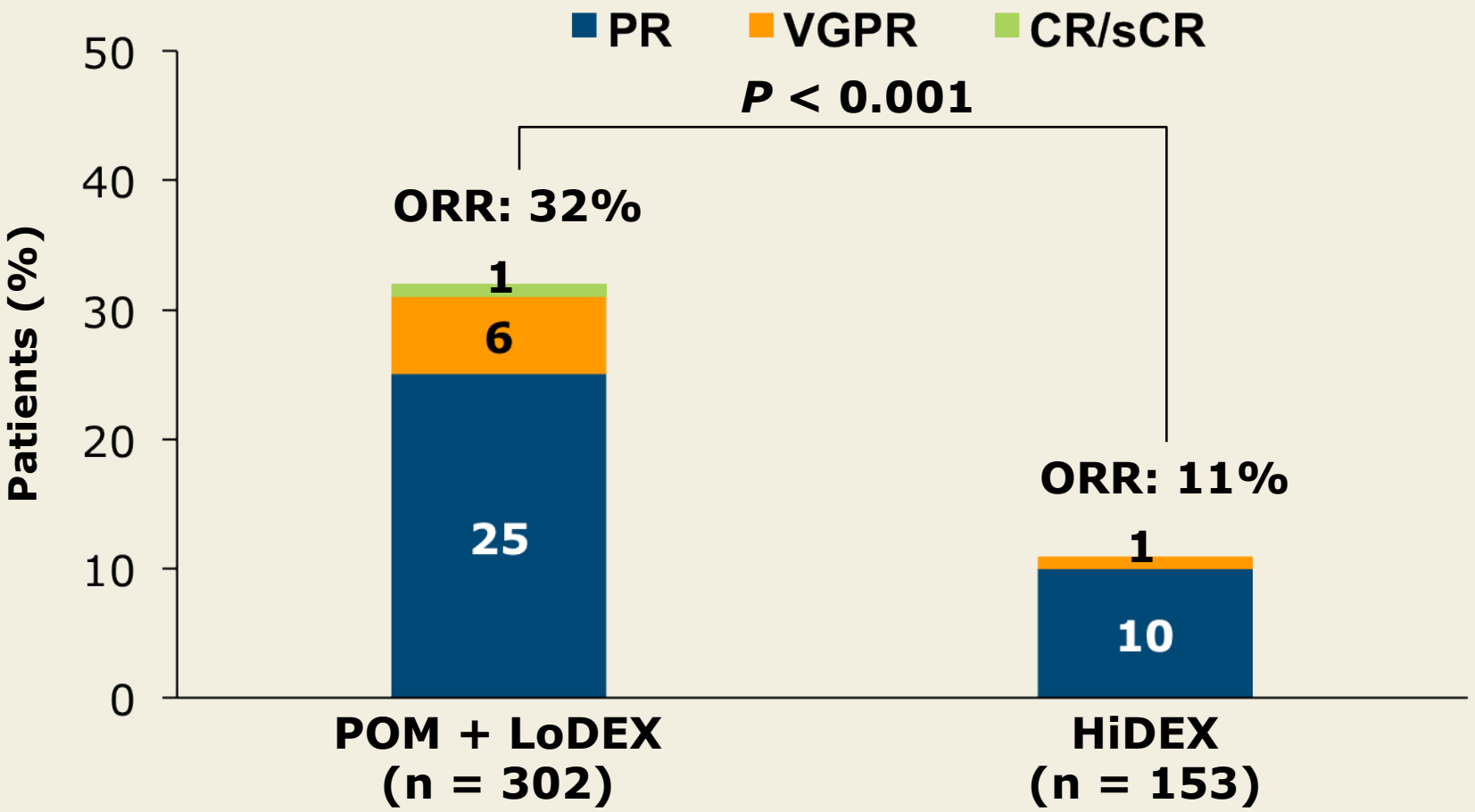
PFS and OS by Cytogenetic Profiling

Del17p/t(4;14)	POM + LoDEX (n = 77)	HiDEX (n = 35)	HR	*p*-value
Median PFS	3.8 months	1.1 months	0.44	<0.001
Median OS	9.9 months	4.9 months	0.67	0.092
Standard risk	**n = 148**	**n = 72**	**HR**	***p*-value**
Median PFS	4.2 months	2.3 months	0.55	<0.001
Median OS	14.0 months	9.0 months	0.85	0.380

- POM + LoDEX significantly improved PFS regardless of the presence of adverse cytogenetics
- 46% of patients with del17p/t(4;14) on the HiDEX arm received POM
- 64% of patients with standard-risk disease on the HiDEX arm received POM

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

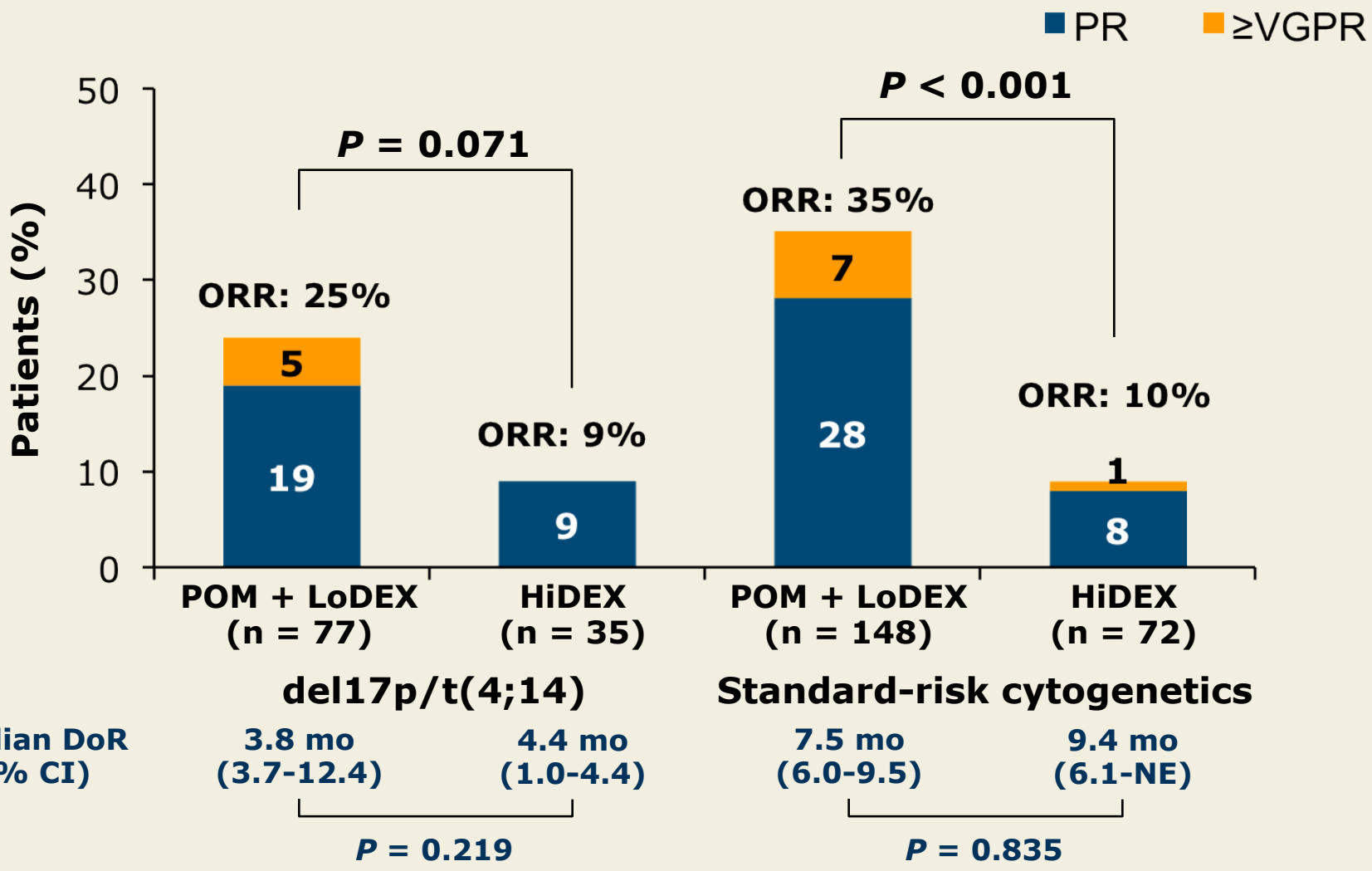
Response Rates in the ITT Population



Median duration of response: 7.5 mo (POM + LoDEX) vs 5.1 mo (HiDEX); $p = 0.031$

With permission from Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Response Rates by Cytogenetic Profiling



With permission from Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Baseline Characteristics Predictive of Long-Term Treatment and Survival with POM + LoDEX

Characteristic	OS ≤3 mo (n = 54)	OS >12 mo (n = 148)	*p*-value
ECOG PS (0 vs 1-2)	19% vs 81%	46% vs 54%	<0.0001
Age (≤65 vs >65 y)	41% vs 59%	57% vs 43%	0.035
ISS stage	46% vs 50%	76% vs 20%	<0.0001
Presence of plasmacytoma	20%	4%	0.0002
Baseline LDH (>1.5 x ULN)	20%	2%	<0.0001
Baseline hemoglobin*	9.4 g/dL	10.3 g/dL	<0.0001
Baseline platelet counts*	98 x 10^9/L	150 x 10^9/L	0.020

* Median value

- The same variables were significant for duration of treatment of ≤3 vs >12 mo

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

Author Conclusions

- Significant OS and PFS benefits for POM + LoDEX versus HiDEX were confirmed with additional follow-up.
- POM + LoDEX is active in patients with high-risk cytogenetics, especially in those with del17p.
- For all patients, normal levels of LDH and albumin and treatment with POM + LoDEX were predictive of longer survival.
- For patients who received POM + LoDEX, better ECOG PS, absence of plasmacytoma, lower ISS stage and normal LDH levels, hemoglobin and platelet counts were predictive of longer duration of treatment and OS.
- POM + LoDEX is a standard treatment for patients with RRMM, including those with adverse cytogenetic features.

Dimopoulos MA et al. *Proc ASH* 2013;Abstract 408.

A Multicenter Open Label Phase II Study of Pomalidomide and Dexamethasone in Progressive Relapsed or Refractory Multiple Myeloma with Deletion 17p and/or Translocation (4;14) Adverse Karyotypic Abnormalities — Interim Analysis

Leleu X et al.

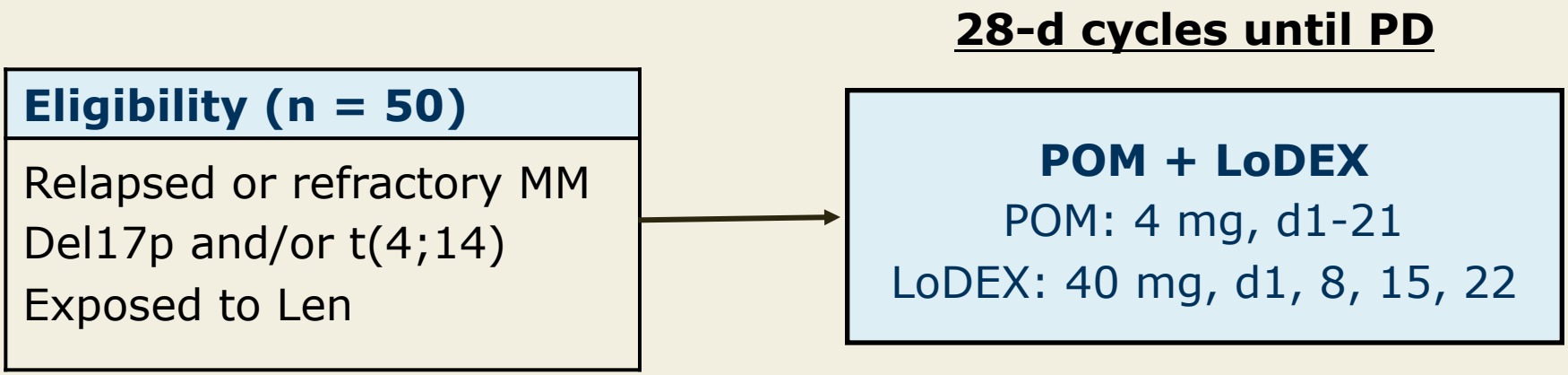
Proc ASH 2013;Abstract 689.

