5 Minute JournalClub

POST-ASH Issue 1, 2016

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the effectiveness of investigational immunotherapeutic approaches, including checkpoint inhibitors and CAR T-cell therapy, for patients with relapsed/refractory MM.
- Evaluate the activity and safety of the recently FDA-approved monoclonal antibodies elotuzumab and daratumumab for the treatment of relapsed/refractory MM.
- Investigate the benefits and risks associated with proteasome inhibitors and/or immunomodulatory agents for relapsed/refractory MM.
- Compare the efficacy of the 3-drug regimen of bortezomib, lenalidomide and dexamethasone (RVd) to that of the 2-drug regimen Rd for the front-line treatment of MM.
- Consider the role of autologous stem cell transplant in the treatment of newly diagnosed MM in young patients.
- Assess the safety of pomalidomide and low-dose dexamethasone for patients with relapsed/refractory MM and renal impairment.

CME Information

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

CME Information (Continued)

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Advisory Committee: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Takeda Oncology; *Consulting Agreements:* Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Takeda Oncology; *Contracted Research:* AstraZeneca Pharmaceuticals LP, Lilly.

5 MinuteJournalClub

POST-ASH Issue 1, 2016

Noopur Raje, MD

On October 2 our CME group traveled to New York for the first stop of our annual 4-city "Year in Review" (YiR) tour. To kick off this daylong multitumor meeting and remind those in attendance about just how much is happening in the field, we presented a slide recapping the new agents and indications approved by the FDA in the previous 3 years, with no idea that by the time we headed to Los Angeles just 7 weeks later for the final event in the series, 7 new approvals would be added to the graphic, providing a stunning example of the current unprecedented explosion in oncology research.

While many corners of oncology have seen upheaval as a result of these monumental developments, nowhere has the flurry of regulatory activity been as profound as in multiple myeloma (MM), where over the course of 15 days in November, 3 new agents — ixazomib, daratumumab and elotuzumab — suddenly became available.

This treasure trove of new myeloma riches is only part of the story, because shortly thereafter in December at ASH several landmark Phase III trials were

presented that solidified a new model for up-front treatment of the disease. To try to sort out how all this new information has affected the current myeloma treatment landscape, after the holidays I sat down with Dr Noopur Raje, Harvard/MGH's myeloma director, to chat about what happened at ASH and how she is integrating these revolutionary trial findings and new agents into her practice. Throughout this in-depth interview I wondered to myself whether someday we might look back to the fall of 2015 as the beginning of the end of this devastating disease.

Below find our summary of the major themes that emerged during this riveting conversation and a related slide set reviewing the salient findings from 23 key ASH MM papers.

1. A new model for up-front management

Over the last few years data from a number of seminal studies have helped support the concept of ***continuous*** antimyeloma treatment using a variety of maintenance strategies. At ASH 2015 we saw initial data from several much-anticipated trials that provide further evidence of the importance of ***depth*** of response.

SWOG-S0777: RVd versus Rd for patients with previously untreated MM without an intent for immediate autologous stem cell transplantation (ASCT) (525 patients, abstract 25)

This first randomized Phase III trial comparing these 2 classic regimens demonstrated a progression-free survival (PFS) and overall survival benefit with the triplet (medians: 43 versus 30 months and 75 versus 64 months, both statistically significant with *p*-values of 0.0018 and 0.0250, respectively). In

keeping with the long-term treatment paradigm, all patients received lenalidomide (len)/dexamethasone maintenance until progression.

IFM 2013-04 trial: Bortezomib, thalidomide and dexamethasone (VTD) versus bortezomib, cyclophosphamide and dexamethasone (CyBorD) prior to ASCT for newly diagnosed MM (340 patients, abstract 393)

These findings have not received as much attention as the SWOG trial results, but they may be no less meaningful, because VTD was shown to be significantly superior to CyBorD in terms of the rates of very good partial response or better and partial response or better after only 4 cycles of therapy. Although thalidomide is largely viewed as an inferior immunomodulatory agent (IMiD) compared to len, this is another example of why using a triplet up front is becoming standard of care in patients with newly diagnosed MM.

IFM/DFCI 2009 trial: Immediate or delayed ASCT after RVD induction (700 patients, abstract 391)

The Intergroupe Francophone du Myelome initially launched this ambitious trial in tandem with the Dana-Farber Cancer Institute to discern the necessity of ASCT "in the era of new drugs." This report assessed 700 French and Belgian patients age 65 or younger with previously untreated MM, and although both arms resulted in a high very good partial response rate at the end of the stipulated 12 months of maintenance therapy (88% versus 78%), at a median follow-up of 39 months patients who had undergone immediate transplant and 1 year of maintenance len experienced longer PFS (median 43 months versus 34 months with a hazard rate of 0.69 and a *p*-value of <0.001). Importantly, minimal residual disease (MRD) assessment by next-generation sequencing was feasible for 92% of patients, and MRD negativity was shown to be highly

predictive of PFS. In addition, PET/CT scan normalization after 3 cycles of RVD and before maintenance therapy was shown to be associated with a significant improvement in PFS and was a predictor for improved overall survival.

Dr Raje believes that a proportion of these patients may be cured but that longer follow-up is required to demonstrate this. The now separate and still ongoing DETERMINATION trial (Dana-Farber's portion of the study) has a similar design but continues maintenance len until disease progression, which may result in deeper and more prolonged remissions.

These landmark studies fit very well into what Dr Raje describes as an evolving individualized model focused on achieving MRD negativity. In discussing this concept she noted that even in the nontransplant arm of the IFM study patients who were MRD-negative had long-term outcomes similarly favorable to those for MRD-negative patients who underwent ASCT, and thus in her mind, how one arrives at MRD negativity is not as critical as simply getting there. She is hopeful that in the future patients who require transplant will be identified prospectively along with the specific agents or regimens most likely to achieve this outcome.

In this regard it is important to consider the perspective of investigators like Memorial's Dr Ola Landgren, who believe that indirect trial comparisons suggest that regimens containing carfilzomib are more likely to achieve MRD negativity than those that include bortezomib. For now this issue may be more theoretical than practical because carfilzomib is not approved or commonly used up front, but hopefully the ongoing ECOG/ACRIN-E1A11 trial comparing RVd to KRd (carfilzomib/Rd) will soon answer this critical question.

Interestingly, a downside of carfilzomib that hampers its convenience is its twice-weekly administration. However, that may be changing as data presented at ASH demonstrate good tolerability and efficacy with **weekly administration** of this agent.

During the interview with Dr Raje I challenged the myeloma community's passionate belief that significant PFS and MRD benefits will translate to an overall survival advantage, but she was unhesitating in defending this position, citing the extraordinary improvements that are now being observed from the introduction and widespread use of proteasome inhibitors and IMiDs.

Finally, in reflecting on the madness of the last months of 2015, I recall that when the ASH abstracts were posted during our 4-city YiR tour, several faculty members from the highly respected Mayo Clinic myeloma team who participated in our conferences noted that just reading the preliminary data led them to switch their usual approach for patients at standard risk away from a 2-drug regimen (mainly Rd) to triplet therapy (RVd).

2. More on the newly approved agents

Not surprisingly, a number of ASH data sets focused on trying to understand how the 4 recently approved agents (including panobinostat) may best fit into practice. While it will likely take years to fully sort this out, the availability of these therapies has created a plethora of practical clinical and research questions, which were addressed by Dr Raje.

Ixazomib

At ASH 2014 the results of the landmark ASPIRE trial showed an impressive PFS advantage when carfilzomib was added to Rd in relapsed/refractory disease, and

at ASH 2015 the results of the Phase III Tourmaline-MM1 trial demonstrated that a similar approach with the oral proteasome inhibitor ixazomib also provided a significant PFS benefit in patients with both high-risk and standard-risk cytogenetics. On the basis of these data this drug was approved in combination with Rd for patients whose MM has progressed after at least 1 prior treatment, and that is mainly how Dr Raje currently uses it. However, her eyes and the eyes of all investigators are fixed squarely on a soon-to-be-reported trial in the up-front setting and other maturing studies evaluating long-term maintenance treatment, for which the convenience of this oral therapy could deliver real quality-of-life benefits that result in greater disease control.

