INTERVIEW

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Tracks 1, 3

DR LOVE: What are some of the issues you discussed in your publication in *Blood* entitled "How I treat high risk myeloma" (Lonial 2015)?

DR LONIAL: There were several key unresolved issues discussed in this paper. The first is the importance of identifying which patients are at high risk at the time of diagnosis, because if you miss that opportunity, you won't know it until they have experienced rapid disease relapse. The second is to make sure that you're aggressive with their treatment and their maintenance because you can ultimately improve their long-term outcomes.

Another issue we explored was when patients should receive maintenance therapy and what regimen they should receive. One aspect we were trying to speak about is the idea that standard single-agent lenalidomide maintenance therapy after ASCT is not sufficient for patients with high-risk multiple myeloma (MM).

An important point I'd like to add to the messages from this paper pertains to recent data on the concept that, in general, undertreatment of MM is a bad thing. I and many others have said, "Two drugs is undertreatment," so lenalidomide/dexamethasone as induction therapy is insufficient (Durie 2015). Every patient should get the best induction up front. If you undertreat a patient at diagnosis, when they experience relapse they do so like a patient with high-risk disease, so you've almost converted them to a high-risk phenotype by undertreating them.

DR LOVE: Would you discuss the pragmatic aspects of bortezomib/lenalidomide/dexamethasone (RVd) maintenance therapy, how long you use it and how the patients fare?

DR LONIAL: Delivery of long-term IV therapy is untenable. What I mean by that is that administering IV bortezomib for 3 years is not a viable option. On the other hand, administering it subcutaneously once a week is a viable option, and we've used that approach on clinical trials. To build on that experience we're now beginning to experiment with replacing bortezomib with ixazomib because we are then using an all-oral combination for patients with high-risk MM that has yielded encouraging results.

DR LOVE: That was the first thing I thought about when I heard about oral proteasome inhibitors and I knew about this interest in maintenance. Have you had patients receive ixazomib for prolonged periods? And how do you find they fare?

DR LONIAL: Yes, we were involved with the original Phase I study that was published in *The Lancet Oncology* by Shaji Kumar evaluating ixazomib/lenalidomide/dexamethasone up front followed by maintenance ixazomib for patients with previously untreated MM (Kumar 2014). I believe the longest we've had a patient receive it was 4 1/2 years. Once you get the dose and schedule right early in the disease course, they fare well after that.

Track 5

DR LOVE: What are your thoughts on the joint IFM/DFCI 2009 trial evaluating immediate or delayed ASCT after RVd induction therapy? The French and Belgian portion of this study has been reported but the US part of the trial has not, correct?

DR LONIAL: Yes, that's correct. On this trial all patients received equal amounts of RVd induction therapy, and patients in the French version received 1 year of maintenance lenalidomide. In the United States they received maintenance lenalidomide until disease progression. What has been reported thus far from the French portion of this trial is that the PFS and overall response rate clearly favored the use of high-dose therapy and transplantation. However, overall survival was similar between the 2 arms (2.1).

Another interesting aspect of these results is that if you consider the patients who achieved minimal residual disease (MRD) negativity ($<10^{-6}$) by next-generation sequencing, it didn't matter whether they underwent a transplant or not. Their PFS and

overall survival looked the same. I was struck by the fact that those patients achieved such good outcomes with only 1 year of maintenance therapy.

DR LOVE: Do you have any idea when we'll see the North American data, and are you expecting them to reflect less of a difference because the maintenance therapy is more effective?

DR LONIAL: The US part of the trial is only now completing enrollment, so it will be a few years before the data are presented with a reasonable median follow-up. I'm a proponent of continuous maintenance in the post-transplant setting, but these results make me wonder: Is there an endpoint at which I would say, "that's enough" in terms of maintenance therapy?

2.1

IFM/DFCI 2009: A Phase III Trial Evaluating Immediate versus Delayed Autologous Stem Cell Transplant (ASCT) After Induction Therapy for Multiple Myeloma

Survival[1]	RVd (n = 350)	RVd + ASCT (n = 350)	Hazard ratio	*p*-value
Median progression-free survival (PFS)	34 mo	43 mo	0.69	<0.001
Complete response rate	46%	58%	—	<0.01
Three-year PFS for patients achieving complete response[2]	**MRD-negative by NGS ($<10^{-6}$)**		**MRD-positive by NGS ($\geq 10^{-6}$)**	
Before maintenance therapy	87%		63%	
After maintenance therapy	92%		64%	

RVd = bortezomib/lenalidomide/dexamethasone; MRD = minimal residual disease; NGS = next-generation sequencing

[1] Attal M et al. *Proc ASH* 2015;**Abstract 391**; [2] Avet-Loiseau H et al. *Proc ASH* 2015;**Abstract 191**.