Background

- Patients who have multiple myeloma (MM) with del17p and/or t(4;14) have a poor survival rate related to early relapse and development of resistance to multiple agents.
- The IFM 2009-02 study demonstrated the efficacy of POM + LoDEX in patients with RRMM treated with Btz and/or Len (*Blood* 2013;121:1968).
- In that study, the median time to disease progression was much shorter for patients with del17p and/or t(4;14) who were previously exposed to a median of 5 to 6 lines of therapy.
- **Study objective**: To evaluate the efficacy and safety of POM in patients with RRMM with del17p and/or t(4;14).

Leleu X et al. *Proc ASH* 2013;Abstract 689.

IFM 2010-02 Study Design



- Aspirin/low-molecular-weight heparin administered once daily
- **Primary endpoint:** Time to progression (TTP)
- **Secondary endpoints:** included safety, response rate, duration of response, OS, PFS

Leleu X et al. *Proc ASH* 2013;Abstract 689.

Patient Characteristics

	ITT (n = 50)
Median no. of prior lines of therapy	3
2 lines	32%
3 lines	38%
>3 lines	22%
Refractory/exposed to	
Len	84%/100%
Btz	54%/96%
Len + Btz	54%
Alkylator	36%/90%

- Patients with del17p: 40%; t(4;14): 60%. Those with del17p and t(4;14) included in both groups

Leleu X et al. *Proc ASH* 2013;Abstract 689.

Response

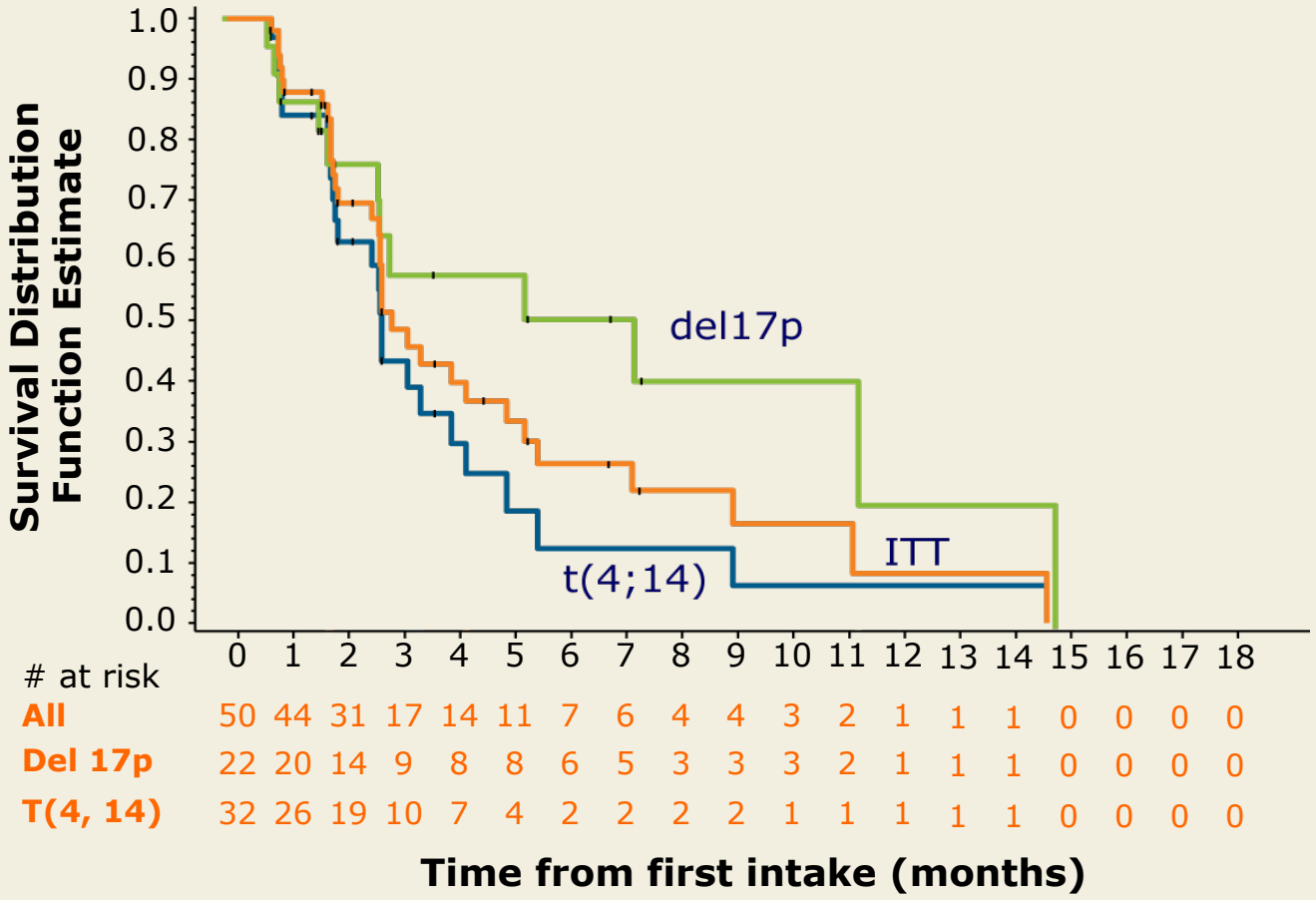
Response	ITT (n = 50)	Del17p (n = 22)*	t(4;14) (n = 32)*
Overall response rate	22%	32%	16%
≥VGPR	6%	9%	3%
PR	16%	23%	12.5%
Progressive disease	14%	18%	16%
Clinical benefit rate (≥MR)	34%	32%	34%
Median duration of response (DoR)	6 mo	8.3 mo	2.4 mo
Patients with 8-mo DoR	44%	67%	25%

* Patients with both del17p and t(4;14) included in both groups

- Median follow-up: 8.2 mo

Leleu X et al. *Proc ASH* 2013;Abstract 689.

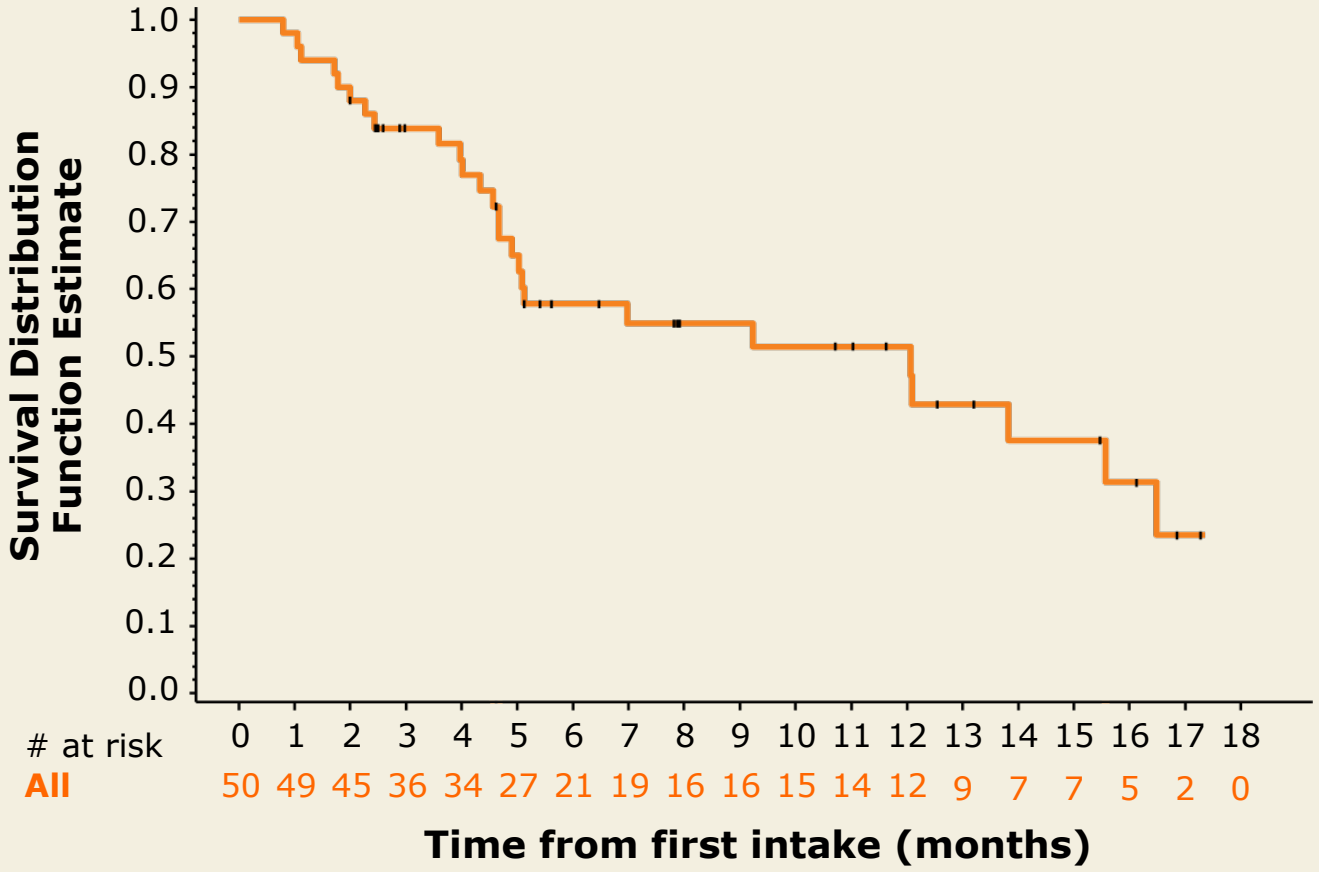
Time to Progression (TTP)



- Median TTP: ITT population 2.9 mo, del17p 7.3 mo, t(4;14) 2.8 mo

With permission from Leleu X et al. *Proc ASH* 2013;Abstract 689.

OS



- Median OS: ITT population 12 mo, del17p 12 mo, t(4;14) 9.2 mo
- 8-mo OS rate: ITT population 55%, del17p 58%, t(4;14) 50%

With permission from Leleu X et al. *Proc ASH* 2013;Abstract 689.

Adverse Events (AEs)

Event (n = 50)	Any AE	Serious AE
Hematologic	72%	16%
Nonhematologic	16%	48%
Drug related	88%	36%

- Grade 3/4 AEs occurred in 90% of patients
- Treatment discontinuation: 72% (16% due to drug-related AEs, 24% due to serious AEs)

Leleu X et al. *Proc ASH* 2013;Abstract 689.

Author Conclusions

- The combination of POM and dexamethasone is manageable and provides responses in patients with adverse cytogenetics.
- Use of POM and dexamethasone earlier in the disease course appears to benefit patients with del17p.
- This benefit was not seen in patients with t(4;14).
- Triplet POM-based regimens should be considered for future studies in patients with adverse cytogenetics, particularly with t(4;14).

Leleu X et al. *Proc ASH* 2013;Abstract 689.

Investigator Commentary: Pomalidomide (POM) and Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)

The studies by Dimopoulos and Leleu confirm that POM is effective for RRMM. Both of the studies evaluated the effects of high-risk cytogenetics in RRMM. The Phase III MM-003 study confirmed that POM with LoDEX is more effective than HiDEX for patients with RRMM. For patients with standard-risk cytogenetics the overall response rate was higher compared to those with high-risk cytogenetics.

Patients with high-risk genetic markers, who are able to receive a fifth or sixth line of therapy, have genetic subtypes that are not as bad because they have experienced responses to prior lines of therapy. Hence, I would be cautious about overinterpreting the results regarding the effects of adverse cytogenetics in RRMM. The validity of high-risk genetic markers is greater in the up-front setting. However, even in the RRMM setting, adverse cytogenetics affect clinical outcomes.

(Continued)

Most of the patients receiving POM have received multiple prior lines of therapy, so myelosuppression can be an issue. This can be managed with dose adjustments and occasionally with the use of growth factors. It is also important that patients receive thromboprophylaxis. Peripheral neuropathy is not a significant side effect with POM. Overall, it is a well-tolerated agent.

Interview with Rafael Fonseca, MD, February 14, 2014

Twice-Weekly Oral MLN9708 (Ixazomib Citrate), an Investigational Proteasome Inhibitor, in Combination with Lenalidomide (Len) and Dexamethasone (Dex) in Patients (Pts) with Newly Diagnosed Multiple Myeloma (MM): Final Phase 1 Results and Phase 2 Data

Richardson PG et al.

Proc ASH 2013;Abstract 535.

