INTERVIEW

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Tracks 1-13

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Track 2 Tailoring induction therapy regimens based on risk stratification

Track 3 Perspective on risk stratification and duration of therapy in MM

Track 4 ECOG-E1A11 (ENDURANCE): A Phase III trial of RVd versus carfilzomib, lenalidomide and low-dose dexamethasone (CRd) → limited or indefinite lenalidomide maintenance for newly diagnosed symptomatic MM

Track 5 Use of hydration in patients initiating carfilzomib

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Track 7 Investigation of ixazomib as maintenance therapy for patients with MM

Track 8 Results of a meta-analysis of randomized trials evaluating lenalidomide maintenance therapy in MM

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Track 11 Role of melphalan in the management of transplant-ineligible MM

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Track 13 Activity, tolerability and ongoing evaluation of triplet regimens containing pomalidomide, carfilzomib or both for relapsed/refractory MM

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: The most commonly used induction regimen for multiple myeloma (MM) in the pretransplant setting is bortezomib/lenalidomide/dexamethasone (RVD). Would you discuss the emerging role of carfilzomib/lenalidomide/dexamethasone (CRd)?

DR KUMAR: Carfilzomib has some distinction from bortezomib in that it doesn't cause as much peripheral neuropathy (PN). Few data are available to compare the 2 regimens. The Phase II studies of CRd for high-risk smoldering, newly diagnosed or relapsed MM showed high efficacy (Jakubowiak 2012; Wang 2013). However, several questions are yet to be answered: Can we compare RVD to CRd head to head and show that one is more efficacious? Is one more convenient? Does a quality-of-life difference exist? These questions are being asked in the ongoing Phase III ECOG-E1A11 (ENDURANCE) trial. Patients with newly diagnosed MM are randomly assigned to receive

lenalidomide/dexamethasone with bortezomib or carfilzomib for 9 months followed by an indefinite duration versus 2 years of lenalidomide maintenance therapy.

DR LOVE: What has your experience been with issues such as dyspnea and cardiac dysfunction with carfilzomib?

DR KUMAR: All patients on early studies involving carfilzomib received aggressive hydration, so fluid overload may have occurred in some patients with this feeling of dyspnea. Also, some patients have received a number of other drugs, so their cardiac reserve may be relatively low. Finally, we need to keep in mind that some patients who live with myeloma for long periods can develop other conditions, like amyloidosis, which can also affect the heart.

The ongoing Phase III trials incorporate a concerted effort to better define who the people are who experience heart failure, what predisposes them to heart failure and which patients experience more of the primary dyspnea sensation and not really heart failure. For now this is something that practitioners should keep in mind when they are administering carfilzomib. If symptoms are present, doctors should follow up appropriately with cardiac biomarkers and echocardiograms.

DR LOVE: What kind of cardiac history would make you not want to use carfilzomib or absolutely preclude you from administering it?

DR KUMAR: A history of heart failure wouldn't stop me from administering carfilzomib, although I would watch those patients much more carefully. But if somebody were in congestive heart failure that was not well controlled with medications, I would be hesitant until we had better control of the heart failure.

Tracks 6-7

DR LOVE: Aside from the convenience factor, what else is known about the oral proteasome inhibitors, such as ixazomib, in MM?

DR KUMAR: Although ixazomib shares some properties with bortezomib, it is distinct in terms of how it binds and how fast it dissociates from the proteasome. It appears to have better distribution within the body and is better able to get outside the bloodstream. This may have implications for how we treat extramedullary disease. Also, the convenience of taking a pill once a week clearly opens up a new paradigm for patients needing proteasome inhibitor therapy.

We have evaluated the combination of ixazomib with lenalidomide/dexamethasone in newly diagnosed MM and demonstrated it to be effective (Kumar 2012). Ongoing Phase II studies are evaluating ixazomib in combination with cyclophosphamide/dexamethasone for newly diagnosed MM (NCT02046070) and previously untreated symptomatic MM (NCT01864018).

DR LOVE: What are your thoughts on oral proteasome inhibitors as maintenance therapy?

DR KUMAR: An oral agent as maintenance therapy will make a huge difference. This is important because many patients who need maintenance therapy have high-risk MM. These patients could gain significant benefit from proteasome inhibitor therapy. The availability of an oral agent would change the dynamics in that it could be conveniently administered to patients on a long-term basis. It's an exciting possibility that is

currently being explored in a Phase III trial evaluating ixazomib maintenance versus no maintenance therapy after stem cell transplant (SCT) (NCT02181413).

Tracks 8-10

DR LOVE: Your group presented a meta-analysis at ASH 2013 evaluating the existing outcomes data from Phase III randomized trials of maintenance lenalidomide. Would you discuss the current role of lenalidomide as maintenance therapy?