Daratumumab

Dr Rafael Fonseca, one of the aforementioned Mayo investigators, recently joked that 38 Special is now the official myeloma rock band, which seems like a bit of a leap for a drug that is currently indicated as monotherapy after 3 prior lines of therapy. However, every investigator I have spoken with, including Dr Raje, believes that the monotherapy, later-line positioning of this agent will be short-lived and that this important CD38-directed monoclonal antibody will become a standard part of earlier combination regimens. At ASH we saw more impressive data that solidify what we know — a 30% response rate as a single agent and 69% 1-year overall survival in very late-line treatment — and provide an indication of what may soon come, namely 70% to 80% overall response rates in combination with len/dexamethasone or pomalidomide/dexamethasone with no additional toxicities.

One issue that may prove to be a bit of a stumbling block for this agent is the need for prolonged infusion time, particularly early on, to mitigate the risk of

acute reactions. Dr Raje believes this problem can be effectively managed but also recognizes that it may create a practical dilemma at locations not adequately staffed to handle the necessary chair times.

Elotuzumab

The third part of the November approval landslide, this SLAMF7-directed immunostimulatory antibody was the subject of several important ASH data sets, including follow-up from the Phase III ELOQUENT-2 trial further demonstrating prolonged PFS (19.4 months versus 14.9 months, $p = 0.0014$) from the very rational combination with Rd. Dr Raje believes "elo/Rd" is a logical choice for patients with lower tumor burden who are len naïve or likely to be len sensitive, and she is interested not only in trials utilizing this agent earlier in the disease but specifically in the intriguing idea of adding elotuzumab to len maintenance. She noted that another 152-patient Phase II randomized trial reported at ASH combined the agent with bortezomib with less impressive results, perhaps due to the lack of the immunologic synergy that occurs with IMiDs.

Panobinostat

This histone deacetylase inhibitor was approved about a year ago in combination with bortezomib and dexamethasone for patients who had received at least 2 prior regimens, but its uptake seems to have been somewhat slow for a variety of reasons, including concerns about toxicity, particularly gastrointestinal problems. At ASH we saw data from 52 patients with the fascinating combination of RVD and this agent, with an excellent overall response rate of 94% and good tolerability. While future research will determine whether a role exists for this regimen, currently Dr Raje and others consider panobinostat/bortezomib an

important option in the common scenario of disease progression occurring on len maintenance.

3. Immunotherapy finally arrives at the myeloma door

One of the most interesting comments Dr Raje made during our interview was her response when asked to identify the biggest myeloma story coming out of ASH this year, and while we have grown accustomed to immunotherapy being cited as the brightest light in almost every corner of oncology, apart from the widespread use of IMiDs there hasn't been much discussion of this approach in myeloma.

That changed in a heartbeat in Orlando with 3 riveting presentations — 2 on the anti-PD-1 antibody pembrolizumab and another on chimeric antigen receptor (CAR) T-cell therapy.

While checkpoint inhibitors haven't been particularly active in limited initial studies of monotherapy, at ASH we saw data on the use of **pembrolizumab combined with IMiDs** (Rd in one study and pomalidomide/dexamethasone in another) for patients who had received these agents previously and whose disease in many cases was resistant. Dr Raje pointed out that the handful of impressive responses observed suggests that checkpoint inhibitors might be able to overcome resistance to IMiDs.

Equally relevant, **another eye-opening presentation** at ASH (abstract LBA-1) demonstrated that CAR T-cell therapy may have legs in myeloma. The therapeutic target is B-cell maturation antigen (BCMA), a TNF-like protein expressed in normal and cancerous plasma cells. In this study of 12 patients with heavily pretreated disease, a single infusion of BCMA-targeted CAR T cells produced a number of impressive responses, with 4 patients achieving partial

response or better and the remaining 8 patients stable disease. Although toxicities — including cytokine response syndrome — were observed, this report is the first solid evidence that CAR-T treatment is effective in myeloma, and these findings were met with great enthusiasm by Dr Raje and every other person who saw the data.

Next on this short series Dr Jeff Sharman shares his perspective on another corner of hemato-oncology that is galloping forward with the goal of long-term disease control or cure — chronic lymphocytic leukemia.

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5 Minute JournalClub

Key Papers in Multiple Myeloma from the December 2015 American Society of Hematology (ASH) 57th Annual Meeting in Orlando, Florida

Editor: Neil Love, MD

Faculty commentator: Noopur Raje, MD

Key Papers in Multiple Myeloma from ASH 2015

IFM/DFCI 2009: Transplant or not? (Abstracts 391, 191, 395)

SWOG-S0777: RVd versus Rd (Abstract 25)

CHAMPION-1: Weekly carfilzomib (Abstract 373)

TOURMALINE-MM1 trial of ixazomib/Rd in relapsed/refractory disease; Ixazomib/Cd as up-front therapy (Abstracts 26, 727)

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BCMA-targeted CAR T cells in relapsed/refractory disease (Late-breaking abstract 1)

Panobinostat/RVD as induction therapy (Abstract 187)

Other relevant abstracts

5 Minute JournalClub

IFM/DFCI 2009 Trial: Autologous Stem Cell Transplantation (ASCT) for Multiple Myeloma (MM) in the Era of New Drugs

- Phase III study of lenalidomide/bortezomib/dexamethasone (RVD), with and without ASCT, followed by 1 year of maintenance lenalidomide
- N = 700 patients with previously untreated MM, age ≤65 years
- **Primary study endpoint:** Progression-free survival (PFS)

Survival	RVD (n = 350)	RVD + ASCT (n = 350)	Hazard ratio, *p*-value
Median PFS	34 mo	43 mo	0.69,<0.001
PFS rate (4 y)	35%	47%	

Attal M et al. *Proc ASH* 2015;Abstract 391.

IFM/DFCI 2009: Conclusions

- For patients with newly diagnosed MM, the addition of ASCT to RVD is associated with a 31% reduced risk of progression or death ($p < 0.001$):
  - Improved time to disease progression ($p < 0.001$) and rate of minimal residual disease (MRD) negativity (80% vs 65%, $p < 0.001$)
- ASCT should remain a standard procedure for young patients with de novo myeloma.
- Further follow-up is needed to make any conclusions about overall survival (OS) as the number of deaths is still low in both arms.
- An ongoing parallel trial in the United States (NCT01208662) uses a similar design but, importantly, administers lenalidomide maintenance continuously until progression in both study arms.

Attal M et al. *Proc ASH* 2015;Abstract 391.

Predictive Value of MRD by Next-Generation Sequencing (NGS) in the IFM/DFCI 2009 Trial

- Bone marrow MRD evaluation before and after maintenance therapy in patients with very good partial response (VGPR) or better
- MRD assessment by flow cytometry (FCM) and NGS
- Prediction of PFS by MRD status as determined by NGS
- **Comparison of MRD sensitivity of NGS and FCM**
  - Sensitivity: FCM = 10^{-4}; NGS = 10^{-6}
  - Of 163 patients MRD-negative by FCM, 84 (51%) were positive by NGS

	Three-year PFS for patients achieving complete response	
	MRD-negative by NGS ($<10^{-6}$)	MRD-positive by NGS ($\geq 10^{-6}$)
Before maintenance	87%	63%
After maintenance	92%	64%

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 191.

Predictive Value of MRD in IFM/ DFCI 2009: Conclusions

- Evaluation of MRD by NGS is feasible in 92% of patients and is highly sensitive ($<10^{-6}$)
  - This sensitivity is achieved in 100% of patients
- MRD negativity at 10^{-6} sensitivity is strongly predictive of PFS at 3 years.
- 13 of 26 patients with t(4;14) and none of 16 patients with del(17p) achieved MRD negativity.
- MRD evaluation may identify patients with MM who are cured. This warrants further evaluation in clinical trials.

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 191.