Background

- Ixazomib (MLN9708) is an investigational oral proteasome inhibitor that rapidly hydrolyzes to the biologically active form, MLN2238.
- Preliminary findings from studies using weekly and twice-weekly schedules of ixazomib in relapsed/refractory MM have suggested evidence of single-agent activity (*Proc ASCO* 2012;Abstract 8034; *Proc ASCO* 2012;Abstract 8017).
- A Phase I/II study suggested the feasibility and activity of weekly ixazomib in combination with lenalidomide (len) and dexamethasone (dex) in newly diagnosed MM (*Proc ASH* 2012;Abstract 332).
- **Study objective:** To determine the efficacy and safety of twice-weekly oral ixazomib in combination with len/dex in newly diagnosed MM requiring systemic therapy.

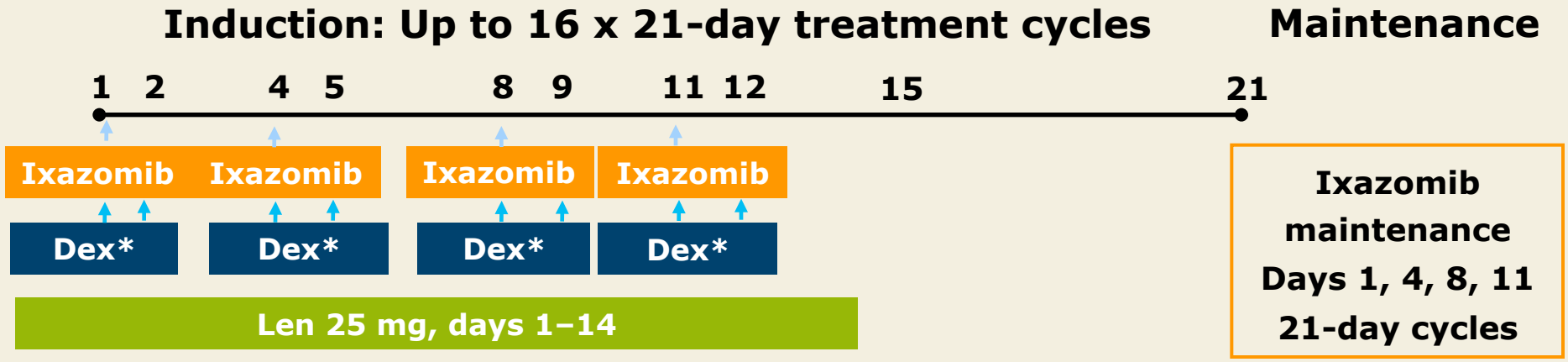
Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Eligibility Criteria and Study Methods

- Previously untreated MM with measurable disease (n = 64)
- No Grade ≥2 peripheral neuropathy
- No prior or concurrent deep vein thrombosis or pulmonary embolism
- All patients required prophylaxis with aspirin or low-molecular-weight heparin while receiving len/dex.
- Protocol allowed for stem cell collection after cycle 4, with ASCT deferred until after 8 cycles.
- Responses were assessed per International Myeloma Working Group (IMWG) uniform response criteria.
- Blood samples for pharmacokinetic analysis were taken at multiple time points during cycles 1 and 2.
- Data cut-off date: October 9, 2013

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Phase I/II Trial Design



* Dex: 20 mg and 10 mg during cycles 1-8 and 9-16, respectively

Ixazomib: 3.0 or 3.7 mg

- Phase I (n = 14): Oral ixazomib dose escalation
  - **Primary endpoints:** Safety, tolerability, maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D)
- Phase II (n = 57): Oral ixazomib at RP2D from Phase I was 3.0 mg
  - **Primary endpoints:** Combined complete response (CR) + very good partial response (VGPR) rate, safety and tolerability

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Preliminary Response

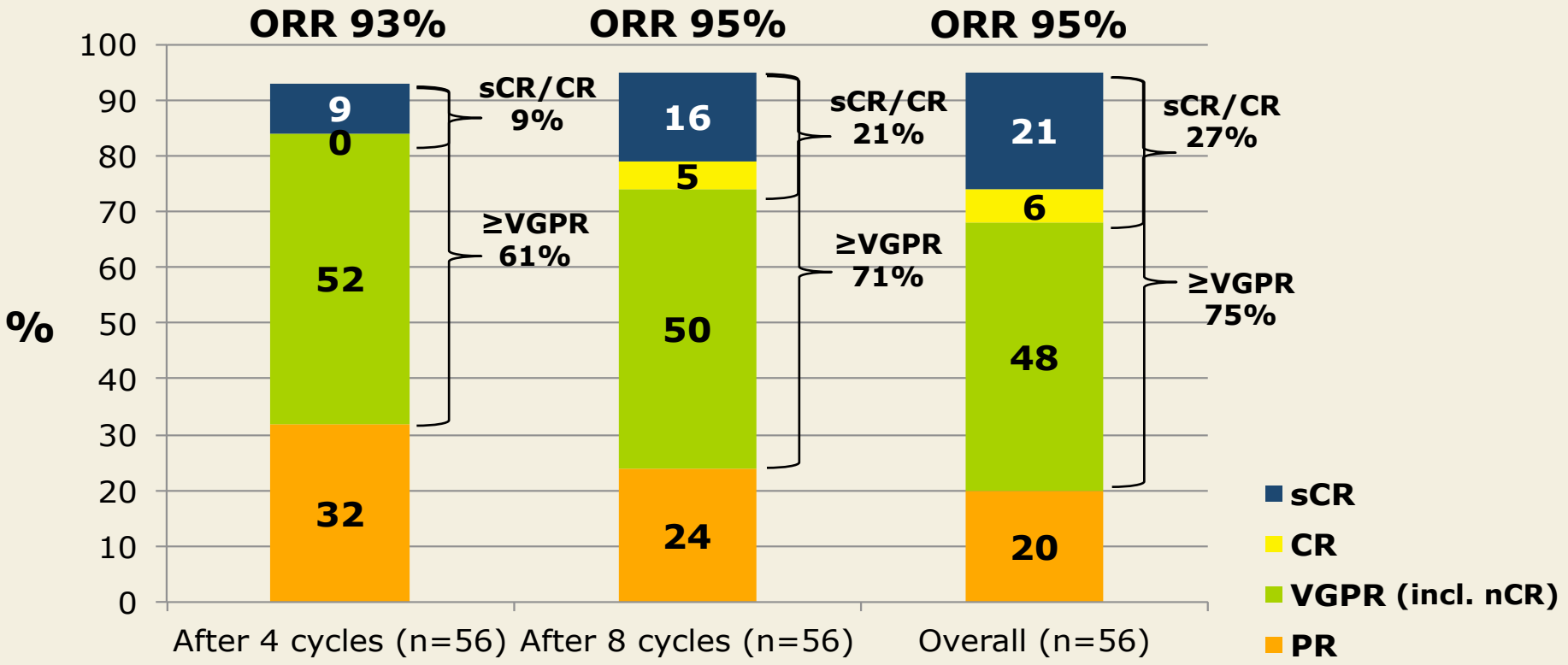
Response rate	Phase I (n = 13)	RP2D (n = 56)	Total (n = 62)
ORR	92%	95%	94%
CR	15%	27%	26%
sCR	0%	21%	19%
nCR	23%	9%	10%
VGPR (including nCR)	62%	48%	48%

ORR = overall response rate; sCR = stringent CR; nCR = near CR

- 62 of 64 patients were evaluable for response
  - 2 patients did not have postbaseline response assessments
- Median follow-up: 10.9 months

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

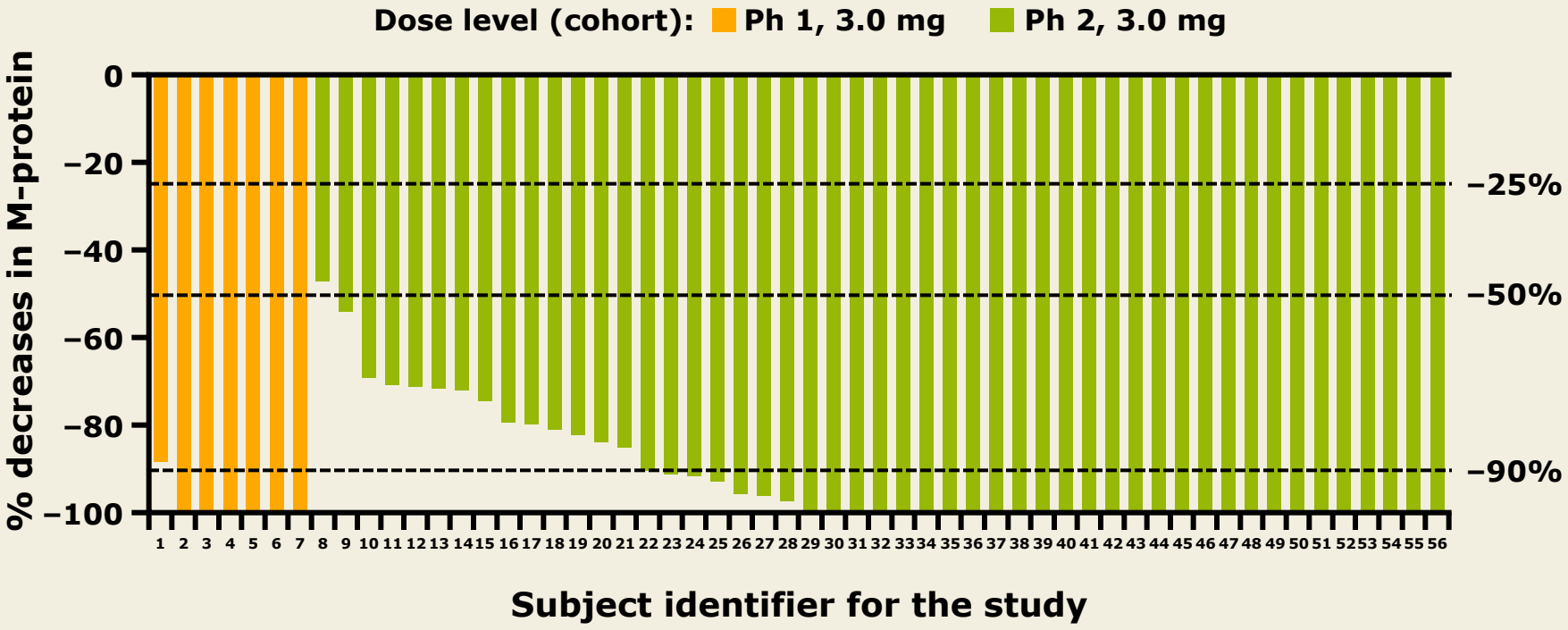
Preliminary Response Over the Course of Treatment at RP2D



- Depth of response increased over the course of treatment
  - Median time to first response: 0.69 months
  - Median time to best response to date: 1.96 months
- Median duration of response to date: 13.8 months

With permission from Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Best M-Protein or Serum Free Light Chain (FLC) Response to Treatment at R2PD



- 56 patients treated at RP2D were evaluable for response
  - Phase I (n = 7)
  - Phase II (n = 49)
- Patients (61%) had 100% decrease in M-protein or serum FLC from baseline

With permission from Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Drug-Related Grade 3 Adverse Events (≥5%)

In ≥5% of total	Phase I (n = 14)	RP2D (n = 57)	Total (n = 64)
Rash-related AEs	36%	11%	16%
Hyperglycemia	21%	9%	8%
Thrombocytopenia	14%	5%	6%
Pneumonia	7%	7%	6%
Peripheral neuropathy (PN)	7%	5%	5%
Neutropenia	7%	5%	5%
Decreased lymphocyte count	0%	5%	5%
Hyponatremia	0%	5%	5%

- There were no drug-related Grade 4 adverse events.

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Phase I Pharmacokinetic (PK) Analysis

- Based on Phase I preliminary PK data, MLN2238 was absorbed quickly with a Tmax of 0.5 to 4 hours.
- The terminal half-life was 2 to 8 days.
- PK data were similar to those obtained from single-agent twice-weekly dosing studies.
  - This suggests that there is no MLN2238 PK interaction with len or dex.

