5 Minute JournalClub

POST-ASH Issue 5, 2014

SAR650984, a CD38 Monoclonal Antibody, for Patients with Selected CD38+ Hematologic Cancers

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel therapeutic options in the treatment of multiple myeloma (MM) and Waldenström's macroglobulinemia (WM) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

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.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Chair, Department of Internal Medicine
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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.

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This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: March 2014
Expiration date: March 2015

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POST-ASH Issue 5, 2014

To go directly to slides and commentary for this issue, **click here**.

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.

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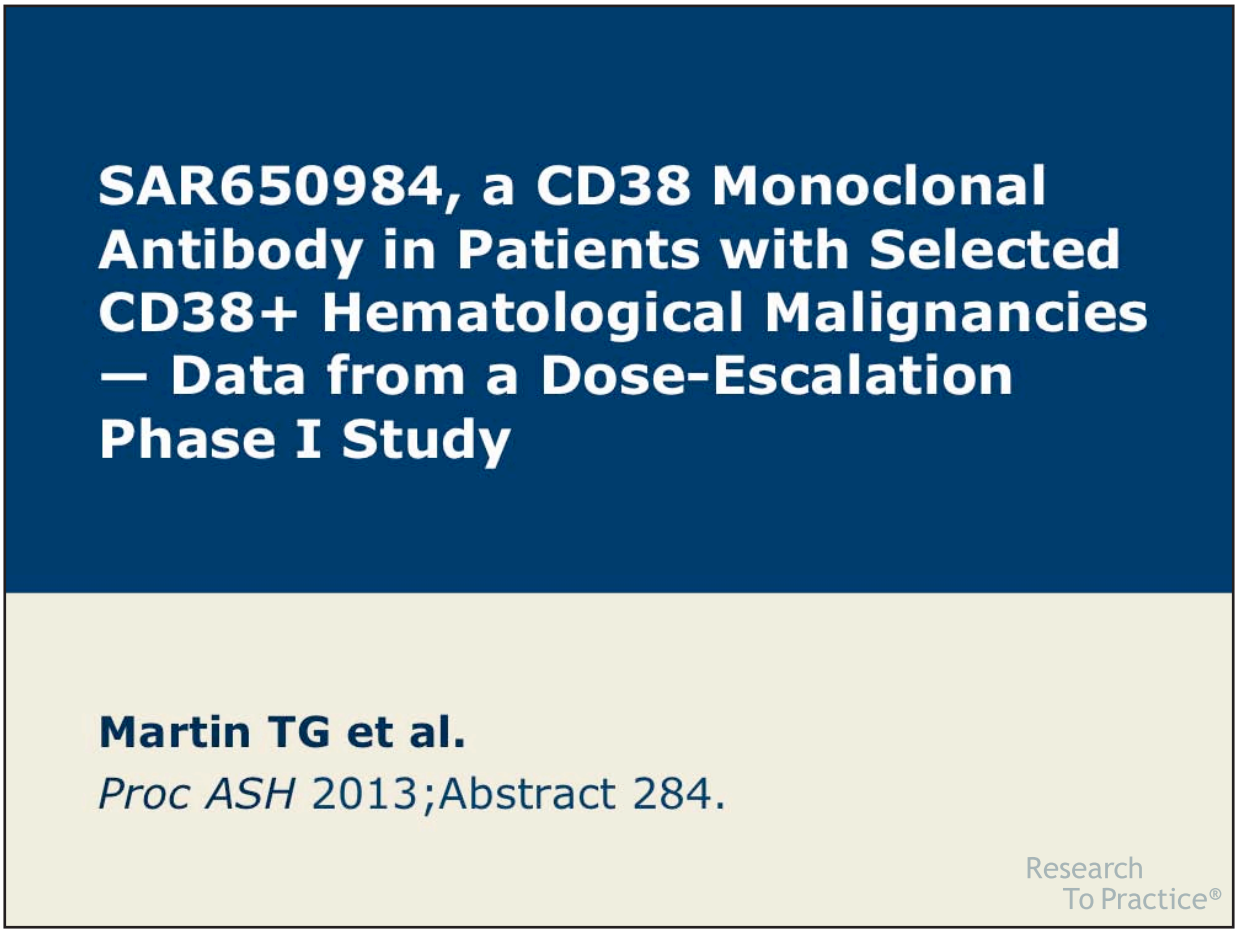
SAR650984, a CD38 Monoclonal Antibody, for Patients with Selected CD38+ Hematologic Cancers

Presentation discussed in this issue

Martin TG et al. **SAR650984, a CD38 monoclonal antibody in patients with selected CD38+ hematological malignancies — Data from a dose-escalation Phase I study.** *Proc ASH* 2013;**Abstract 284**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Rafael Fonseca, MD (2/14/14)



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.