IMAJEM Study: Evaluation of MRI and PET-CT in Patients with MM in the IFM/DFCI 2009 Trial

- Comparison of whole-body PET-CT to MRI of the spine and pelvis among 134 patients at diagnosis, after 3 cycles of RVD and before maintenance therapy

	Correlation with PFS (*p*-value)	Correlation with OS (*p*-value)
MRI normalization		
After RVD (3 cycles)	0.29	0.61
Before maintenance	0.30	0.30
PET-CT normalization		
After RVD (3 cycles)	0.04	0.12
Before maintenance	<0.001	0.003

Moreau P et al. *Proc ASH* 2015;Abstract 395.

IMAJEM: Conclusions

- The 2 modalities are equally effective in detecting bone involvement at diagnosis (MRI: 94.7%; PET-CT: 91%).
- Normalization of MRI after 3 cycles of RVD and before maintenance therapy has no prognostic value for PFS or OS.
- PET-CT normalization after 3 cycles of RVD and before maintenance therapy is associated with a significant improvement in PFS.
- Normalization of PET-CT before maintenance was a predictor for improved OS.
- PET-CT should be incorporated in the follow-up of young patients receiving novel agent-based therapy, to predict outcome.

Moreau P et al. *Proc ASH* 2015;Abstract 395.

Investigator Commentary: FM/DFCI 2009 Trial of RVD with or without ASCT for MM

All 3 presentations were based on the IFM trial comparing ASCT to continued RVD treatment. Dr Attal presented the interim analysis with 700 patients, which showed a PFS benefit with transplant (median 43 mo vs 34 mo), but the rate of VGPR or better at the end of the designated 12-month maintenance therapy was high in both arms (88% and 78%).

MRD testing by NGS was performed for 41% of patients (n = 289) at the initiation and the end of maintenance, and those data were presented by Dr Avet-Loiseau. MRD negativity by NGS was highly predictive of PFS, and testing was feasible for 92% of patients: With MRD negativity achieved, a portion of patients may be cured, but longer follow-up is required to demonstrate this. The DETERMINATION trial is using lenalidomide maintenance until disease progression, which may contribute to deepening remissions and increased MRD negativity.

In an imaging trial with 134 of the 700 patients, 95% and 91% had positive MRIs or PET CT scans, suggesting high sensitivity for detecting bone disease. MRI did not change before maintenance therapy for 83%, but PET CT was normalized for 79% and correlated well with PFS, which suggests its value as a predictive tool in subsets of patients.

Interview with Noopur Raje, MD, February 10, 2016

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SWOG-S0777 Trial: Bortezomib/Lenalidomide/ Dexamethasone (RVd) for Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant

- Phase III study of RVd versus lenalidomide/dexamethasone (Rd)
- N = 525 patients with previously untreated multiple myeloma
- **Primary study endpoint:** Progression-free survival (PFS)

Efficacy	RVd	Rd	HR	*p*-value
Median PFS	43 mo	30 mo	0.712	0.0018
Median overall survival	75 mo	64 mo	0.709	0.0250
Overall response rate	81.5%	71.5%	—	—

HR = hazard ratio

Durie B et al. *Proc ASH* 2015;Abstract 25.

SWOG-S0777: Conclusions

- RVd with continuous Rd maintenance significantly improves PFS and overall survival versus Rd alone with ongoing maintenance.
- Both regimens are safe, but RVd is associated with significantly more Grade 3 pain (12% vs 4%), sensory neuropathy (23% vs 3%) and gastrointestinal adverse events (22% vs 8%) than Rd.
- RVd induction followed by continuous Rd is a potential new standard therapy.

Durie B et al. *Proc ASH* 2015;Abstract 25.

Investigator Commentary: Phase III SWOG-S0777 Study of RVd versus Rd for Untreated Multiple Myeloma

This is the first randomized trial in the up-front setting comparing 2 drugs to 3 drugs. The randomization assigned 525 patients to receive RVd or Rd. Patients were stratified based on ISS stage and intent to transplant at disease progression. All patients received Rd maintenance therapy. This study showed both a PFS and an overall survival benefit favoring the triplet combination, with the medians being 43 versus 30 months and 75 versus 64 months, respectively. The toxicity was worse with RVd mainly because of neuropathy and gastrointestinal toxicity. However, at the time this trial was designed, bortezomib was administered intravenously on a twice-weekly schedule.

Given the survival advantage of the triplet combination, this data set has once again proved that patients should be offered combination strategies. An ongoing trial (NCT01863550) is evaluating the combination of CRd (carfilzomib/lenalidomide/dexamethasone) versus RVd to determine which triplet combination is superior.

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CHAMPION-1 Trial: Weekly Carfilzomib with Dexamethasone for Relapsed/ Refractory (R/R) Multiple Myeloma (MM)

- Phase I/II study of weekly carfilzomib/dexamethasone
  - Carfilzomib d1, 8, 15 q28d; on d1 of cycle 1 only, 20 mg/m^2
- N = 104 patients with R/R MM and 1 to 3 prior lines of therapy
- **Primary endpoints:** Maximum tolerated dose (MTD), objective response rate

Carfilzomib at MTD of 70 mg/m^2	
Objective response rate	77%
Stringent complete response rate	5%
Complete response rate	13%
Very good partial response rate	30%

Berenson J et al. *Proc ASH* 2015;Abstract 373.

CHAMPION-1: Conclusions

- Once-weekly 70 mg/m^2 carfilzomib with dexamethasone demonstrated promising efficacy and acceptable safety and tolerability for patients with R/R MM.
- Rates of Grade ≥3 adverse events and therapy discontinuation are similar to or lower than with twice-weekly dosing.
- Phase III ARROW superiority study in R/R MM is comparing the approved twice-weekly carfilzomib dose schedule to the once-weekly schedule from CHAMPION-1.

Berenson J et al. *Proc ASH* 2015;Abstract 373.

Investigator Commentary: Phase I/II CHAMPION-1 Study of Weekly Carfilzomib/Dexamethasone for R/R MM

The CHAMPION-1 study evaluated the safety and efficacy of weekly carfilzomib with dexamethasone in patients with R/R MM. The MTD was 70 mg/m^2, and data on 104 patients were presented. Of those patients, 84% had been exposed to prior bortezomib with 52% being considered refractory. The median duration of response was 16.3 months with an objective response rate of 77%. Five deaths occurred on study, of which 1 was MM related — others were attributable to renal and cardiopulmonary conditions.

The weekly dosing is much more convenient than the twice-weekly schedule, and as long as toxicities can be managed well, this should be the preferred way of administering carfilzomib.

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All-Oral Ixazomib-Based Induction Regimen for Transplant-Ineligible Newly Diagnosed Multiple Myeloma (MM)

- Phase II study of ixazomib with 2 different doses of cyclophosphamide (300 mg/m^2 and 400 mg/m^2) and low-dose dexamethasone (ICd) followed by maintenance ixazomib
- N = 70 patients with previously untreated, symptomatic MM ineligible for stem cell transplant
- **Primary study endpoint:** Complete response (CR) + very good partial response (VGPR)

	ICd-300 (n = 32)	ICd-400 (n = 34)	Overall (n = 66)
CR + VGPR	28%	21%	26%
Overall response rate	78%	65%	71%
12-month PFS rate	68%	91%	80%

PFS = progression-free survival

Dimopoulos MA et al. *Proc ASH* 2015;Abstract 26.

Conclusions

- ICd is an all-oral proteasome inhibitor-based combination active as front-line therapy for elderly patients with MM who are not candidates for more intensive treatments.
- Toxicities were manageable and in line with prior ixazomib studies:
  - Most common Grade ≥3 adverse events included neutropenia (14% and 35%), anemia (11% and 15%) and pneumonia (8% and 9%).
- The indicated dose of cyclophosphamide in this combination is 300 mg/m^2, as higher toxicity was associated with the 400 mg/m^2 dose.
- At this early phase, a significant number of patients achieved VGPR with continuous induction and maintenance therapy, suggesting that response rates may improve over time.

Dimopoulos MA et al. *Proc ASH* 2015;Abstract 26.

