Managing Myeloma

EHA Annual Meeting Highlights 2015 Live:
Advances in Multiple Myeloma Treatment and Management

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Lonial: Hello, I am Dr. Sagar Lonial, from the Winship Cancer Institute of Emory University, and I am joined today with Dr. Nikhil Munshi from the Dana-Farber Cancer Institute of Harvard Medical School, and we are live at EHA. We are going to talk a little bit about some of the data which have been coming out this spring, so let's start off talking about a hot topic from the patient perspective, and that is MRD, minimal residual disease. What have we learned in the last few weeks?

Munshi: So, I think, in the last few weeks here at the EHA and little bit more than a week ago at ASCO there has been a lot of new information that has come out about how do we measure the minimal disease that we observe in patients. [1-4] We measure CR—which everybody knows, that only measures up to a certain level—and we know all the CR patients relapse. So, now, we have a method that we can use, and there are various methods to detect even deeper response where there are virtually no myeloma cells. So, we can detect only a few cells if they are present. These methods now allow us to detect those kind of patients where myeloma is not detectable even by the most sensitive method, and the studies are beginning to show that, if we can find patients with MRD negativity, they do better.

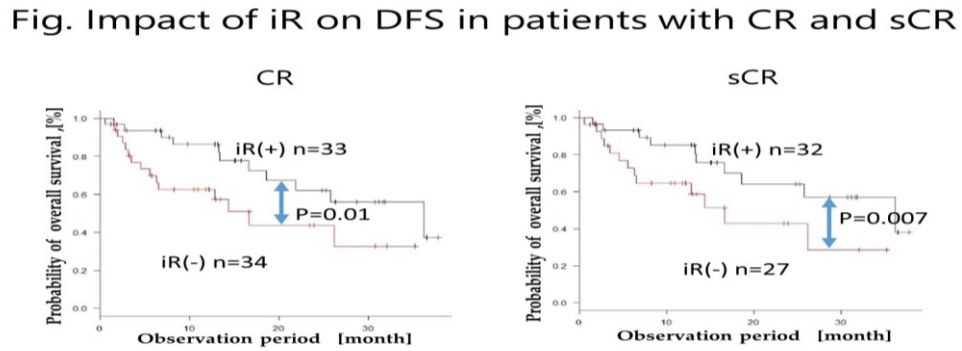
Significant Impact of Minimal Residual Disease (MRD) Status on Survival Outcomes in Patients with Multiple Myeloma (MM) Who Achieve Complete Response (CR): A Meta-Analysis. **[2]**

> *A total of 302 published articles were retrieved and 25 articles were identified through the reference sections of recently published articles. Of these, 18 reported overall survival (OS) or progression-free survival (PFS) results, as well as MRD status. Overall, 2,208 patients were evaluated for MRD by methods including multiparameter flow cytometry (n=1,606), PCR (n=492), or high-throughput sequencing (n=110). Nine publications reported conventional CR at the time of MRD measurement; however only 4 represented unique data sets. In total, there were 496 evaluable patients (362 were MRD-negative and 134 MRD-positive). The presence of MRD predicted shorter PFS (odds ratio [OR] 0.36; 95% confidence interval [CI] 0.26–0.50; P < .0001). Median PFS was 60 months for MRD-negative patients versus 36 months for MRD-positive patients; PFS at 3 years was 72% versus 50%, respectively, and at 5 years was 50% versus 29%. MRD-negativity reduced the odds of death by 59% (OR 0.41; 95% CI 0.26–0.63; P < .0001); median OS was not reached for MRD-negative patients versus 82 months for MRD-positive patients. OS was higher for MRD-negative patients*

versus MRD-positive patients at 3 years (93% vs 79%) and 5 years (78% vs 60%). Presence of MRD was predictive of outcome in patients with adverse cytogenetic profiles. Overall, 37% of MRD-negative patients versus 7% of MRD-positive patients were progression-free at 8 years. There was no significant difference between studies in the impact of achieving MRD-negativity on outcome, indicating that the predictive value of MRD status does not depend on the type of treatment.

These results show that MRD negativity, as determined by various high-sensitivity methods, predicted for substantially better PFS and OS in patients with MM who had achieved CR. Furthermore, nearly all MRD-positive patients had disease progression within 8 years, whereas a third of MRD-negative patients remained progression-free. This large cohort, meta-analysis confirms that MRD status is a crucial marker of long-term outcomes in patients with MM. It is, therefore, a key endpoint in MM clinical trials and clearly also has an important role as a surrogate marker of OS.