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Author Conclusions

- Ixazomib in combination with len/dex is the first completely oral combination regimen including an IMiD and a proteasome inhibitor for patients with newly diagnosed MM.
- The data suggest that twice-weekly oral ixazomib in combination with len/dex is feasible and active.
  - 25% of patients remain on study
- The rates of rash, PN and dose reductions appear lower in the parallel study using weekly ixazomib, with similar response rates and better convenience (*Proc ASH* 2012;Abstract 332).
- Because the Phase III VISTA study showed that greater proteasome inhibitor exposure produces better outcomes (*Proc ASH* 2013;Abstract 1968), the administration of oral ixazomib may be best positioned to provide patients with this benefit in the future.

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Author Conclusions (Continued)

- The data support the use of ixazomib in several ongoing Phase III trials:
  - Weekly ixazomib in combination with len and dex for patients with relapsed/refractory MM (NCT01564537, TOURMALINE-MM1)
  - Weekly ixazomib in combination with len and dex for patients with newly diagnosed MM (NCT01850524, TOURMALINE-MM2)
  - Weekly MLN9708 in combination with dex for patients with relapsed or refractory AL amyloidosis (NCT01659658, TOURMALINE-AL1)

Richardson PG et al. *Proc ASH* 2013;Abstract 535.

Investigator Commentary: Phase I/II Trial of Ixazomib with Lenalidomide and Dexamethasone for Newly Diagnosed MM

This is a convenient oral regimen. If it has similar efficacy to the RVD regimen and a good toxicity profile, it could easily displace other regimens because we can treat completely on an oral basis. Importantly, ixazomib was administered twice weekly. Other studies in which it was administered weekly demonstrated a lower rate of peripheral neuropathy. This study is important because it provides response rates that are similar to those with some of the other up-front triplet regimens. From the preliminary response data, ORR was 95% at RP2D. If CR is added to VGPR, a response rate of 75% results. Out of 27% who achieved CR, 21% attained sCR. An additional 9% achieved nCR. One might argue that the depth of response is important and that the CR rate should be higher. However, in this clinical scenario it's difficult to make these comparisons. I believe that the 75% rate of ≥VGPR is an impressive result.

(Continued)

One could envision that in the future of myeloma, instead of starting with the up-front dichotomy of transplant or not, an oral triplet regimen like this could be used. As the patient's condition improves, a reassessment of transplant eligibility can be made after 4 or 8 cycles or after 2 years of therapy. Some patients will then undergo transplant and others will continue with some form of maintenance therapy.

Interview with Rafael Fonseca, MD, February 14, 2014

SAR650984, a CD38 Monoclonal Antibody in Patients with Selected CD38+ Hematological Malignancies — Data from a Dose-Escalation Phase I Study

Martin TG et al.

Proc ASH 2013;Abstract 284.

Background

- SAR650984 (SAR) is a naked humanized IgG1 monoclonal antibody (mAb) that binds selectively to CD38, an antigen highly expressed on multiple myeloma (MM) cells and other hematologic cancers.
- SAR kills tumor cells via 3 different mechanisms: antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity and induction of apoptosis.
- Potent single-agent activity has been demonstrated with SAR in vivo (*Proc AACR* 2013;Abstract 4735).
- **Study objective:** To determine the maximum tolerated dose/maximum administered dose, safety and efficacy of SAR from the first-in-human, Phase I dose-escalation study for patients with select CD38+ hematologic cancers.

Martin TG et al. *Proc ASH* 2013;Abstract 284.

Ongoing Phase I Study Design (NCT01084252)

Eligibility (target accrual = 60)

- Select hematologic cancers: MM, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), acute leukemias (AML, ALL)
- Confirmed CD38 expression
- Relapsed disease

SAR

Accelerated escalation
1 patient/cohort (cohort 1-5)

0.0001 mg/kg	q2wk	1 MM
0.001 mg/kg	q2wk	1 MM
0.01 mg/kg	q2wk	1 MM
0.03 mg/kg	q2wk	2 MM
0.1 mg/kg	q2wk	1 NHL

Basic escalation
3-6 patients/cohort (cohort 6-12)

0.3 mg/kg q2wk	5 MM, 1 NHL, 1 CLL
1 mg/kg q2wk	3 MM
3 mg/kg q2wk	5 MM, 1 CLL
5 mg/kg q2wk	3 MM
10 mg/kg q2wk	6 MM, 1 NHL
10 mg/kg q1wk	2 MM
20 mg/kg q2wk	5 MM

Expansion cohort

At recommended Phase II dose in patients with MM

Martin TG et al. *Proc ASH* 2013;Abstract 284.

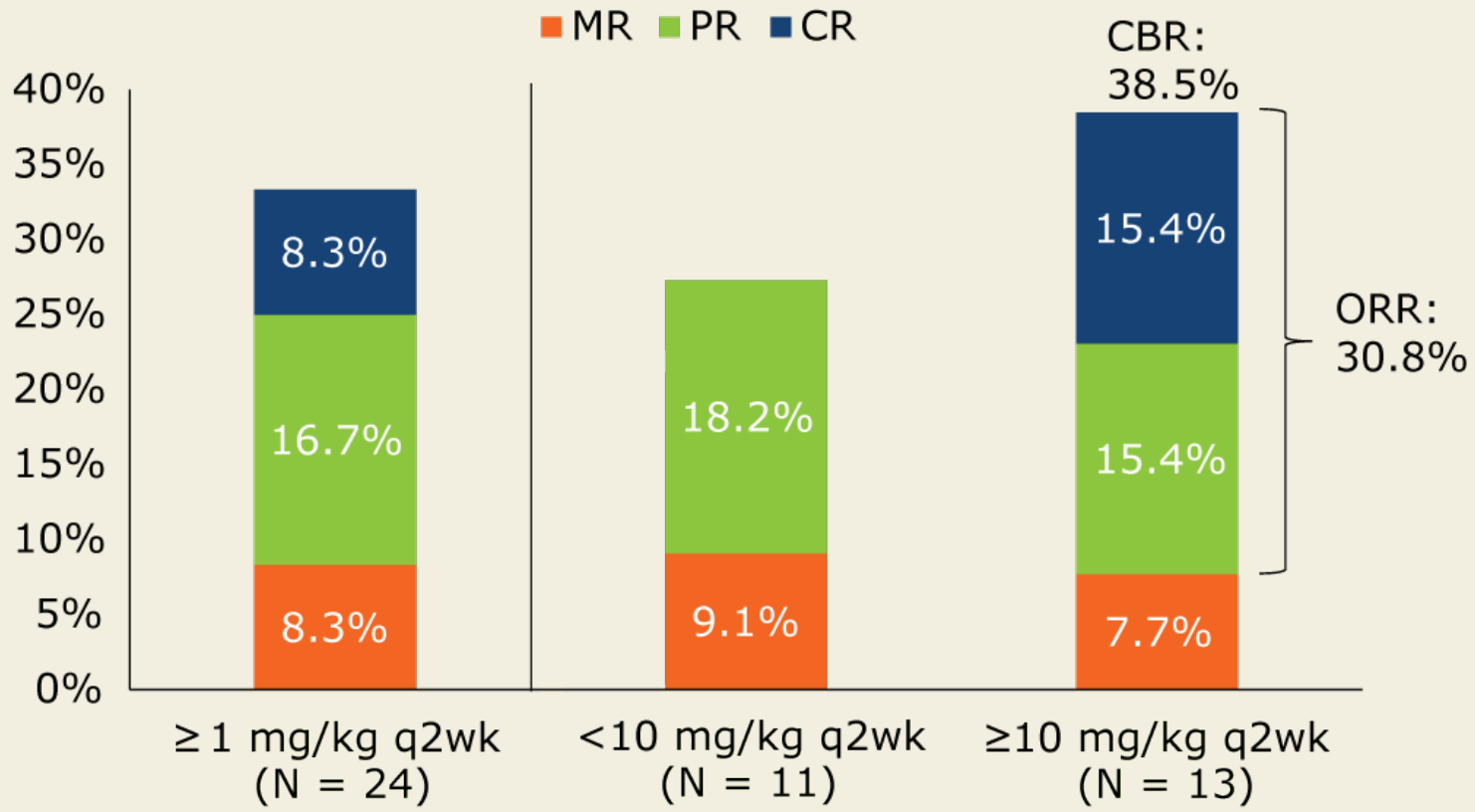
Baseline Characteristics

- 39 patients treated across dose levels
- Prior therapies for patients with MM (n = 34):
  - Median = 6
  - At ≥0.3 mg/kg, all received prior lenalidomide and bortezomib
  - At ≥10 mg/kg, 69% received carfilzomib and/or pomalidomide

	Accelerated doses	0.3 mg/kg q2wk	1 mg/kg q2wk	3 mg/kg q2wk	5 mg/kg q2wk	10 mg/kg q2wk	10 mg/kg q1wk	20 mg/kg q2wk	Overall
No. of patients (no. of patients with MM)	6 (5)	7 (5)	3 (3)	6 (5)	3 (3)	7 (6)	2 (2)	5 (5)	39 (34)
No. of prior treatments, all patients — median (range)	5 (4-9)	6 (1-12)	8 (7-9)	7 (3-14)	4 (4-10)	5 (2-9)	8.5 (4-13)	5 (4-7)	6 (1-14)
Prior carfilzomib	0	0	0	3	1	4	2	2	12
Prior pomalidomide	0	0	2	0	2	0	1	2	7

Martin TG et al. *Proc ASH* 2013;Abstract 284.

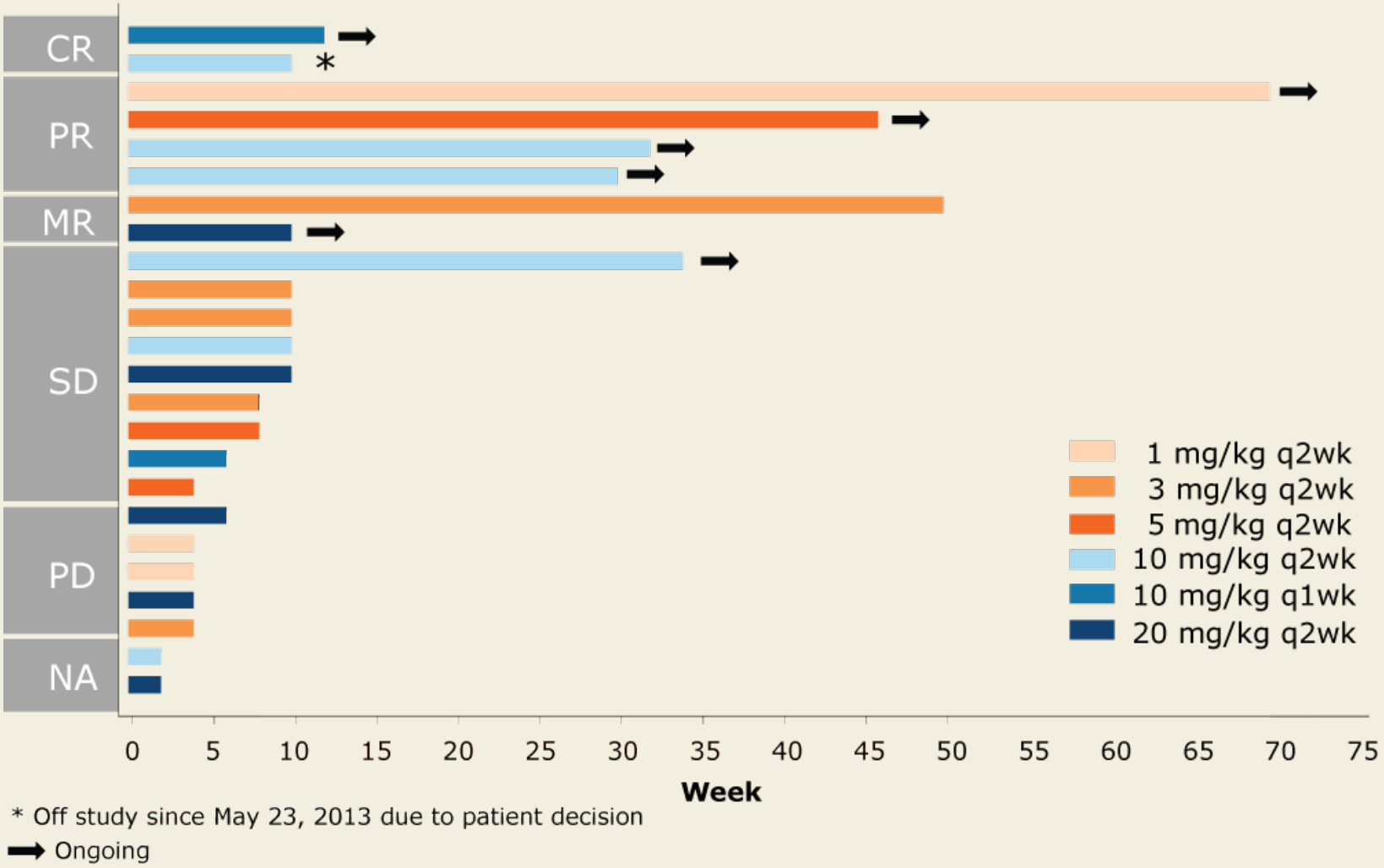
Response to SAR



- Overall response rate (ORR): ≥1-mg/kg cohort = 25%; ≥10-mg/kg cohort = 31%
- Clinical benefit rate (CBR): ≥1-mg/kg cohort = 33%; ≥10-mg/kg cohort = 38%
- Median follow-up: 6.5 mo; median time to initial response: 6.1 wk