Tourmaline-MM1 Trial: Ixazomib with Lenalidomide/Dexamethasone (IRd) for Relapsed/Refractory (R/R) MM

- Phase III study: IRd versus placebo/Rd
- N = 722 patients with R/R MM
- **Primary endpoint:** PFS

PFS (months)	IRd (n = 360)	Rd (n = 362)	HR (*p*-value)
Median PFS	20.6	14.7	0.74 (0.012)
High-risk cytogenetics	21.4	9.7	0.543 (NR)
Standard-risk cytogenetics	20.6	15.6	0.640 (<0.05)

HR = hazard ratio; NR = Not reported

Moreau P et al. *Proc ASH* 2015;Abstract 727.

Tourmaline-MM1: Conclusions

- IRd significantly extends PFS in R/R MM:
  - Median PFS = 20.6 mo versus 14.7 mo with Rd
  - Significant improvement in time to disease progression and overall response rate
  - PFS benefit similar for all prespecified patient subgroups examined, including patients with standard- and high-risk cytogenetics
- Safety profile with IRd is tolerable with no substantial increase in toxicity compared to that with Rd.
- IRd may become the new standard therapy for patients with R/R MM.

Moreau P et al. *Proc ASH* 2015;Abstract 727.

Investigator Commentary: Phase III Tourmaline-MM1 Study of IRd for R/R MM

The Tourmaline-MM 1 study was a large randomized trial comparing the triplet IRd to Rd for 722 patients with MM who had received 1 to 3 lines of prior therapy. These patients' disease was required to be proteasome inhibitor and lenalidomide sensitive. The addition of ixazomib resulted in a significant improvement in PFS (20.6 months versus 14.7 months). The regimen was well tolerated with excellent quality of life for patients — it was difficult to discern the difference between placebo and ixazomib in terms of side-effect profile.

This regimen therefore provides an excellent combination strategy for patients with relapsed disease. It will also be considered in the future as a maintenance option because of its tolerability.

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- **Three-year update of ELOQUENT-2 trial of elotuzumab/Rd; Two-year update of elotuzumab/Vd (Abstracts 28, 510)**
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- Other relevant abstracts

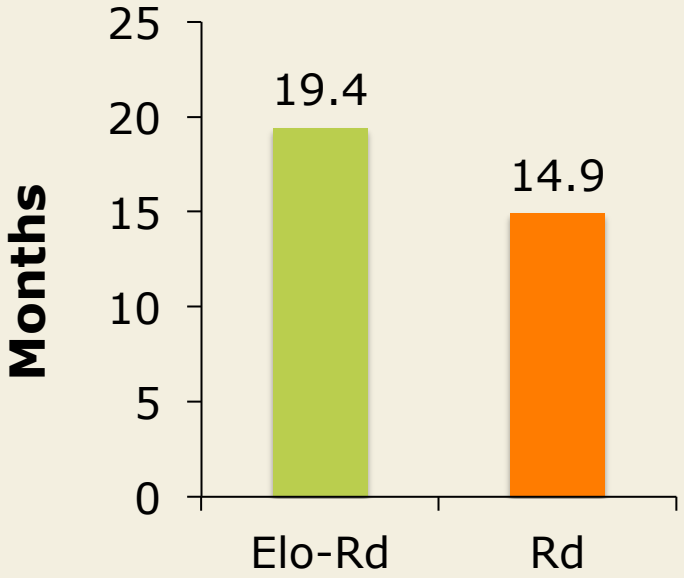
5 Minute JournalClub

ELOQUENT-2 Trial: Three-Year Update

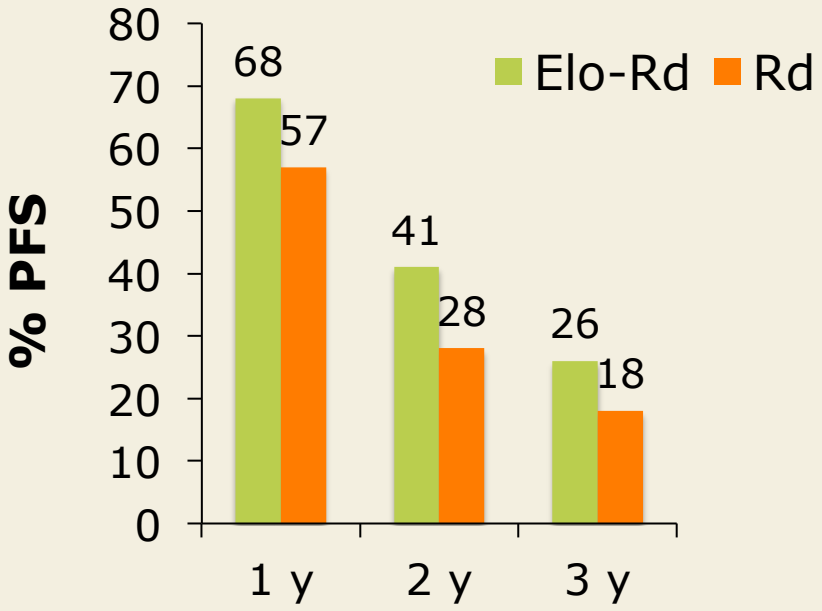
- Phase III trial of elotuzumab and lenalidomide/dexamethasone (Elo-Rd) versus Rd alone
- N = 646 patients with relapsed/refractory (R/R) multiple myeloma (MM)
- **Primary endpoints:** Progression-free survival (PFS) and overall response rate (ORR)

Median PFS

Hazard ratio (HR) = 0.73, p = 0.0014



PFS rate



Dimopoulos MA et al. *Proc ASH* 2015;Abstract 28.

ELOQUENT-2: Conclusions

- After 3 years of follow-up, the addition of Elo to Rd had demonstrated an effective and durable benefit in R/R MM:
  - 27% reduction in risk of disease progression or death in comparison to Rd alone
  - ORR: 79% vs 66%
- Interim overall survival (OS) analysis demonstrated a trend in favor of Elo-Rd:
  - 43.7 vs 39.6 months (HR = 0.77, p = 0.0257)
- Elo-Rd toxicity profile was consistent with prior findings, with minimal incremental toxicities associated with the addition of Elo.

Dimopoulos MA et al. *Proc ASH* 2015;Abstract 28.

Two-Year Update: Bortezomib/ Dexamethasone with Elo in R/R MM

- Phase II randomized trial of bortezomib/dexamethasone (Vd) with or without Elo
- N = 152 patients with R/R MM and 1 to 3 prior therapies
- **Primary endpoint:** PFS

Clinical variable	Elo-Vd (n = 77)	Vd (n = 75)	HR
Median PFS	9.7 mo	6.9 mo	0.76
Two-year PFS rate	18%	11%	
Median OS	NE	34.7 mo	0.75

NE = not estimable

Palumbo A et al. *Proc ASH* 2015;Abstract 510.

Conclusions

- This first randomized controlled trial of Elo combined with a proteasome inhibitor demonstrated that after 2 years of follow-up, Elo-Vd continues to show durable efficacy versus Vd alone:
  - 24% reduction in risk of disease progression/death
- The OS analysis demonstrated a trend in favor of Elo-Vd.
- The safety profile of Elo-Vd is comparable to that of Vd alone, and no new safety signals were identified with longer follow-up.

Palumbo A et al. *Proc ASH* 2015;Abstract 510.

Investigator Commentary: Elo in Combination with Rd or Bortezomib/Dexamethasone for R/R MM

Elo has no single-agent activity. Updated data with Elo in combination with Rd (n = 646) and with bortezomib/dexamethasone (n = 152) were presented at ASH. Although PFS was improved with Elo in both studies, the magnitude of improvement was greater with Rd: The 2-year PFS rate was 41% versus 27%, which was sustained at 3 years of follow-up. Elo was well tolerated aside from some infusion-related reactions.

In view of the fact that this agent works via an NK cell-mediated mechanism, it is no surprise that it works better with an IMiD. Its exact place in the treatment of MM needs to be further delineated, but it should be considered when Rd is being considered as treatment for a patient.

Elo-Rd takes time to work but provides durable responses, so using it in a patient with low tumor burden whose disease is lenalidomide naïve or lenalidomide sensitive is reasonable. Moving forward, perhaps Elo-Rd will be used earlier in the course of the disease or in the maintenance setting.