Figure. **Prognostic Impact of Immunophenotypic Response and Normalization of Serum Free Light Chain Among Patients with Multiple Myeloma. [1]**



Overall survival (OS) and disease free survival (DFS); OS was defined from the day of diagnosis to death from any cause, with censoring performed the date of last contact. DFS was calculated from the date of achieved CR, sCR, or iR to relapse from the respective response date. Survivals were analyzed by the Kaplan–Meier method, and differences between curves were calculated by two-sided log-rank test. Subjects were classified into four categories; MFC positive or negative and κ-λ ratio normal or abnormal, and PFS and OS were compared between groups.

And so, even when they have gotten CR, measure MRD—those who are negative, they do better. Those who are positive, they do not do so well as the negative; they still do well, but not as good as negative. And, the studies are beginning to show that, with any good intervention, almost half of the patients end up being in the MRD-negative group, and that is what we want to get. The importance of this is that those who get MRD-negative—as I mentioned—do better. And so, now, we are beginning to think, Can we use this to tailor our treatment? And, should our

goal be, ultimately, to get everybody into MRD negativity? So, we do what we do: induction; transplant; maintenance; in some cases, consolidation; then, measure whether they are MRD negative or not. And once we confirm they are MRD negative, currently, we do just a regular maintenance. And moving forward, we will have studies that may do different interventions. More importantly, those who are in CR but MRD negative, we are beginning to think that, maybe we should do more. I think this is a major advance, and it is a major advance for studies. We look at patients' progression. Now, the MRD negative could be a surrogate for progression.

Lonial: Do you think we are ready right now to make treatment decisions based on MRD negativity?

Munshi: Not exactly, so it is a very good prognostic marker. It says who is going to do better. However, we do not have a study to say we should do less if they are MRD negative and we should do more if they are MRD positive. We still treat them as CR, but we are at the stage that we should now start thinking of doing studies and not do anything different outside of the studies to understand if that is feasible.

Lonial: And do you think we are ready with the best method to move forward?

Munshi: That is a little tougher question. The good news is we have a lot of choices. [5] We have two wonderful studies showing elotuzumab [anti-signaling lymphocytic activation molecule F7 (SLAMF7)] efficacy. [6,7] We have studies showing daratumumab [anti-CD38] efficacy. [8-10]