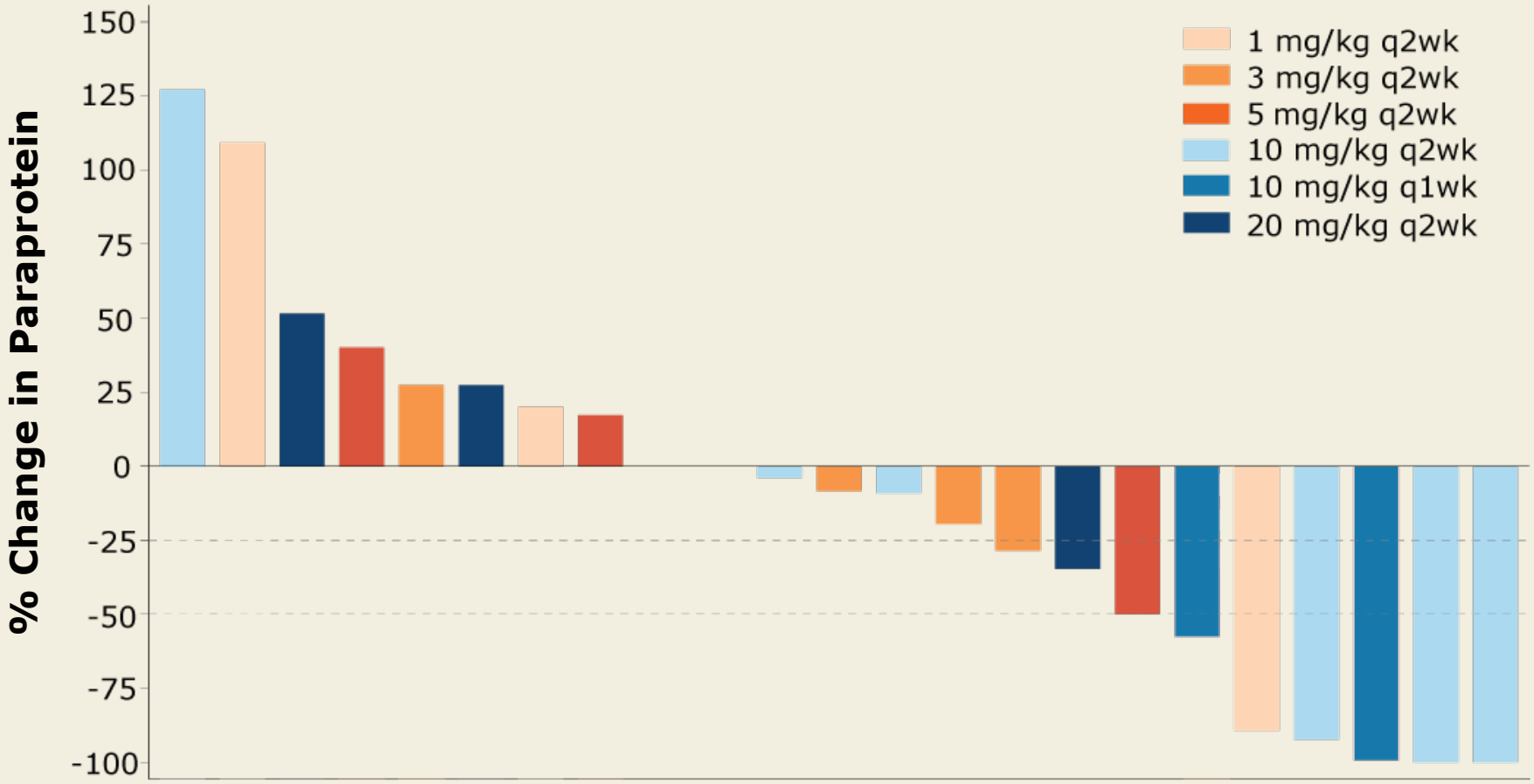
With permission from Martin TG et al. *Proc ASH* 2013;Abstract 284.

Time on Treatment by Best Response (MM Treated at ≥1 mg/kg)



With permission from Martin TG et al. *Proc ASH* 2013;Abstract 284.

Maximal Change in Paraprotein (MM Treated at ≥1 mg/kg)



1 patient at 3.0 mg/kg and 20 mg/kg with 0% change; 1 patient at 20 mg/kg not evaluable

With permission from Martin TG et al. *Proc ASH* 2013;Abstract 284.

Reduction in Bone Marrow Plasma Cells (MM Treated at ≥1 mg/kg)

Cohort (N)	% reduction in bone marrow plasma cells	Investigator's assessment (EBMT/IMWG criteria)
1 mg/kg q2wk (N = 3)	16%	PR
3 mg/kg q2wk (N = 5)	60%	MR
5 mg/kg q2wk (N = 3)	33%	PR
10 mg/kg q2wk (N = 6)	5%	CR
	19%	PR
	30%	PR
10 mg/kg q1wk (N = 2)	17%	CR
20 mg/kg q2wk (N = 5)	20%	MR

Martin TG et al. *Proc ASH* 2013;Abstract 284.

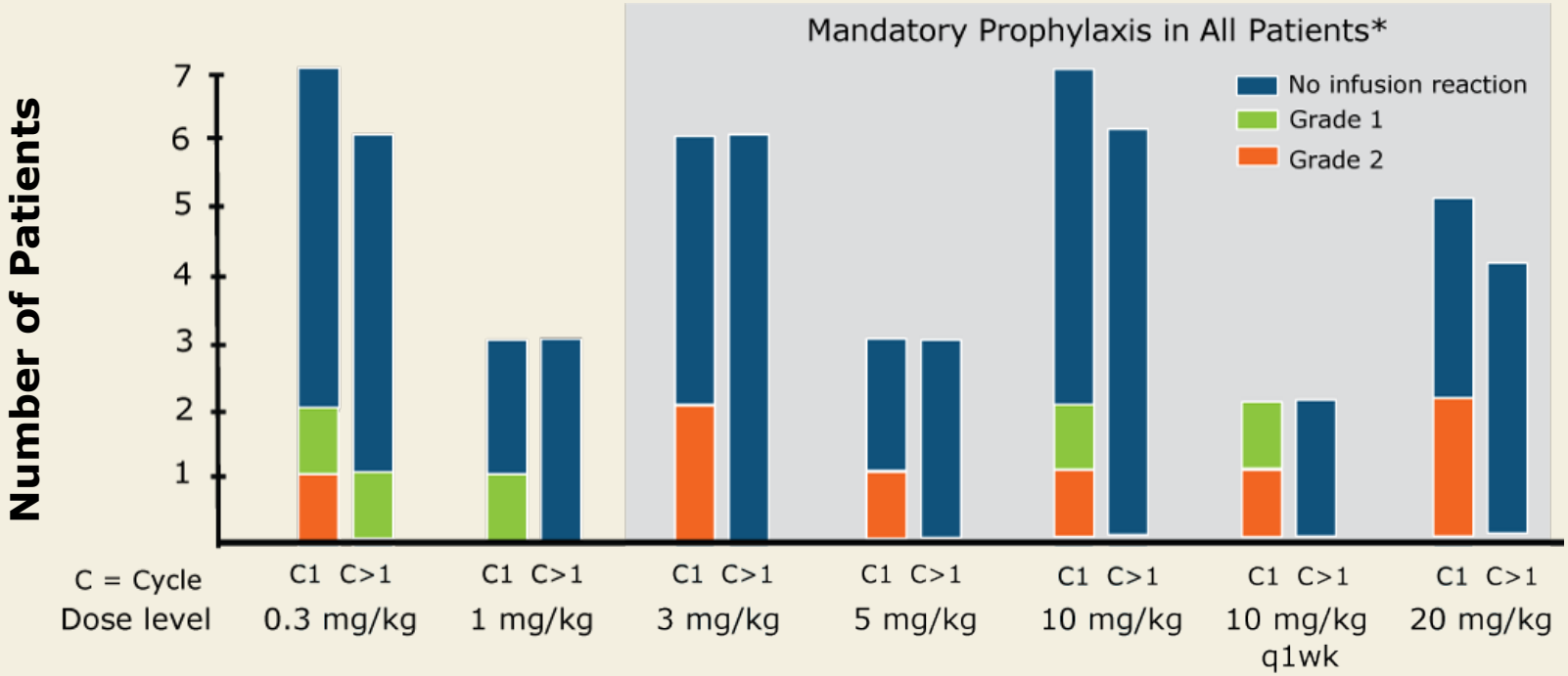
Select Adverse Events (≥10% Incidence)

Event (n = 39)	All grades	Grade 3/4
Fatigue	43.6%	0%
Nausea	33.3%	0%
Fever	25.6%	2.6%
Anemia	20.5%	5.1%
Diarrhea	15.4%	0%
Dyspnea	15.4%	0%
Thrombocytopenia	10.3%	7.7%

Grade 3/4 drug-related serious AEs: pneumonia (n = 3); apnea, gastric obstruction, pyrexia, flushing, hypoxia, infusion-related reaction, nasal congestion, vomiting (n = 1 each)

Martin TG et al. *Proc ASH* 2013;Abstract 284.

Infusion Reactions (at ≥0.3 mg/kg)



* Methylprednisolone 100 mg IV, diphenhydramine 50 mg IV, ranitidine 50 mg IV and acetaminophen 650-1,000 mg po (or equivalents)

Symptoms of Infusion Reactions (N; max severity):
Nausea (5; G 2); pyrexia (4; G 1); drug hypersensitivity, chills (3; G 2); headache (3; G 1); vomiting, hypoxia (2; G 2); cytokine release syndrome, dyspnea, flushing, nasal congestion, bronchospasm, tracheal stenosis, laryngospasm (1; G 2); influenza-like illness, abdominal pain, blurred vision, increased lacrimation, rhinorrhea, cough, restlessness (1; G 1)

With permission from Martin TG et al. *Proc ASH* 2013;Abstract 284.

Author Conclusions

- SAR, an anti-CD38 mAb, has shown a favorable safety profile.
  - Predominantly Grade 1/2 infusion reactions
  - Maximum tolerated dose not reached
- The nonlinear pharmacokinetic profile is consistent with target mediated clearance (data not shown).
- A higher receptor occupancy correlates with increasing dose (data not shown).
- In 9 of 34 patients with heavily pretreated MM a reduction of at least 25% in paraprotein was observed.
- Clinical response correlates with clearance of plasma cells from the bone marrow in patients with MM (data not shown).
- At ≥10 mg/kg SAR, the ORR was 30.8%, including 2 complete responses, and the CBR was 38.5%.

Martin TG et al. *Proc ASH* 2013;Abstract 284.

Investigator Commentary: A Phase I Study of SAR in Selected CD38+ Hematologic Cancers

CD38 is expressed in a number of hematologic cancers but is a prime target in MM. The majority of patients with MM express CD38, which is, in fact, a standard clinical measurement for the disease. Exciting data have been presented on anti-CD38 antibodies, and proof of principle with the anti-CD38 antibody daratumumab was demonstrated in a study presented at ASCO last year (*Proc ASCO* 2013;Abstract 8512). This current study reported that the anti-CD38 mAb SAR was well tolerated. Infusion reactions were not a major limitation of the study. Patients who received SAR at a dose of ≥10 mg/kg every 2 weeks experienced an ORR of 31% and a CBR of 38.5%. This is objective evidence of a mAb having a direct effect in MM.

I believe that this is probably one of most important molecules for future MM therapy. It's a biologic agent that elicits an immune response to myeloma cells and is a completely different class of drug. This agent has the potential to be effective in high-risk disease. I believe that it will move fast through clinical development in Phase II and Phase III trials. This agent could have promise in the up-front setting in MM and should be investigated in that setting also.