Interview with Noopur Raje, MD, February 10, 2016

Key Papers in Multiple Myeloma from ASH 2015

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BCMA-targeted CAR T cells in relapsed/refractory disease (Late-breaking abstract 1)

Panobinostat/RVD as induction therapy (Abstract 187)

Other relevant abstracts

5 Minute JournalClub

Daratumumab (Dara) Monotherapy for Heavily Pretreated Relapsed/Refractory (R/R) Multiple Myeloma (MM)

- Combined analysis of 2 Phase II trials of 16 mg/kg dara for R/R MM:
  - MMY2002 (Sirius): N = 106 patients with ≥3 prior therapies including a proteasome inhibitor, an immunomodulatory drug (IMiD) or both
  - GEN501: N = 42 patients who experienced relapse after or whose MM was refractory to ≥2 prior therapies

Combined analysis	MMY2002 (n = 106)	GEN501 part 2 (n = 42)	Total (n = 148)
Overall response rate (ORR)	29.2%	35.7%	31.1%
Overall survival (OS) rate (1 year)	65%	77%	69%

Usmani S et al. *Proc ASH* 2015;Abstract 29.

Conclusions

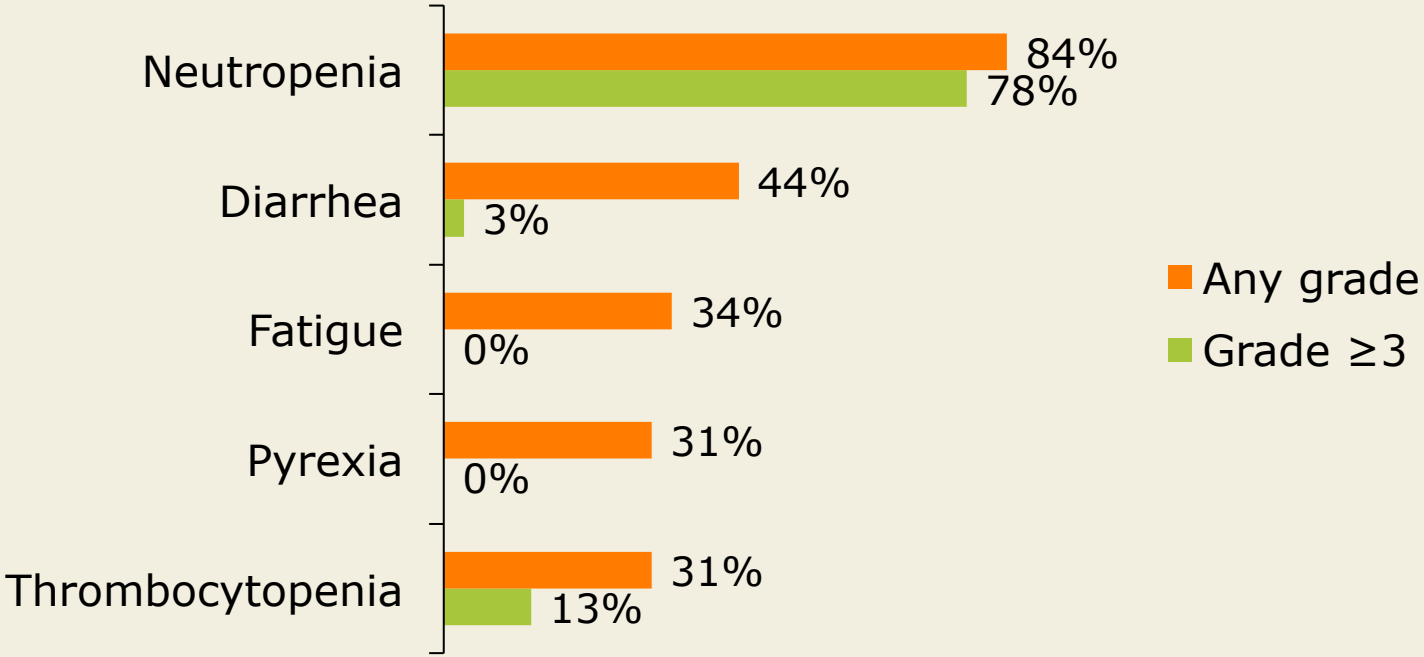
- Single-agent dara induced rapid, deep and durable responses in patients with heavily pretreated, highly refractory MM.
- Remarkable depth of response was observed in patients with MM refractory to newer agents, including pomalidomide (pom) and carfilzomib.
- Dara conferred an OS benefit even for patients with stable disease or minimum response:
  - Studies are ongoing to further examine this finding.
- Updated analysis of the combined data set from the GEN501 and MMY2002 studies did not identify any new safety signals.

Usmani S et al. *Proc ASH* 2015;Abstract 29.

GEN503 Trial: Dara with Lenalidomide (Len)/Dexamethasone (Dex) for R/R MM

- Phase I/II study comprising dose escalation (n = 13) and expansion cohorts (n = 32)
- **Primary study endpoint:** Incidence of adverse events (AEs) in the expansion cohort

Select treatment-emergent AEs (n = 32)



Plesner T et al. *Proc ASH* 2015;Abstract 507.

GEN503: Conclusions

- Dara can be combined with len/dex with no additional safety signals.
- Dara + len/dex induced rapid, deep and durable responses:
  - ORR = 81%, including 28% very good partial response (VGPR) and 34% complete response/stringent complete response at 15.6 months median follow-up
  - Median time to first response was 1 month
  - 18-month progression-free survival (PFS) rate = 72%
  - 18-month OS rate = 90%
- Randomized Phase III studies of dara are ongoing:
  - POLLUX: Dara with or without len/dex in R/R MM
  - MAIA: Dara with or without len/dex in newly diagnosed MM

Plesner T et al. *Proc ASH* 2015;Abstract 507.

MMY1001 Trial: Dara with Pom/Dex for R/R MM

- Phase Ib study of dara in combination with pom/dex
- N = 98 patients with ≥2 lines of prior therapy and refractory or R/R MM

	Dara + pom/dex (n = 75)
ORR	71%
ORR, double-refractory MM	67%
Six-month PFS rate	66%

Chari A et al. *Proc ASH* 2015;Abstract 508.

MMY1001: Conclusions

- Dara with pom/dex induced rapid, deep and durable responses in a population of patients with heavily pretreated MM:
  - Median of 4 prior lines of therapy
  - 67% refractory to both a proteasome inhibitor and an IMiD
  - ORR = 71%, including 43% VGPR or better and 5% stringent complete response
- No additional safety signals were observed:
  - 45/98 (46%) of patients required GCSF and 24/98 (25%) required blood transfusions during treatment.
  - Infusion-related reactions were predominantly Grade ≤2 and were managed with premedication and reduced infusion rates.
- These data support a Phase III study evaluating this novel combination.

Chari A et al. *Proc ASH* 2015;Abstract 508.

Investigator Commentary: Dara Alone or in Combination with Len/Dex or Pom/Dex for R/R MM

Updated data were presented on the efficacy of dara either alone or in combination with len or pom. As a single agent in a multiple-refractory patient population, dara shows a response rate of 31%, and patients maintain their responses for a median duration of 7.6 months.

Infusion-related reactions occur in about 50% of patients, usually in the first 1 to 3 cycles. Reactions can usually be tempered by slowing the infusion rate and administering steroids. One of the biggest challenges is planning for a long day of dara infusion, especially for the first few doses.

When dara was combined with either len or pom, response rates for patients with R/R MM were 70% to 80%. In the future dara will likely be considered as a backbone drug and will be combined with our existing IMiDs and proteasome inhibitors.