Tracks 13-14

DR LOVE: Would you talk about some of your research on strategies for promoting Bcl-2 dependence in MM and how that relates to sensitivity to venetoclax?

DR LONIAL: About 85% of myeloma tumor cells are Mcl-1 dependent, which means they will be intrinsically resistant to Bcl-2 inhibitors. That leaves about 15% of patients who have Bcl-2-dependent disease, and it turns out that many of them harbor an 11;14 translocation. Their tumors look more B-cell like than those in the average patient with MM. Thus, the tumors tend to express CD20.

One of the strategies that we employ is adding dexamethasone, not because it kills myeloma cells but because dexamethasone pushes cells toward Bcl-2 dependence (Matulis 2016). Once you make the tumor cells Bcl-2 dependent, you have an opportunity to kill them with venetoclax.

DR LOVE: Have clinical responses been observed with venetoclax in MM?

DR LONIAL: Yes, although in the general patient population the response rate may not be so robust. If you focus on the subset that is enriched for the 11;14 translocation, it's quite striking — the single-agent venetoclax response rate is about 40% to 45% for those patients (Kumar 2016).

As an example, we cared for a young woman with MM that was refractory to almost any standard agent you can imagine, and she was about to be sent for supportive care. Laboratory analysis indicated that she would be an excellent candidate for this approach, and she has received single-agent venetoclax and has been in complete remission (CR) now for 2 years.

DR LOVE: Another interesting novel approach I'd like to ask you about is CAR T-cell therapy. What is known about that approach in MM?

DR LONIAL: We know that when you use CD19 as a target you may get a few responses but they're not long, durable responses. The real issue with CAR T cells in MM is whether we can find a better target than CD19. CD38 is one option, but to me a more interesting candidate is B-cell maturation antigen (BCMA). The NIH group has tested a CAR T cell against BCMA in MM and the response rate was impressive (Ali 2016; [2.2]). We don't yet know about response duration, and cytokine release syndrome continues to be an issue among patients receiving the highest dose of therapy, but CAR T cells are clearly effective and they will provide a way to treat many diseases down the road. ■

2.2

T Cells Expressing an Anti-B-Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor Cause Remissions of Multiple Myeloma (MM)

"These results demonstrate for the first time that CAR T-cells targeting an antigen other than CD19 can induce complete remissions of a hematologic malignancy. Importantly, we have shown that CAR-BCMA T cells have powerful activity against MM that was resistant to standard therapies. These results should encourage further efforts to enhance anti-BCMA CAR T cell therapies. The striking activity of anti-BCMA CAR T cells against MM indicates that CAR T cells targeting BCMA have great potential to be an effective new treatment of MM. Further development of anti-BCMA CAR T-cell therapies is a very promising area of research."

Ali SA et al. *Blood* 2016;128(13):1688-700.

SELECT PUBLICATIONS

Ali SA et al. **T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma.** *Blood* 2016;128(13):1688-700.

Attal M et al. **Autologous transplantation for multiple myeloma in the era of new drugs: A phase III study of the Intergroupe Francophone du Myelome (IFM/DFCI 2009 trial).** *Proc ASH* 2015;**Abstract 391**.

Avet-Loiseau H et al. **Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial.** *Proc ASH* 2015;**Abstract 191**.

Bajpai R et al. **Targeting glutamine metabolism in multiple myeloma enhances BIM binding to BCL-2 eliciting synthetic lethality to venetoclax.** *Oncogene* 2016;35(30):3955-64.

Durie B et al. **Bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): Results of the randomized phase III trial SWOG S0777.** *Proc ASH* 2015;**Abstract 25**.

Kumar SK et al. **Venetoclax monotherapy for relapsed/refractory multiple myeloma: Safety and efficacy results from a Phase I study.** *Proc ASH* 2016;**Abstract 488**.

Kumar SK et al. **Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: An open-label phase 1/2 study.** *Lancet Oncol* 2014;15(13):1503-12.

Lonial S et al. **How I treat high risk myeloma.** *Blood* 2015;126(13):1536-43.

Matulis SM et al. **Dexamethasone treatment promotes Bcl-2 dependence in multiple myeloma resulting in sensitivity to venetoclax.** *Leukemia* 2016;30(5):1086-93.