DR KUMAR: This is probably one of the most hotly debated topics these days. We must consider maintenance from the perspective of the ideal duration of therapy. It all boils down to continuous versus fixed-duration therapy. In the post-transplant setting this strategy has been referred to as maintenance therapy. However, in maintenance therapy for many other cancer types, patients receive a lower dose of treatment or a different kind of treatment after consolidation and induction therapy. So it may have different implications for a patient receiving SCT than for a transplant-ineligible patient.

For transplant-eligible patients, who receive 4 to 6 months of therapy and a single SCT, the question is whether to stop or continue treatment. The data are mixed in that setting. The US-based CALGB-100104 study reported a clear overall survival benefit with maintenance therapy. The more mature French IFM 2005-02 study, which did not allow crossover, reported no improvement in overall survival despite a similar improvement in progression-free survival to that in the US study (Singh 2013; [3.1]).

One of the fundamental differences in the design of the 2 studies is that patients on the control arm of the French study initially received 2 months of lenalidomide/dexamethasone consolidation. This raises the question of whether a group of patients exists who don't need continuous therapy and only need a couple of cycles of lenalidomide after SCT. The important aspect is to identify patients who would benefit the most from maintenance therapy.

In the transplant-ineligible population the story is different. Several trials have evaluated treatment continuation with thalidomide with or without bortezomib and showed an improvement in progression-free and overall survival. In this setting the debate is,

3.1

Meta-Analysis of Randomized Trials of Lenalidomide Maintenance Therapy in Multiple Myeloma

	Overall survival		PFS	
Phase III trial	HR*	*p*-value	HR*	*p*-value
IFM 2005-02	1.060	0.664	0.500	<0.001
CALGB-100104	0.610	0.008	0.480	<0.001
MM-015	0.790	0.251	0.340	<0.001
RV-MM-P1209	0.620	0.018	0.520	<0.001
Summary estimate	**0.767**	**0.071**	**0.491**	**<0.001**

* HR < 1 favors lenalidomide maintenance over no maintenance therapy.

PFS = progression-free survival; HR = hazard ratio

Singh PP et al. *Proc ASH* 2013;**Abstract 407**.

are we truly evaluating maintenance or are we trying to define what the duration of the ideal therapy should be?

DR LOVE: What are your thoughts on the results of the Phase III FIRST trial evaluating limited or continuous lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM (Benboubker 2014)?

DR KUMAR: The authors reported that overall survival was better with continuous Rd than with MPT. However, no difference was observed in overall survival between Rd administered continuously and Rd administered for 18 months. This suggests that early relapse after a patient stops receiving lenalidomide can be successfully salvaged by restarting lenalidomide or initiating a different therapy. The jury is still out on the ideal duration of therapy in this setting.

DR LOVE: You were also involved in a meta-analysis evaluating the incidence of second primary cancers with lenalidomide in newly diagnosed MM (Palumbo 2014; [3.2]). What were the study outcomes, and how do you approach this issue?

DR KUMAR: That analysis is important because it collected data from multiple institutions and asked a specific question: For patients initially receiving lenalidomide therapy, if that therapy is continued long term, is the risk of second primary cancer increased? The simple answer is no. However, the increase in second primary cancer with lenalidomide occurs in patients also receiving an alkylating agent, particularly melphalan.

I don't believe that lenalidomide is the cause of second primary cancer per se, but it's a facilitator. This is reassuring for patients with newly diagnosed MM who initially receive lenalidomide/dexamethasone and no alkylator. For a patient who achieved a good response to lenalidomide before SCT, I would strongly advocate for its use, but for a limited duration of 2 years. However, the decision should be made after a discussion of the risks and benefits. ■

3.2

Meta-analysis of Risk of Second Primary Cancer with Lenalidomide for Newly Diagnosed Multiple Myeloma

"Exposure to lenalidomide plus oral melphalan significantly increased haematological second primary malignancy risk versus melphalan alone (HR 4.86; $p<0.0001$). Exposure to lenalidomide plus cyclophosphamide … or lenalidomide plus dexamethasone … did not increase haematological second primary malignancy risk versus melphalan alone … These results suggest that alternatives, such as cyclophosphamide or alkylating-free combinations, should be considered instead of oral melphalan in combination with lenalidomide for myeloma."

Palumbo A et al. *Lancet Oncol* 2014;15(3):333–42.

SELECT PUBLICATIONS

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906–17.

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801–9.

Kumar SK et al. **A phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM).** *Proc ASH* 2012;**Abstract 332**.

Wang M et al. **Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma.** *Blood* 2013;122(18):3122–8.