Interview with Noopur Raje, MD, February 10, 2016

Key Papers in Multiple Myeloma from ASH 2015

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5 Minute JournalClub

KEYNOTE-023 Trial: Pembrolizumab in Relapsed/Refractory (R/R) Multiple Myeloma (MM)

- Open-label, Phase I, multicenter, nonrandomized, dose-escalation study of pembrolizumab with lenalidomide/dexamethasone
- N = 34 patients with R/R MM after failure of ≥2 prior therapies including a proteasome inhibitor and an immunomodulatory drug (IMiD)
- **Primary endpoints:** Safety and antitumor activity
- Maximum tolerated dose: Pembrolizumab 200 mg, lenalidomide 25 mg, dexamethasone 40 mg
- Objective response rate (ORR):
  - All evaluable patients: 13/17 (76%)
  - Lenalidomide-refractory disease: 5/9 (56%)
- No death or treatment discontinuation for toxicity
- Few, low-grade immune-related adverse events
- No infusion-related reactions

San Miguel J et al. *Proc ASH* 2015;Abstract 505.

GCC1454 Trial: Pembrolizumab in R/R MM

- Phase II study of pembrolizumab with pomalidomide/ dexamethasone
- N = 33 patients with R/R MM after failure of 2 prior therapies including a proteasome inhibitor and an IMiD
- **Key endpoints:** Safety and response

	All N = 27	**Double refractory N = 20**	**High-risk cytogenetics N = 12**
ORR (PR or better), %			
sCR	1	0	0
CR	0	0	0
VGPR	4	2	1
PR	11	9	5
	60%	**55%**	**50%**
Stable disease	8 (30%)	6 (30%)	5 (42%)
Progressive disease	3 (10%)	3 (15%)	1 (8%)

sCR = stringent complete response; CR = complete response

Badros AZ et al. *Proc ASH* 2015;Abstract 506.

GCC1454: Conclusions

- Pembrolizumab with pomalidomide/dexamethasone demonstrated a predictable and manageable side-effect profile:
  - No infusion-related reactions
  - Few immune-related adverse events, including hypothyroidism, transaminitis and pneumonitis
  - 5 patients with pomalidomide dose reductions due to rash, neutropenia, palpitations and fatigue
- This regimen shows promising antimyeloma activity (ORR: 60%).
- Under investigation:
  - Role of PD-L1 as a biomarker (FISH, IHC, sequencing)
  - Defining functional (myeloma specific) T-cell subsets

Badros AZ et al. *Proc ASH* 2015;Abstract 506.

Investigator Commentary: Pembrolizumab in Combination with Lenalidomide/Dexamethasone or Pomalidomide/ Dexamethasone for R/R MM

These 2 abstracts were our first experience with checkpoint blockade in MM. Pembrolizumab is a PD-1 antibody, and when combined with lenalidomide/dexamethasone or pomalidomide/dexamethasone it improved response rates, even for patients with MM refractory to these agents alone.

Although the data are preliminary, it is encouraging to discover that checkpoint inhibition can result in overcoming de novo IMiD resistance. In the study presented by Jesus San Miguel, for example, many of these patients had MM that was refractory to lenalidomide, but when they were exposed to pembrolizumab their sensitivity to lenalidomide was restored with an efficacy of almost 60%. The story was the same with the combination of pembrolizumab and pomalidomide/dexamethasone. This is quite remarkable. The fact that resistance to these IMiDs can be overcome is, in my mind, most exciting.

Interview with Noopur Raje, MD, February 10, 2016

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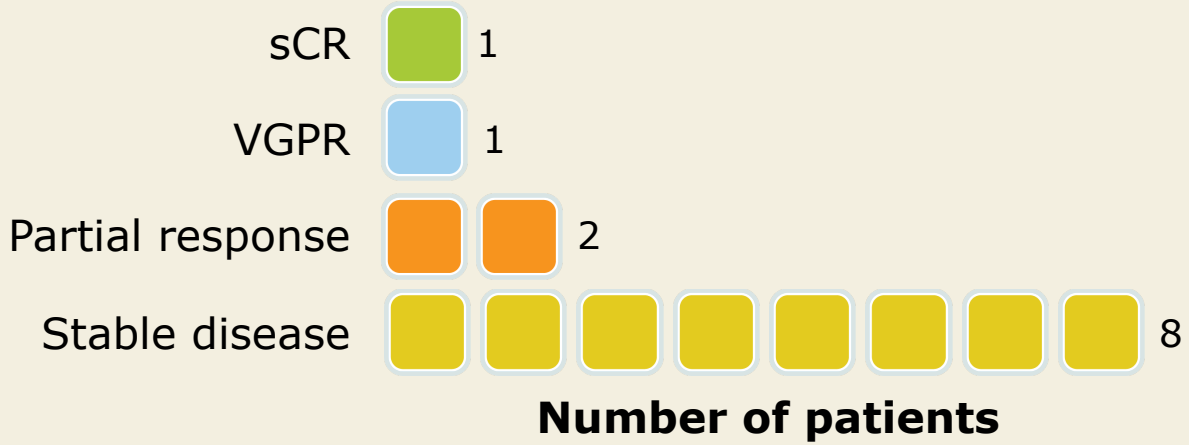
Other relevant abstracts

5 Minute JournalClub

B-Cell Maturation Antigen (BCMA)-Targeted Chimeric Antigen Receptor (CAR) T Cells in Advanced Multiple Myeloma (MM)

- First-in-human Phase I study
- N = 12 patients with advanced relapsed/refractory MM, ≥3 prior lines of therapy and uniform BCMA expression on MM cells
- Single infusion of anti-BCMA CAR (CAR-BCMA) T cells after a 3-day regimen of cyclophosphamide/fludarabine

Response to CAR-BCMA T-cell therapy



sCR = stringent complete response; VGPR = very good partial response

Ali SA et al. *Proc ASH* 2015;Abstract LBA1.

Conclusions

- This study demonstrates for the first time that CAR T cells can have powerful activity against measurable MM.
- CAR-BCMA T cells eliminated plasma cells and, importantly, did not cause direct damage to essential organs.
- Responses included ongoing sCR in one patient with a high burden of chemotherapy-resistant MM.
- Significant antimyeloma responses were associated with the highest levels of CAR-BCMA T cells in the blood.
- Toxicity was substantial but reversible.
- CAR-BCMA T cells are a promising therapy for MM.

Ali SA et al. *Proc ASH* 2015;Abstract LBA1.

Investigator Commentary: BCMA-Targeted CAR T Cells in Advanced MM

This late-breaking abstract was the first report of CAR T-cell therapy directed against BCMA, a protein expressed on all plasma cells. Data were presented on 12 patients whose MM was heavily pretreated with a median of 7 prior lines of therapy. At the highest dose level tested, complete responses and VGPRs were noted. These are exciting data on cellular immunotherapy. Obviously, one must consider cytokine response syndrome, a toxicity that can now be appropriately treated with antibodies such as tocilizumab.

Such a strategy holds much promise for long-term disease control in MM.

Interview with Noopur Raje, MD, February 10, 2016

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IFM/DFCI 2009: Transplant or not? (Abstracts 391, 191, 395)

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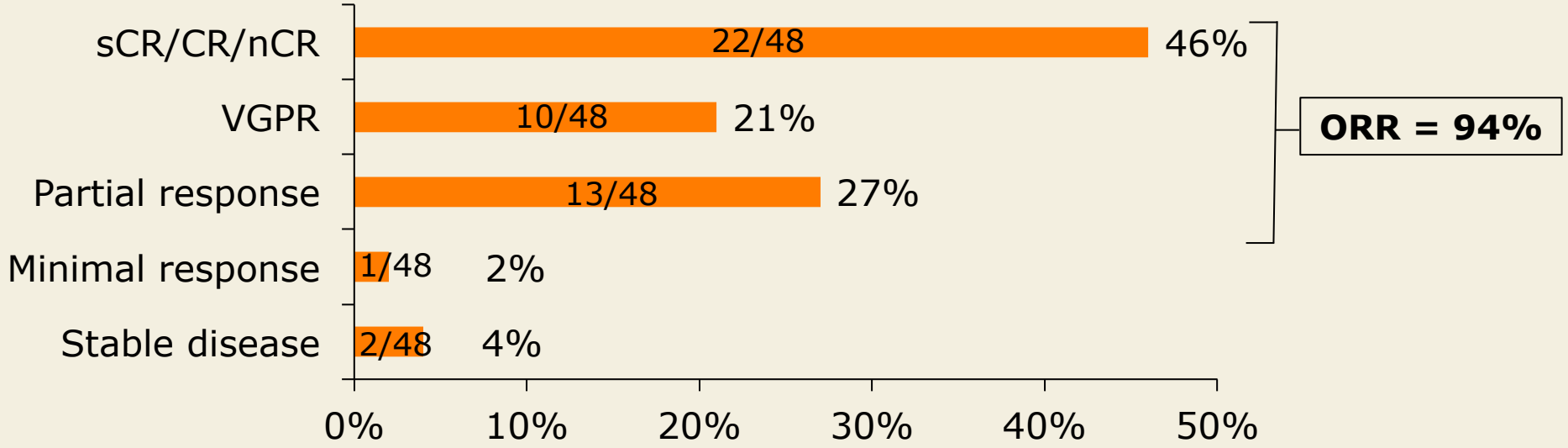
Other relevant abstracts