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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)			Basic escalation 3-6 patients/cohort (cohort 6-12)		Expansion cohort
0.0001 mg/kg	q2wk	1 MM	0.3 mg/kg q2wk	5 MM, 1 NHL, 1 CLL	At recommended Phase II dose in patients with MM
0.001 mg/kg	q2wk	1 MM	1 mg/kg q2wk	3 MM	
0.01 mg/kg	q2wk	1 MM	3 mg/kg q2wk	5 MM, 1 CLL	
0.03 mg/kg	q2wk	2 MM	5 mg/kg q2wk	3 MM	
0.1 mg/kg	q2wk	1 NHL	10 mg/kg q2wk	6 MM, 1 NHL	
			10 mg/kg q1wk	2 MM	
			20 mg/kg q2wk	5 MM	

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

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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.

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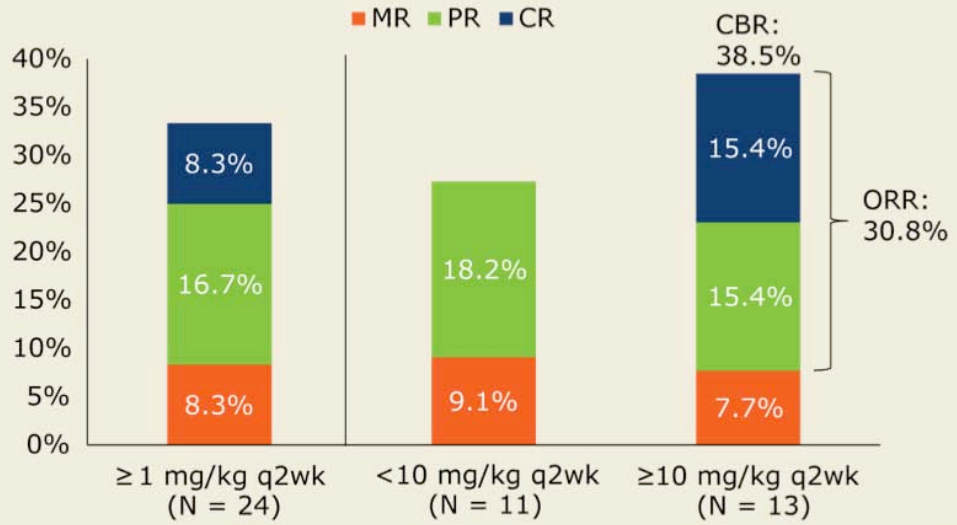
Response to SAR



- 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

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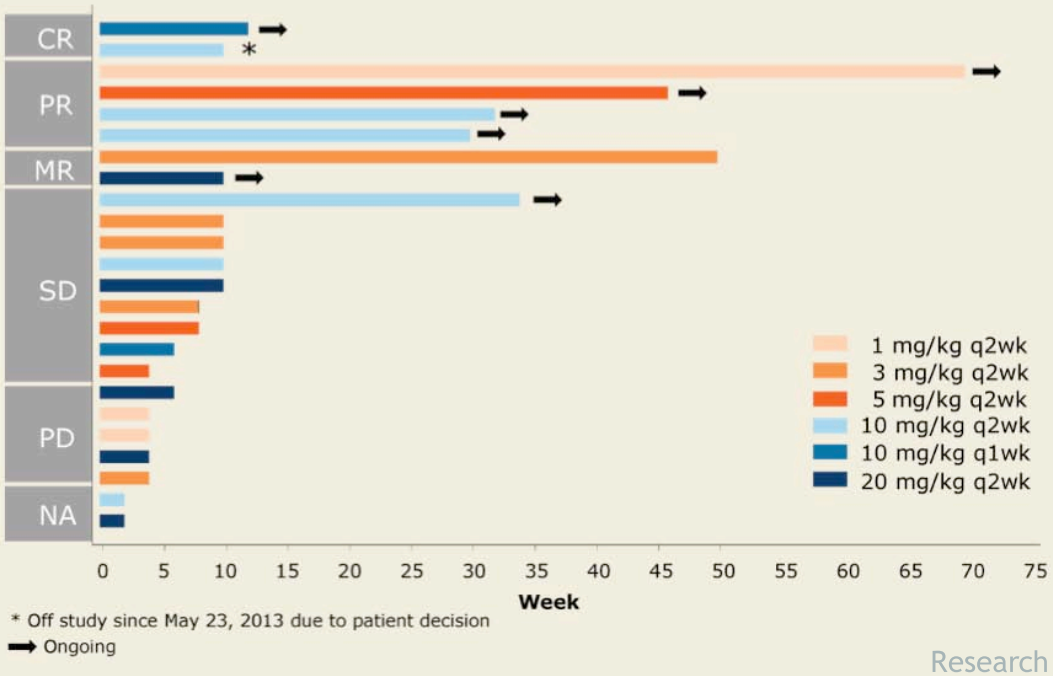
Time on Treatment by Best Response (MM Treated at ≥1 mg/kg)