(Continued)

The identification of patients who will respond to SAR and other mAbs such as daratumumab and elotuzumab has not been addressed yet by clinical trials. One factor that should be considered is the background immunity of these patients. If patients have previously received treatment with drugs that are cytotoxic to lymphocytes, those patients may not be the best candidates for treatment with these therapeutic antibodies. If the expectation is that the host immune system will help resolve and destroy some myeloma cells, then the function of these antibodies may be affected in a patient with lymphopenia and immunosuppression.

Interview with Rafael Fonseca, MD, February 14, 2014

Prolonged Survival and Improved Response Rates with ARRY-520 (Filanesib) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients with Low α-1 Acid Glycoprotein (AAG) Levels: Results from a Phase 2 Study

Lonial S et al.

Proc ASH 2013;Abstract 285.

Background

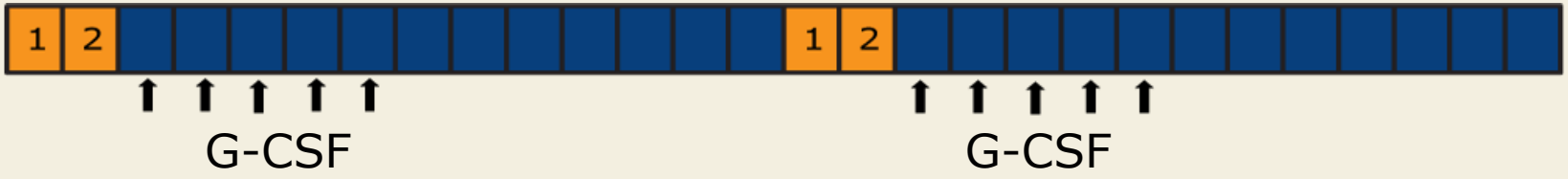
- Filanesib (ARRY-520) is a potent, selective inhibitor of the novel drug target kinesin spindle protein (KSP).
- KSP is a microtubule motor protein critical to the function of proliferating cells, and inhibition of KSP induces aberrant mitotic arrest and rapid cell death.
- Filanesib has shown single-agent activity in multiple myeloma (MM) (*Leukemia* 2013;[Epub ahead of print]).
- The acute-phase protein α1-acid glycoprotein (AAG) can bind filanesib, reducing free drug and possibly resulting in reduced treatment effect in patients with high levels of AAG.
- **Study objective:** To evaluate the efficacy and safety of filanesib alone or in combination with dexamethasone in RRMM.

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Phase II ARRAY-520-212 Trial Design

Cohort 1: Filanesib Single Agent

Filanesib 1.5 mg/m^2 q2 weeks



Cohort 2: Filanesib/Dexamethasone Combination

Filanesib 1.5 mg/m^2 q2 weeks

Dexamethasone 40 mg PO weekly

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Eligibility and Cohorts

- RRMM
- Cohort 1: Single-agent filanesib (n = 32)
  - ≥2 prior treatment regimens, including bortezomib and an IMiD
  - Disease progression during or after last regimen
- Cohort 2: Filanesib with dexamethasone (n = 55)
  - ≥2 prior treatment regimens
  - Refractory to last regimen (progression during or within 60 days)
  - ≥2 consecutive cycles of prior treatment that included lenalidomide and bortezomib
    - Refractory to lenalidomide, bortezomib and dexamethasone
    - Adequate prior alkylator therapy

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Low AAG Correlates with High ORR

Outcome	Filanesib			Filanesib + dexamethasone		
	All pts[1] (n = 32)	AAG high (n = 6)	AAG low (n = 21)	All pts[2] (n = 55)	AAG high (n = 15)	AAG low (n = 36)
ORR (≥PR)	16%	0%	24%	15%	0%	19%
CBR (≥MR)	22%	0%	33%	20%	0%	28%
Time to next treatment	3.7 mo	2.6 mo	5.3 mo	3.4 mo	2.0 mo	5.1 mo
OS	19.0 mo	4.5 mo	23.3 mo	10.5 mo	2.9 mo	10.8 mo

ORR = overall response rate; CBR = clinical benefit rate; OS = overall survival

[1] Five patients had no baseline AAG measurement
[2] Four patients had no baseline AAG measurement, including 1 responder

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Activity of Filanesib in Patients Who Previously Received New MM Drugs

Filanesib + Dexamethasone Cohort

Response	Prior pomalidomide and/or carfilzomib and/or MLN9708		
	All pts (n = 19)	High AAG (n = 5)	Low AAG (n = 13)
≥PR	21%	0	31%

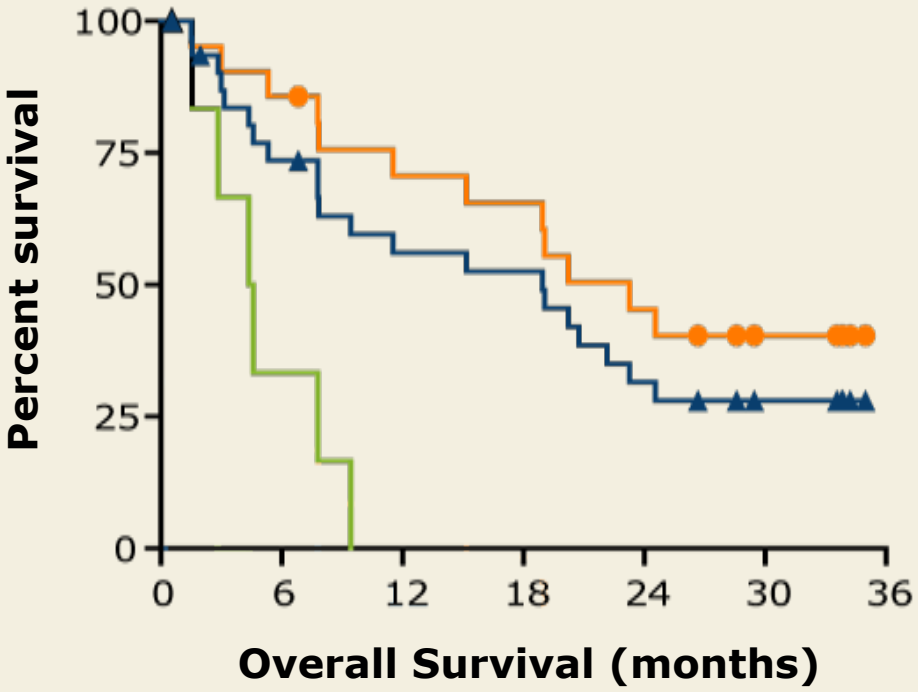
Filanesib maintains activity in myeloma resistant to multiple drugs.

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Correlation of AAG Level and OS

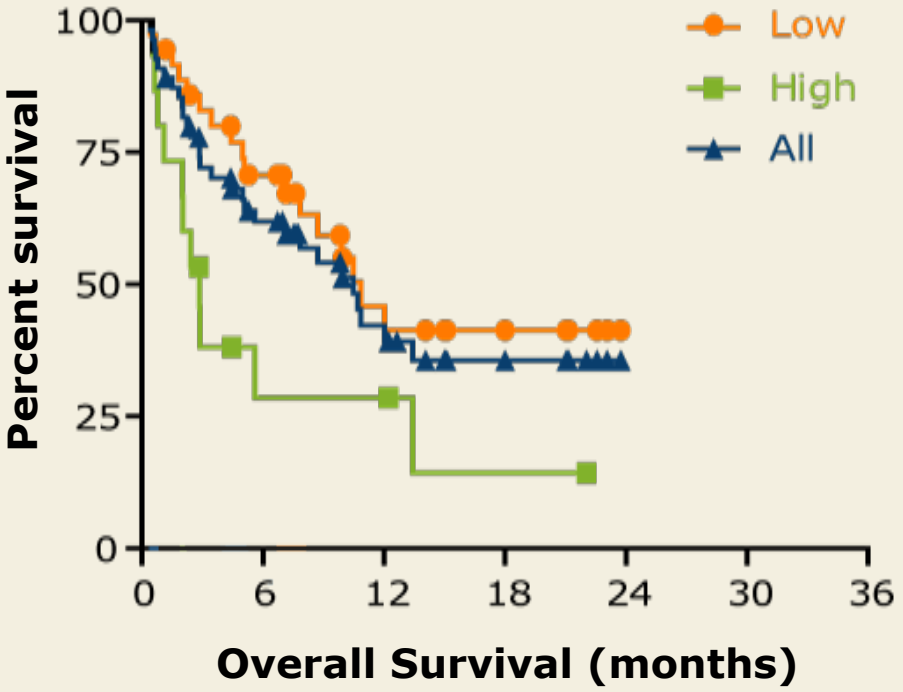
Filanesib Single-agent

Median 6 prior therapies



Filanesib + Dex

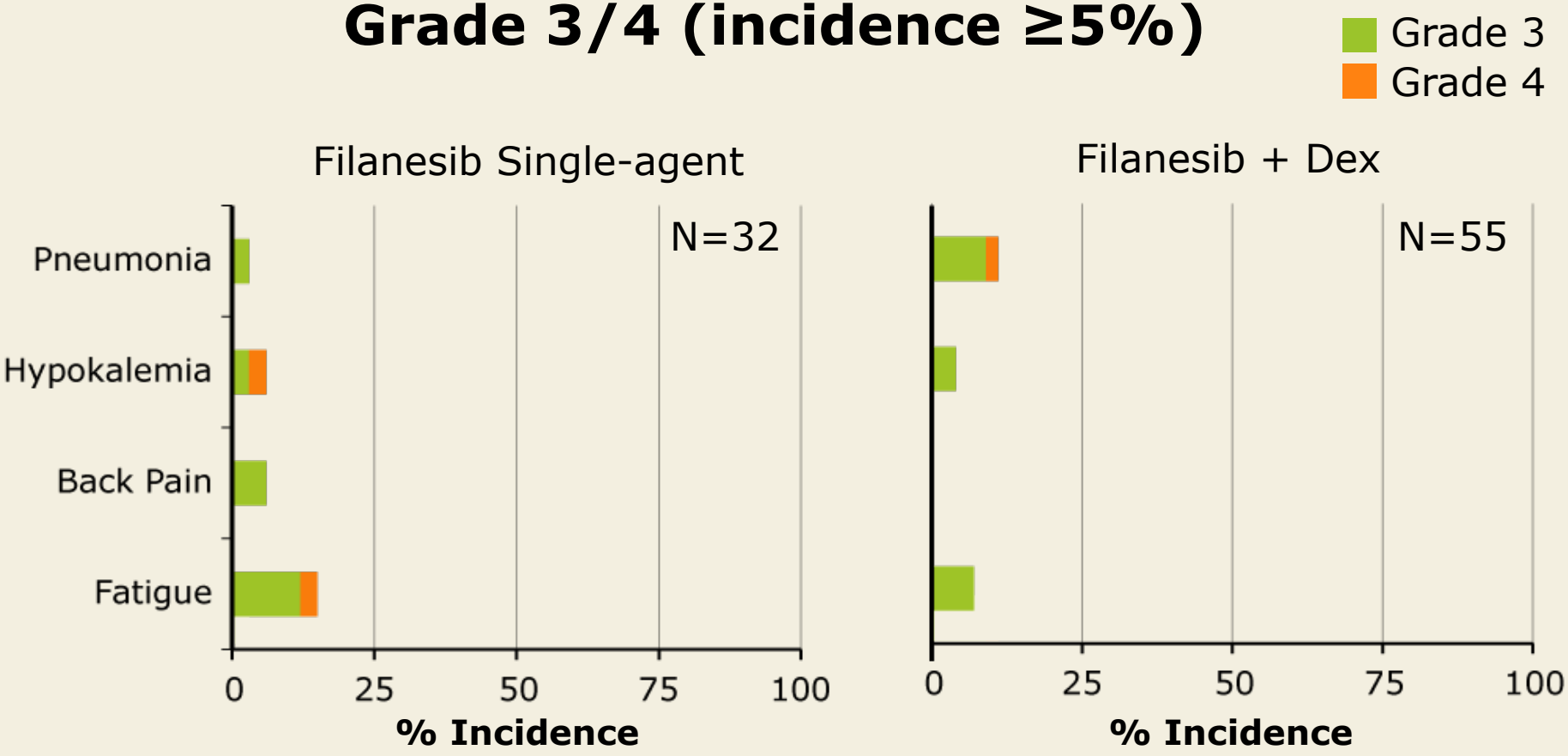
Median 8 prior therapies



With permission from Lonial S et al. *Proc ASH* 2013;Abstract 285.