5 Minute JournalClub

Panobinostat with Lenalidomide/ Bortezomib/Dexamethasone (RVD) for Transplant-Eligible Patients with Newly Diagnosed Multiple Myeloma (NDMM)

- Phase I/II trial evaluating the addition of panobinostat to RVD induction therapy followed by maintenance lenalidomide/dexamethasone + panobinostat or autologous stem cell transplant
- N = 52 patients with NDMM
- **Objectives:** Safety and efficacy

Response after 1 to 4 cycles (N = 48)



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

Shah JJ et al. *Proc ASH* 2015;Abstract 187.

Select Adverse Events (AEs)

Hematologic AEs (n = 50)	Any grade	Grade ≥3
Thrombocytopenia	76%	36%
Anemia	76%	10%
Leukopenia	60%	8%
Neutropenia	44%	14%

Select nonhematologic AEs (n = 50)	Any grade	Grade ≥3
Nausea	66%	6%
Constipation	60%	4%
Diarrhea	58%	8%
Vomiting	28%	2%
Peripheral sensory neuropathy	56%	4%

Shah JJ et al. *Proc ASH* 2015;Abstract 187.

Conclusions

- Panobinostat 10 mg can safely be combined with full-dose RVD in NDMM:
  - No unexpected toxicity was reported with the combination.
  - Grade 3 and 4 AEs were limited and transient.
- The combination led to rapid disease control with a high response rate after 1 to 4 cycles of therapy (ORR = 94%) and significant depth of response (sCR/CR/nCR = 46%).
- Maintenance therapy with panobinostat/lenalidomide/dexamethasone is safe, and long-term administration is feasible.
- Panobinostat had no effect on stem cell mobilization/collection or quality of graft.

Shah JJ et al. *Proc ASH* 2015;Abstract 187.

Investigator Commentary: Panobinostat with RVD Induction Before Stem Cell Transplant

The combination of panobinostat with RVD has demonstrated remarkable responses. It becomes difficult to understand the data because RVD itself produces high response rates — it's unclear how much panobinostat is adding. Longer-term follow-up will be useful in helping to determine whether adding panobinostat is the best approach or if something different should be added.

Panobinostat faces a challenge in the way it's approved, in combination with bortezomib, because this combination does have increased toxicity. The PANORAMA studies, however, used twice-weekly bortezomib, administered intravenously. Weekly subcutaneous bortezomib may be better tolerated with panobinostat. Additionally, panobinostat in combination with the immunomodulatory drugs (IMiDs) may have a more favorable toxicity profile, but we need to see mature data.

Off trial, if I had a patient who received RVD, underwent a transplant, received maintenance lenalidomide for 18 months and then experienced progression with significant bone disease, I would like to change from an IMiD to a proteasome inhibitor. In this situation, bortezomib with panobinostat would be a perfectly reasonable approach.

Interview with Noopur Raje, MD, February 17, 2016

Other Relevant Abstracts

IFM 2013-04: VTD versus VCD in newly diagnosed multiple myeloma (Abstract 393)

- Subset analyses of special patient populations in the FIRST, ASPIRE and MM-013 trials (Abstracts 730, 731, 374)
- Novel treatment approaches for relapsed disease (Abstracts 394, 378)
- Doxycycline for patients with advanced cardiac amyloidosis (Abstract 732)

IFM 2013-04 Trial: Bortezomib/Thalidomide/Dexamethasone (VTD) Is Superior to Bortezomib/Cyclophosphamide/ Dexamethasone (VCD) Before Autologous Stem Cell Transplant (ASCT) for Newly Diagnosed Multiple Myeloma (MM)

- First Phase III prospective study of VTD versus VCD
- N = 340 patients age ≤65 years with untreated, symptomatic MM
- **Primary endpoint:** Very good partial response (VGPR) after 4 cycles

Response after 4 cycles (ITT population)	VTD (n = 169)	VCD (n =169)	*p*-value
CR or better	13.0%	8.9%	0.22
VGPR or better	66.3%	56.2%	0.05
PR or better	92.3%	83.4%	0.01

CR = complete response; PR = partial response

Moreau P et al. *Proc ASH* 2015;Abstract 393.

IFM 2013-04: Conclusions

- VGPR and PR rates are significantly superior in the VTD arm, suggesting synergistic activity of proteasome inhibitor + immunomodulatory drug.
- Median number of CD34-positive stem cells harvested was higher on the VTD arm (p = 0.05).
- Incidence of hematologic toxicity was higher on the VCD arm:
  - Anemia (9.5% vs 4.1%)
  - Neutropenia (33.1% vs 18.9%)
  - Thrombocytopenia (10.6% vs 4.7%)
- Rate of peripheral neuropathy was higher on the VTD arm (7.7% vs 2.9%).
- These data support the preferential use of VTD rather than VCD in preparation for ASCT.

Moreau P et al. *Proc ASH* 2015;Abstract 393.

Other Relevant Abstracts

- IFM 2013-04: VTD versus VCD in newly diagnosed multiple myeloma (Abstract 393)
- **Subset analyses of special patient populations in the FIRST, ASPIRE and MM-013 trials (Abstracts 730, 731, 374)**
- Novel treatment approaches for relapsed disease (Abstracts 394, 378)
- Doxycycline for patients with advanced cardiac amyloidosis (Abstract 732)

FIRST (MM-020) Trial: Impact of Cytogenetics on Outcomes with Continuous Lenalidomide and Low-Dose Dexamethasone (Rd) in Newly Diagnosed Multiple Myeloma (NDMM)

- Phase III study for transplant-ineligible patients with NDMM who received continuous Rd, Rd x 18 cycles (Rd18) or melphalan/prednisone/thalidomide (MPT).
- N = 762 of 1,623 patients with validated FISH cytogenetic profiles:
  - High risk: del(17p), t(4;14), t(14;16)
  - Nonhigh risk: All others
- **Primary endpoint:** Progression-free survival (PFS) by risk status

Risk	Three-year PFS rate			Three-year OS rate		
	Rd	Rd18	MPT	Rd	Rd18	MPT
High (n = 142)	3%	10%	3%	41%	40%	47%
Nonhigh (n = 620)	45%	20%	26%	77%	71%	65%

OS = overall survival

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 730.

FIRST (MM-020): Conclusions

- Regardless of cytogenetic risk, overall response rate (ORR) and depth of response (complete response [CR] + very good partial response [VGPR]) were higher with continuous Rd than with MPT:
  - ORR: 80% vs 70% CR + VGPR: 46% vs 34%
- In the nonhigh-risk group, continuous Rd resulted in PFS and OS benefits in comparison to MPT:
  - Median PFS: 31 vs 25 mo; 3-y OS: 77% vs 65%
  - For the high-risk group, conclusions cannot be drawn between treatment arms because of the small N and baseline imbalances
  - The safety profile of continuous Rd was manageable and consistent between cytogenetic risk groups
- These results support continuous Rd as a standard treatment option for transplant-ineligible patients with NDMM, especially those without high-risk cytogenetics.

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 730.