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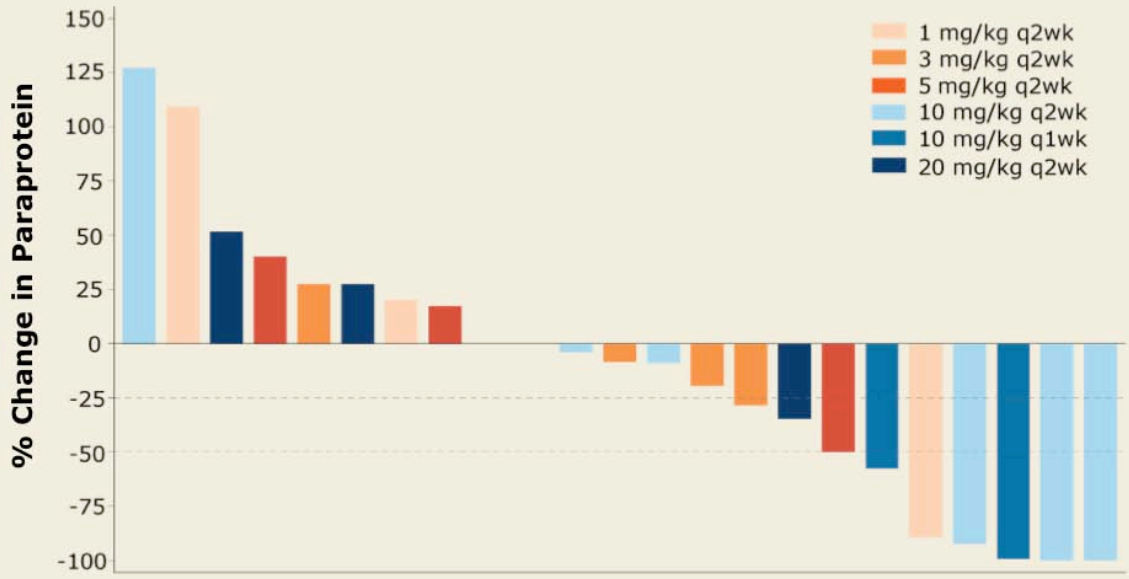
Maximal Change in Paraprotein (MM Treated at ≥1 mg/kg)



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

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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.

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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.

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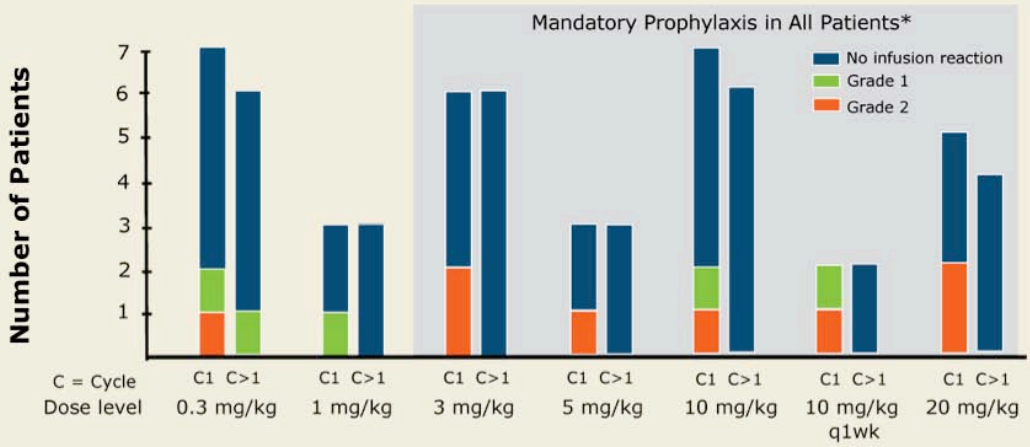
Infusion Reactions (at ≥0.3 mg/kg)



* 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)

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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.

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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