Nonhematologic Adverse Events

Grade 3/4 (incidence ≥5%)

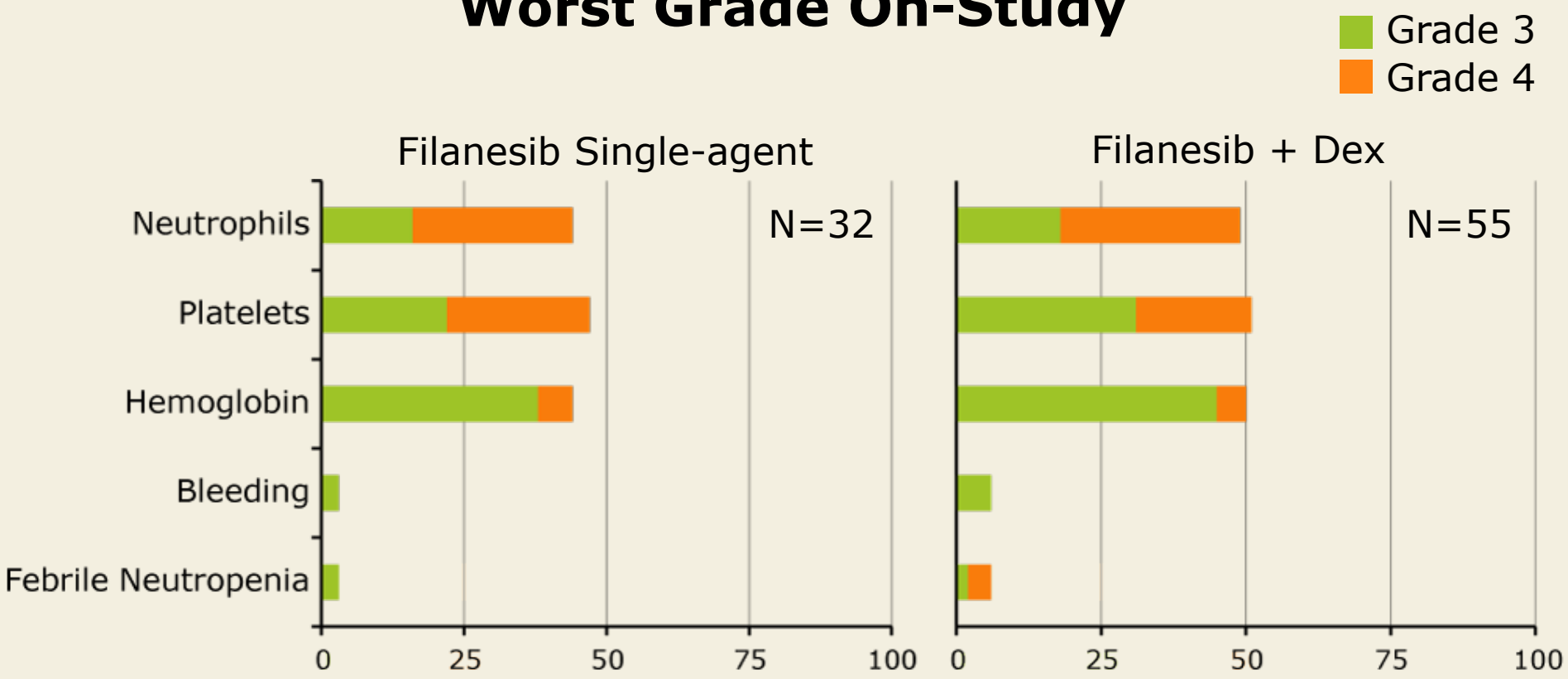


- Filanesib was not associated with peripheral neuropathy
- No cumulative toxicity with long-term administration

With permission from Lonial S et al. *Proc ASH* 2013;Abstract 285.

Hematologic Adverse Events

Worst Grade On-Study



Hematological toxicity predicted based on mechanism of action
- Managed with supportive care
- Low incidence of febrile neutropenia or bleeding events

With permission from Lonial S et al. *Proc ASH* 2013;Abstract 285.

Author Conclusions

- Treatment with filanesib, a first-in-class KSP inhibitor, is a novel approach in MM, distinct from IMiDs or protease inhibitors (PIs).
- AAG may identify patients who do not benefit from filanesib.
- Filanesib demonstrated single-agent activity in heavily pretreated RRMM:
  - Activity in patients with MM previously treated with IMiD/PI
  - Improved response and survival for patients with low serum AAG
- A well-tolerated safety profile was observed, with supportive care:
  - Low incidence of nonhematologic AEs
  - Hematologic events were generally reversible and not cumulative

Lonial S et al. *Proc ASH* 2013;Abstract 285.

Investigator Commentary: A Phase II Study of Filanesib in RRMM

Filanesib acts by targeting KSP and inhibiting mitosis, a unique mechanism of action in MM. This study showed an overall response rate of 15% to 16% with filanesib alone or in combination with dexamethasone. The main highlight of the study is that AAG appears to be a biomarker that may identify patients with a higher likelihood of responding to filanesib. Patients with high AAG levels do not experience a response to the agent. Those with low AAG levels who responded to filanesib experienced a median OS of more than 2 years. This is much higher than would be expected for patients with heavily pretreated disease. Data are also promising with filanesib in combination with carfilzomib and bortezomib in the relapsed setting. I believe this would be a great drug in the relapsed/refractory setting.

Interview with Sagar Lonial, MD, January 22, 2014

Investigator Commentary: A Phase II Study of Filanesib in RRMM (Continued)

Some evidence in the literature indicates that microtubule inhibitors could potentially be used as therapeutic tools against MM. In fact, our center is currently conducting a Phase II clinical trial of *nab* paclitaxel for patients with fairly advanced myeloma. It is interesting then that filanesib represents a new treatment approach for MM.

Importantly, the drug was not associated with peripheral neuropathy, a potential side effect and complication of tubulin inhibitors that one would consider in the context of long-term myeloma therapy. Clear evidence of an antitumor response was observed in patients with RRMM. The fact that filanesib is effective as a single agent positions both the pathway and this molecule as promising in the treatment of MM.

Interview with Rafael Fonseca, MD, February 14, 2014

Novel AKT Inhibitor Afuresertib in Combination with Bortezomib and Dexamethasone Demonstrates Favorable Safety Profile and Significant Clinical Activity in Patients with Relapsed/Refractory Multiple Myeloma

Voorhees PM et al.

Proc ASH 2013;Abstract 283.

Background

- AKT is a critical signaling node in multiple myeloma (MM) and other hematologic cancers.
- Afuresertib (GSK2110183) is a potent pan-AKT inhibitor that demonstrated synergy with bortezomib in preclinical models of MM and single-agent activity in patients with heavily pretreated disease in a Phase I, first-in-human study (*Proc ASH* 2011;Abstract 1856).
- **Study objective:** To evaluate the safety and preliminary efficacy of afuresertib in combination with bortezomib and dexamethasone for patients with relapsed or refractory (R/R) MM.

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

PKB115125: Phase IB Study Design

Part 1: Dose escalation

- Modified 3 + 3 dose-escalation design
- Cycles 1-8 induction
  - Bortezomib IV/SC d1, 4, 8, 11
  - Dexamethasone PO d1, 4, 8, 11
  - Afuresertib PO d1-21
- Cycle 9 and beyond
  - Afuresertib monotherapy daily
- PK/PD cohort at the maximum tolerated dose (MTD) (n = 10)

Primary objective: Safety, tolerability, MTD

Part 2: Safety expansion

Eligibility (n = 81)

R/R MM

Bortezomib naïve or sensitive

Bortezomib + dexamethasone + afuresertib (8 cycles)

Afuresertib (Cycle 9 onward)

Two-stage design (stop for futility):
Stage 1 (n = 15): <5 PR = stop, ≥5 = expand
Stage 2: Expand for efficacy (n = 40 total)

Primary objective: Safety, tolerability, response rate

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Key Eligibility Criteria

- ECOG PS 0 to 2
- Absolute neutrophil count ≥1.0 x 10^9/L, hemoglobin count ≥8.0 g/dL, platelet count ≥50 x 10^9/L
- Creatinine clearance ≥30 mL/min
- Total bilirubin/AST/ALT ≤1.5 x ULN
- Grade <2 peripheral neuropathy
- ≥1 prior line of therapy
- Part 1: Bortezomib naïve or R/R
- Part 2: Bortezomib naïve or relapsed

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Clinical Activity

	Dose cohort		
Best unconfirmed response	**Part 1 (n = 34)**	**Part 2 (n = 37)**	**PK/PD (n = 10)**
Overall response rate (ORR)	50%	65%	40%
Clinical benefit rate (CBR)	56%	73%	40%

Clinical activity (ORR) by prior bortezomib exposure				
Bortezomib exposure	**Part 1**	**Part 2**	**PK/PD**	**Total**
Naïve (n = 13)	2/3 (67%)	6/10 (60%)	NA	62%
Relapsed (n = 44)	10/18 (56%)	17/26 (65%)	NA	61%
Refractory (n = 23)	5/13 (38%)	1/1 (100%)	4/9 (44%)	43%
Unknown (n = 1)	—	—	—	0/1 (0%)

PK = pharmacokinetics; PD = pharmacodynamics

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Dose-Limiting Toxicities (DLTs)

Afuresertib	Bortezomib	Dexamethasone	n	DLT*	Comment
75 mg	1.0 mg/m^2	20 mg	4	None	—
100 mg	1.3 mg/m^2	20 mg	6	1/6	ALT increase (Grade 2)
125 mg	1.3 mg/m^2	20 mg	6	1/6	Erythema multiforme (Grade 3)
150 mg	1.3 mg/m^2	20 mg	6	None	—
175 mg	1.3 mg/m^2	20 mg	6	2/6	Patient 1: Rash Patient 2: Rash, diarrhea thrombocytopenia (all were Grade 3)
150 mg	1.3 mg/m^2	40 mg	6	NA	—

* All DLTs were reversible

MTD/recommended Phase II dose

Afuresertib	150 mg PO daily
Bortezomib	1.3 mg/m^2 IV or SC on days 1, 4, 8 and 11
Dexamethasone	40 mg PO on days 1, 4, 8 and 11

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Adverse Events (AEs)

Nonhematologic	All grades	Grade ≥3
Fatigue	51%	2%
Diarrhea	49%	14%
Nausea	37%	1%
Constipation	33%	2%
Dyspepsia	32%	1%
Hyperglycemia	28%	7%
Vomiting	27%	2%
Peripheral neuropathy	22%	0%
Insomnia	20%	0%
Rash	20%	7%

Serious AEs

Recorded in 31 pts

- Infection
- Acute renal injury
- Skin disorders
- Gastrointestinal
- Bone-related events
- Vascular events

- 1 death: septic shock (F, age 61 years)
- Rate of discontinuation for AEs = 23%

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Adverse Events (continued)

Hematologic	All grades	Grade ≥3
Thrombocytopenia	38%	27%
Anemia	22%	10%
Neutropenia	11%	7%
Febrile neutropenia	2%	1%

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Author Conclusions

- Afuresertib can be administered safely in combination with bortezomib and dexamethasone:
  - GI and dermatologic AEs were common but manageable.
- Afuresertib's PK profile is not affected by bortezomib or dexmethasone (data not shown).
- Bortezomib's PK profile is not affected by afuresertib, but dexamethasone exposure is increased by 30% to 50% with afuresertib (data not shown).
- Afuresertib leads to increased phospho-AKT levels in MM cells, demonstrating achievement of target inhibition at the 150-mg daily dose (data not shown).
- Afuresertib shows promising clinical activity in combination with bortezomib/dexamethasone:
  - Responses in patients with bortezomib-refractory disease suggest that afuresertib might overcome bortezomib resistance in some cases.
- Further studies are planned to confirm the clinical efficacy of afuresertib in combination with other active agents in MM.

Voorhees PM et al. *Proc ASH* 2013;Abstract 283.

