5 Minute JournalClub

POST-ASH Issue 1, 2016

Additional Abstracts of Interest in Multiple Myeloma at ASH 2015

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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. 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 unmatched 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 agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory multiple myeloma (MM) 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

- 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.

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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 2016
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To go directly to slides and commentary for this issue, **click here**.


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 (**click to hear it**) 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 (**click here**).

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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Additional Abstracts of Interest in Multiple Myeloma at ASH 2015

Presentations discussed in this issue

Moreau P et al. **Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial.** *Proc ASH* 2015;**Abstract 393**.

Avet-Loiseau H et al. **Impact of cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide plus low-dose dexamethasone in the FIRST (MM-020) trial.** *Proc ASH* 2015;**Abstract 730**.

Avet-Loiseau H et al. **Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone in patients with relapsed multiple myeloma based on cytogenetic risk status: Subgroup analysis from the phase 3 study Aspire (NCT01080391).** *Proc ASH* 2015;**Abstract 731**.

Ramasamy K et al. **Safety of treatment (Tx) with pomalidomide (POM) and low-dose dexamethasone (LoDEX) in patients (pts) with relapsed or refractory multiple myeloma (RRMM) and renal impairment (RI), including those on dialysis.** *Proc ASH* 2015;**Abstract 374**.

Cook G et al. **A salvage autologous stem cell transplant (ASCT2) induces superior overall survival following bortezomib-containing re-induction therapy for relapsed multiple myeloma (MM): Results from the Myeloma X (Intensive) trial.** *Proc ASH* 2015;**Abstract 394**.

Shah JJ et al. **Oprozomib, pomalidomide, and dexamethasone (OPomd) in patients (pts) with relapsed and/or refractory multiple myeloma (RRMM): Initial results of a phase 1b study (NCT01999335).** *Proc ASH* 2015;**Abstract 378**.

Wechalekar A et al. **Oral doxycycline improves outcomes of stage III AL amyloidosis — A matched case control study.** *Proc ASH* 2015;**Abstract 732**.

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)

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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.

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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.

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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.

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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.

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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.

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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.

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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)

5 Minute JournalClub

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.

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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.

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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)**

5 Minute JournalClub

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.

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