ASPIRE Trial: Subgroup Analysis by Cytogenetic Risk Status

- Phase III study of carfilzomib/lenalidomide/dexamethasone (KRd) versus lenalidomide/dexamethasone (Rd)
- N = 417/792 patients with relapsed/refractory multiple myeloma (RRMM), 1 to 3 prior lines of therapy and available baseline cytogenetic risk status
- **Primary endpoint:** PFS according to baseline cytogenetic risk status

	High risk		Standard risk	
	KRd (n = 48)	**Rd (n = 52)**	**KRd (n = 147)**	**Rd (n = 170)**
Median PFS	23.1 mo	13.9 mo	29.6 mo	19.5 mo
Best ORR	79.2%	59.6%	91.2%	73.5%
sCR/CR	29%	6%	38%	7%
Median DoR	22.2 mo	14.9 mo	30.4 mo	20.4 mo

PFS = progression-free survival; ORR = overall response rate; sCR = stringent complete response; CR = complete response; DoR = duration of response

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 731.

ASPIRE Subgroup Analysis: Conclusions

- Among patients with high-risk cytogenetics, treatment with KRd resulted in a 9-month improvement in PFS relative to treatment with Rd.
- Treatment with KRd versus Rd also led to a 10-month improvement in median PFS among patients with standard-risk cytogenetics.
- Treatment with KRd versus Rd also led to higher response rates, deeper responses and longer DoR among patients with high- or standard-risk cytogenetics.
- KRd demonstrated a favorable benefit-risk profile for patients with RRMM irrespective of baseline cytogenetic risk status, and it improved outcomes for patients with high-risk disease.

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 731.

MM-013 Trial: Pomalidomide (Pom)/Low-Dose Dexamethasone (Dex) and Multiple Myeloma (MM)-Related Renal Impairment (RI)

- Ongoing Phase II study of pom/dex
- N = 47 patients with relapsed/refractory MM, ≥1 prior treatment and MM-related RI
- **Study endpoints reported:** Treatment-emergent adverse events (TEAEs) and pharmacokinetics

Select Grade 3 or 4 TEAEs	Moderate RI (n = 16)	Severe RI, no dialysis (n = 21)	Severe RI, dialysis (n = 10)
Neutropenia	50%	52%	60%
Anemia	6%	33%	60%
Thrombocytopenia	31%	19%	40%
Leukopenia	6%	5%	40%
Pneumonia	13%	5%	0%

Ramasamy K et al. *Proc ASH* 2015;Abstract 374.

MM-013: Conclusions

- Pom/dex was generally well tolerated, and the safety profile is consistent with pivotal trials:
  - 5 patients with TEAE-related pom dose reductions
  - Slightly higher number of Grade 3 and 4 TEAEs among patients with severe RI requiring dialysis
  - 10 patients with Grade 3 or 4 infections
  - No thromboembolic events or second primary cancer
- Pom exposure and plasma concentration appear to be similar in the 3 study cohorts.
- Pom at the 4-mg starting dose can be safely administered with low-dose dex in patients with moderate or severe RI, including those on dialysis.

Ramasamy K et al. *Proc ASH* 2015;Abstract 374.

Other Relevant Abstracts

- IFM 2013-04: VTD versus VCD in newly diagnosed multiple myeloma (Abstract 393)
- Subset analyses of special patient populations in the FIRST, ASPIRE and MM-013 trials (Abstracts 730, 731, 374)
- **Novel treatment approaches for relapsed disease (Abstracts 394, 378)**
- Doxycycline for patients with advanced cardiac amyloidosis (Abstract 732)

Myeloma X Relapse (Intensive) Trial: Second Autologous Stem Cell Transplant (ASCT2) as Salvage Therapy

- Updated results from a Phase III trial of ASCT2 or low-dose consolidation chemotherapy (nontransplant consolidation, NTC) after reinduction with a bortezomib-based regimen
- N = 174 patients with multiple myeloma relapse after first ASCT
- **Study endpoints:** Overall survival (OS), response, time to disease progression (TTP)

Clinical variable	ASCT2 (n = 89)	NTC (n = 85)	HR (*p*-value)
Median OS	67 mo	52 mo	0.56 (0.0169)
sCR/CR	39.3%	22.4%	— (0.012)
TTP	19 mo	11 mo	— (<0.0001)

HR = hazard ratio; sCR = stringent complete response; CR = complete response
Median follow-up 52 months

Cook G et al. *Proc ASH* 2015;Abstract 394.

Myeloma X Relapse (Intensive): Conclusions

- A clear OS advantage is demonstrated with ASCT2 versus consolidation therapy in this long-term follow-up analysis.
- Factors associated with improved OS in favor of ASCT2:
  - sCR/CR to reinduction therapy (HR 0.14, $p = 0.032$)
  - TTP >24 months after ASCT1 (HR 0.60, $p = 0.089$)
  - Absence of high-risk cytogenetics (HR 0.36, $p = 0.007$)
- The delay of salvage ASCT to the 3rd line does not confer the same degree of OS benefit as that seen with salvage transplant in the 2nd line when compared to NTC:
  - 4-year OS rate (ASCT2 vs 3rd-line ASCT vs NTC): 69% vs 61% vs 50% (ASCT2 vs NTC, $p = 0.005$; 3rd-line ASCT vs NTC, $p = 0.139$)

Cook G et al. *Proc ASH* 2015;Abstract 394.

OPZ007 Trial: Dose Schedule of Oprozomib (OPZ) with Pomalidomide/Dexamethasone in Relapsed/ Refractory (RR) Multiple Myeloma (MM)

- Phase Ib dose-escalation study of OPZ/pomalidomide/ dexamethasone (OPomd)
- N = 31 patients with RR MM who had previously received bortezomib and either lenalidomide or thalidomide
- **Primary endpoints:** Determine recommended Phase III dose of OPZ in the OPomd regimen and safety of the regimen
- OPomd demonstrates encouraging antimyeloma activity:
  - 5/14 schedule (OPZ 150 mg/d) overall response rate (ORR) = 2/4 (50%)
  - 2/7 schedule (OPZ 240 mg/d) ORR = 5/10 (50%)
  - 2/7 schedule (OPZ 210 mg/d) ORR = 12/17 (71%)
- Most common Grade ≥3 adverse events (AEs):
  - 2/7 schedule: Anemia (47%) and diarrhea (11%)

Maximum tolerated dose of OPZ was not defined on either schedule, but the 2/7 (210 mg/d) schedule was chosen for the expansion cohort.

Shah JJ et al. *Proc ASH* 2015;Abstract 378.

Other Relevant Abstracts

- IFM 2013-04: VTD versus VCD in newly diagnosed multiple myeloma (Abstract 393)
- Subset analyses of special patient populations in the FIRST, ASPIRE and MM-013 trials (Abstracts 730, 731, 374)
- Novel treatment approaches for relapsed disease (Abstracts 394, 378)
- **Doxycycline for patients with advanced cardiac amyloidosis (Abstract 732)**

Oral Doxycycline Improves Outcomes of Stage III AL Amyloidosis

- Matched case control study in which patients received oral doxycycline as adjuvant to standard chemotherapy
- N = 30 patients with cardiac AL amyloidosis and 73 controls (matched for cardiac disease stage, absolute NT-proBNP level, age and presenting dFLC) from the ALChemy study
- **Primary endpoints:** Overall survival, hematologic and cardiac response

	Median overall survival		*p*-value
	Doxycycline (n = 30)	**Control (n = 73)**	
All patients 24-mo survival	Not reached 82%	13 mo 40%	<0.0001
Stage II/IIIA	Not reached	20 mo	—
Stage IIIB	8.8 mo	5.1 mo	—

Wechalekar A et al. *Proc ASH* 2015;Abstract 732.

Conclusions

- Treatment with doxycycline in combination with chemotherapy significantly improves overall survival for patients with advanced cardiac Stage IIIA AL amyloidosis but not for those with very advanced Stage IIIB disease.
- Complete response/very good partial response rate was significantly higher with doxycyline (66%) compared to controls (43%), which translated into a significantly higher number of cardiac responses:
  - Cardiac response by NT-proBNP: 60% vs 18%
- This larger study confirms the previous preliminary results of using adjuvant doxycycline for AL amyloidosis and strongly supports the rationale to proceed with a randomized trial.

Wechalekar A et al. *Proc ASH* 2015;Abstract 732.