Investigator Commentary: Novel AKT Inhibitor Afuresertib in Combination with Bortezomib and Dexamethasone for Patients with R/R MM

A strong rationale exists for why AKT may be important in the biology of MM, and single-agent activity has been reported with the AKT inhibitor afuresertib in MM (*Proc ASH* 2011;Abstract 1856). The current study used a Phase I dose-escalation regimen followed by a Phase II expansion to evaluate afuresertib in combination with bortezomib and dexamethasone in the R/R setting. In total, 81 patients received treatment based on demographic descriptions that are standard for this patient population. The trial also included a subset of patients with bortezomib-refractory MM.

The Phase II ORR was 65%, and the CBR was 73%. Regarding DLTs, it is important to note some instances of rash. Other noted side effects included Grade ≥3 diarrhea, which was observed in 14% of patients, and hematologic toxicities. We will need to dissect what's observed because of afuresertib, the new compound, versus what may be an effect of bortezomib.

(Continued)

How to position new molecules in combination with bortezomib in MM is a fiercely competitive world, but this particular molecule has single-agent activity and now appears to show clear evidence of activity in combination. It will have to be tested in larger studies but shows good proof of concept for future investigation.

Interview with Rafael Fonseca, MD, February 14, 2014

Carfilzomib, Rituximab and Dexamethasone (CaRD) Is Highly Active and Offers a Neuropathy Sparing Approach for Proteasome-Inhibitor Based Therapy in Waldenstrom's Macroglobulinemia

Treon SP et al.

Proc ASH 2013;Abstract 757.

Background

- The combination of bortezomib, rituximab and dexamethasone has a high degree of activity as up-front therapy for patients with Waldenström's macroglobulinemia (WM) (*Blood* 2013;122:3276).
  - Response rates of ~85% with deep remissions, including very good partial responses (VGPR) and complete responses (CR), and median progression-free survival close to 4 years
- However, an issue with the use of bortezomib is peripheral neuropathy, which is accentuated in patients with WM, perhaps due to underlying IgM and amyloid neuropathy.
- The second-generation proteasome inhibitor carfilzomib, which is approved for relapsed/refractory myeloma, also has a well-recognized neuropathy-sparing role in multiple myeloma.
- **Study objective:** To evaluate the efficacy and safety of carfilzomib, rituximab and dexamethasone (CaRD) in patients with symptomatic, proteasome inhibitor- and rituximab-naïve WM.

Treon SP et al. *Proc ASH* 2013;Abstract 757.

Study Methods

- Treatment consisted of 6 induction cycles, then maintenance beginning 8 weeks after induction (given every 8 weeks for 8 cycles).
- Dose and schedule of **induction therapy**:
  - Carfilzomib (IV) 20 mg/m^2 (cycle 1), then 36 mg/m^2 (cycles 2 and beyond)
  - Dexamethasone (IV) 20 mg on days 1, 2, 8, 9
  - Rituximab 375 mg/m^2 on days 2, 9 of each 21-day cycle
- Dose and schedule of **maintenance therapy**:
  - Carfilzomib 36 mg/m^2, dexamethasone 20 mg on days 1, 2 and rituximab 375 mg/m^2 on day 2
- Patients with IgM level >4,000 mg/dL underwent plasmapheresis and/or had rituximab held until IgM <4,000 mg/dL to prevent symptomatic IgM flare.
- Patients received oral acyclovir (400 mg twice daily) and famotidine (20 mg twice daily) as concomitant medications.

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Patient Characteristics

Characteristic (median)	n = 31
Age	61 years
Number of prior therapies	0 (range: 0-1)
Hematocrit levels	32.3%
Hemoglobin levels	10.7 g/dL
Serum IgM	3,375 mg/dL
Serum M-protein	2.185 g/dL
B2M	3.6 mg/L
Bone marrow disease involvement	60%
No prior therapy	87%

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Study Results

- For all 31 patients, median serum IgM levels and M-protein declined to 749 mg/dL and 0.7 g/dL, respectively ($p < 0.00001$).
- Median hematocrit and hemoglobin rose to 40.9% and 13.7 g/dL, respectively ($p < 0.00001$).
- A total of 30 patients concluded induction therapy with bone marrow tumor involvement reduced to a median of 7.5% ($p = 0.0003$).

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Response Evaluation

	n = 31
Best overall response rate,* n (%)	25 (81.0%)
CR	1 (3.2%)
VGPR	8 (25.8%)
Partial response	12 (38.7%)
Minor response (MR)	4 (12.9%)

* Using criteria adapted from the Third International Workshop on WM

- Median follow-up = 8 cycles
- Median time to response (for MR or better) = 2.1 months
- 22 patients remain on study, including 20 currently on maintenance therapy

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Adverse Events (AEs) and Treatment Discontinuation

Grade >2 AEs	n = 31
Asymptomatic lipase elevation	12.9%
Hyperglycemia (dexamethasone-related)	6.5%
Reversible neutropenia	9.7%
Cardiomyopathy	3.2%
Peripheral neuropathy	0%

- **Treatment discontinuation occurred for the following reasons:**
  - Nonresponse (n = 8)
  - Cardiomyopathy in a patient with multiple cardiac risk factors (n = 1)
  - Progressive disease (n = 1)

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Author Conclusions

- The combination of carfilzomib, rituximab and dexamethasone is active as front-line therapy for patients with WM.
  - Overall response rate = 81%, including a third of patients achieving VGPR or better
- Significant improvements in serum IgM, hematocrit and bone marrow disease burden were observed in most patients (data not shown).
- The CaRD combination was well tolerated.
- This combination represents a neuropathy-sparing approach for the treatment of patients with WM.

Treon SP et al. *Proc ASH* 2013;Abstract 757.

Investigator Commentary: CaRD for Newly Diagnosed WM

Given the experience with carfilzomib in myeloma, studying it in WM is exciting. The rituximab/dexamethasone combination is commonly used in WM, so this study put 3 "power players" together. Patients with IgM levels >4,000 mg/dL underwent plasmapheresisto prevent the hyperviscosity associated with rituximab therapy, and patients also received acyclovir prophylaxis, which is important with proteasome inhibitors because of the significant risk of herpes zoster associated with administration of these agents.

The authors reported an 81% response rate — 1 patient experienced a CR, and 8 VGPRs, 12 PRs and 4 MRs were achieved. Patients seemed to tolerate the combination well, and the time to response was typical for this disease. Grade 2 or greater peripheral neuropathy was not reported, which is important. So carfilzomib continues to be positioned in various stages of myeloma treatment, and Waldenström's is a natural extension of this.

(Continued)

The problem that plagues Waldenström's is that it's a rare enough disease that almost no one runs clinical trials for registration of these agents. We've always had to work around factors such as insurance coverage because almost everything that is done in WM is essentially off label. So perhaps we have more freedom, but we also face greater challenges in how to integrate some of these new agents for the treatment of patients with this disease.

Interview with Rafael Fonseca, MD, February 14, 2014

A Prospective Multicenter Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Patients with Relapsed or Refractory Waldenstrom's Macroglobulinemia

Treon SP et al.

Proc ASH 2013;Abstract 251.

Background

- Whole genome sequencing has revealed highly prevalent somatic mutations in Waldenström's macroglobulinemia (WM) (*Proc ICML* 2013;Abstract 093).
- MYD88 L265P mutation is present in >90% of patients with WM and supports malignant growth via signaling involving Bruton's tyrosine kinase (BTK).
- Ibrutinib inhibits BTK and in vitro induces apoptosis of WM cells bearing MYD88 L265P (*Blood* 2013;122:1222).
- WHIM-like mutations in CXCR4 are present in one third of patients with WM, and their expression induces BTK activity and confers decreased sensitivity to ibrutinib-mediated growth suppression in WM cells (*Proc ASH* 2013;Abstract 4424).
- **Study objective:** To evaluate the efficacy and tolerability of ibrutinib in relapsed/refractory WM and examine the impact of MYD88 L265P and WHIM-like CXCR4 mutations on ibrutinib response.

Treon SP et al. *Proc ASH* 2013;Abstract 251.

Study Methods

- Sixty-three patients with symptomatic WM who received at least 1 prior treatment, including 17 patients with relapsed disease, were enrolled on this prospective clinical trial.
- Intended therapy consisted of 420 mg of oral ibrutinib daily for 2 years or until progression or unacceptable toxicity.
- Sanger sequencing was used to determine MYD88 and CXCR4 mutations in sorted bone marrow lymphoplasmacytic cells from 43 and 40 patients, respectively.
- Forty of 43 (93%) and 10 of 40 (25%) patients had MYD88 L265P and WHIM-like CXCR4 mutations, respectively.

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Baseline Patient Characteristics

Characteristic — median	n = 63
Age	63 years (range: 44-86)
Number of prior therapies	2 (range: 1-6)
Hematocrit levels	30.8% (range: 24.5-41.5)
Hemoglobin levels	10.5 g/dL (range: 8.2-13.8)
Serum IgM	3,610 mg/dL (range: 735-8,390)
Serum M-protein	2.14 g/dL (range: 0.5-5.4)
B2M	3.9 mg/L (range: 1.3-14.2)
Bone marrow disease involvement	65% (range: 3.2-95)

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Study Results

- At best response, median serum IgM levels and M-protein declined to 1,340 mg/dL and 0.84 g/dL, respectively ($p < 0.00001$).
- Median hematocrit and hemoglobin rose to 38.1% and 12.6 g/dL, respectively ($p < 0.00001$).
- Post-treatment bone marrow assessment at 6 months was available for 34 patients and indicated a reduction in WM disease involvement from 70% to 45% ($p = 0.0006$).

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Response Evaluation

	n = 63
Best overall response rate (≥minor response [MR])*	51 (81.0%)
Very good partial response (VGPR)	4 (6.3%)
Partial response (PR)	32 (50.8%)
MR	15 (23.8%)
Stable disease	11 (17.5%)
Nonresponsive	1 (1.6%)
Major response rate (≥PR)	36 (57.1%)

* Using consensus criteria adapted from the Third International Workshop on WM

- Median follow-up = 6 cycles (range: 2-15)
- Median time to response = 4 weeks

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Adverse Events (AEs)

Grade >2 AEs	n = 63
Neutropenia	19.1%
Thrombocytopenia	14.3%
Stomatitis	1.6%
Atrial fibrillation	1.6%
Diarrhea	1.6%
Herpes zoster	1.6%
Hematoma	1.6%
Hypertension	1.6%
Epistaxis	1.6%

- 59 patients remain on study with 7 on reduced doses of ibrutinib.

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Tumor Sequencing

- Attainment of major responses was affected by mutations in CXCR4 but not MYD88 L265P in patients who underwent tumor sequencing.
- Major response rate was 77% for patients with wild-type CXCR4 versus 30% for those with WHIM-like CXCR4 mutations ($p = 0.018$).
- Decreases in serum IgM ($p = 0.047$) and IgM M-spike ($p = 0.012$) and improvements in hemoglobin ($p = 0.058$) were greater in patients with wild-type CXCR4.
  - Patients with wild-type CXCR4 also had increased peripheral lymphocytosis after ibrutinib treatment compared to those with WHIM-like CXCR4 mutations ($p = 0.001$).

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Author Conclusions

- Ibrutinib is highly active and well tolerated in patients with relapsed or refractory WM.
- Rapid reductions in serum IgM and improved hematocrit occur in most patients receiving ibrutinib.
- The presence of WHIM-like CXCR4 mutations affects responses and peripheral lymphocytosis in patients with WM undergoing ibrutinib treatment.

Treon SP et al. *Proc ASH* 2013;Abstract 251 (abstract only).

Investigator Commentary: A Prospective Multicenter Study of the BTK Inhibitor Ibrutinib in Patients with Relapsed or Refractory WM

The development of BTK inhibitors in WM is truly a bench-to-bedside story. The group from Dana-Farber, using genome sequencing, described a mutation now known as MYD88, which supports malignant growth via signaling involving BTK, in virtually all patients with Waldenström. And obviously, with the recent availability of the BTK inhibitor ibrutinib, this study made sense. The authors reported on 63 patients with WM — 17 of whom were considered to have refractory disease — and reported that patients had significant evidence of antitumor activity after ibrutinib therapy. With a reported median follow-up of 6 cycles, the best overall response rate was 81% with 4 VGPRs, 32 PRs and a PR or better rate of 57%. These are clear data that this agent will be effective in this setting.

The agent seems to be manageable with regard to toxicity. Obviously, ibrutinib has been tested more in the relapsed/refractory setting. But, with this toxicity profile and tolerability, I believe studies for larger populations of patients in the up-front setting are clearly needed.

Interview with Rafael Fonseca, MD, February 14, 2014