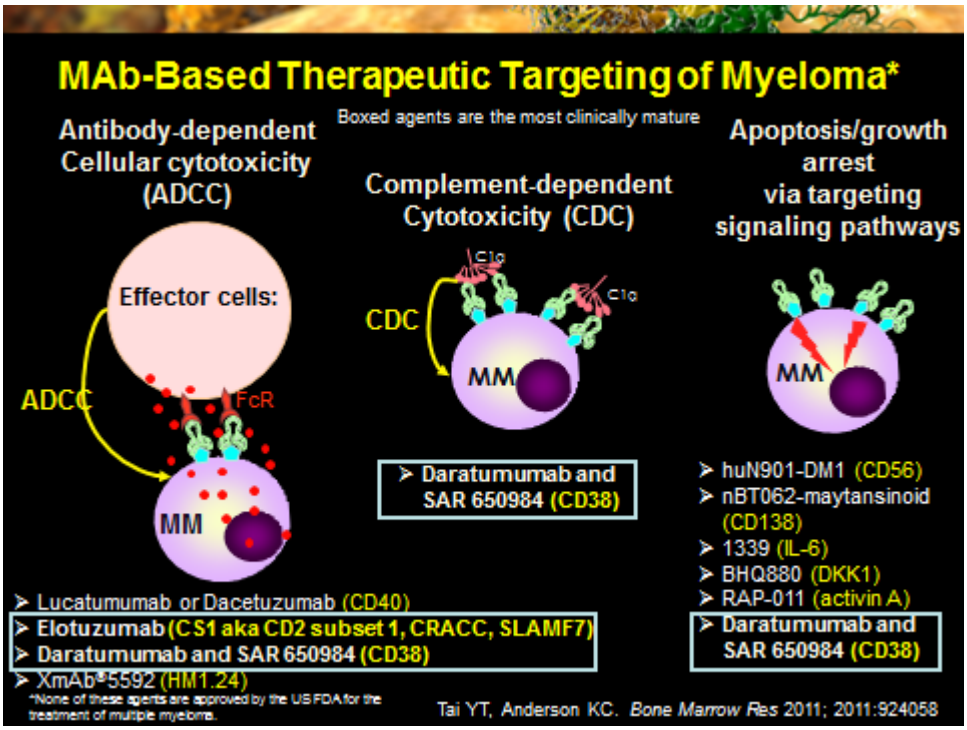
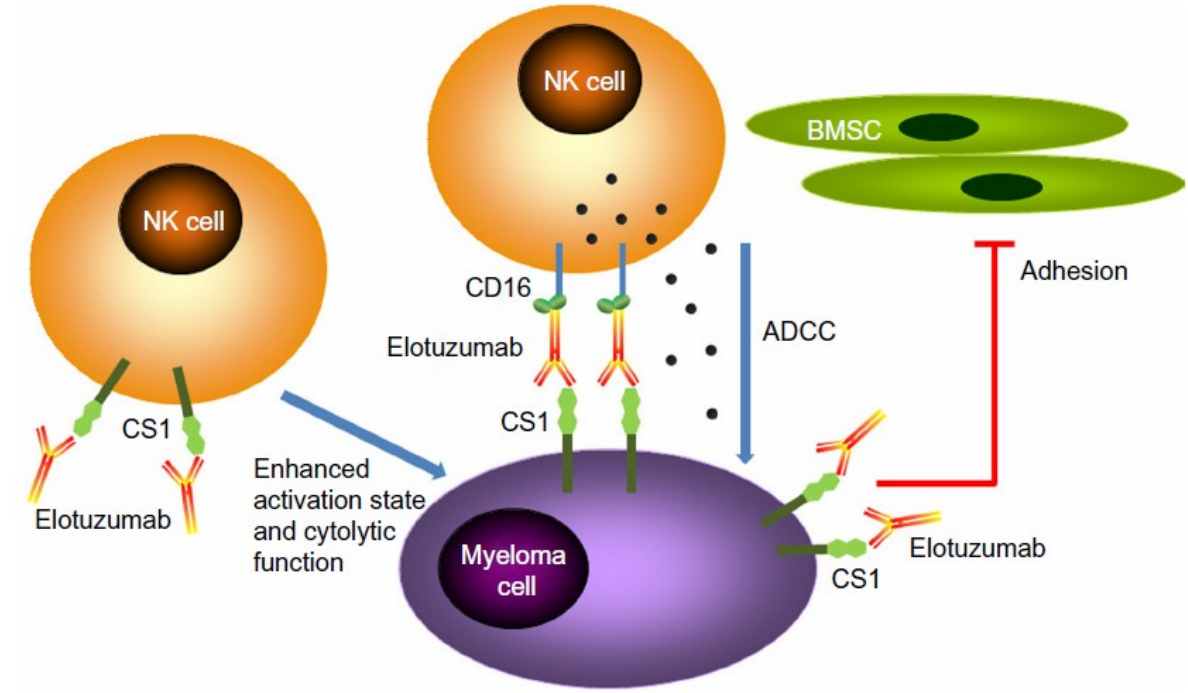


Figure. Elotuzumab's (anti-SLAMF7/CS1 mAb) Unique Passive-Specific, Active-Non-specific and Active-specific Potential Immunotherapeutic Mechanisms of Action.



Elotuzumab (anti-SLAMF7/CS-1 has three unique potential mechanisms of action. Elotuzumab can target not only SLAMF-7 presented on myeloma tumor (MM) cells but independent of the presence or absence of MM cells it can also act as an activating antibody of NK Cells that express SLAMF7/CS1receptors and thus it has properties of an active, non-specific immunotherapy. Finally, elotuzumab may enhance interaction of NK Cells and myeloma cells through cross binding, thus further facilitating antibody-dependent cellular cytotoxicity (ADCC). [11,12]

We have carfilzomib giving rise to deeper responses with the immunomodulatory drugs, and then exosome is around. [13-16] So, there are a lot of drugs that can be combined. However, which one is the best one? Which one will get to the MRD negativity in the maximum number of patients? I think we do not know yet. So, those are the studies we need to do to decide what are the combinations we can use for the MRD positivity conversion to negativity?

Lonial: Okay. So, that was a nice introduction to the idea of immune-based therapies. We know monoclonals are really important, but what other immune-based therapies do you think we have seen some encouraging data?

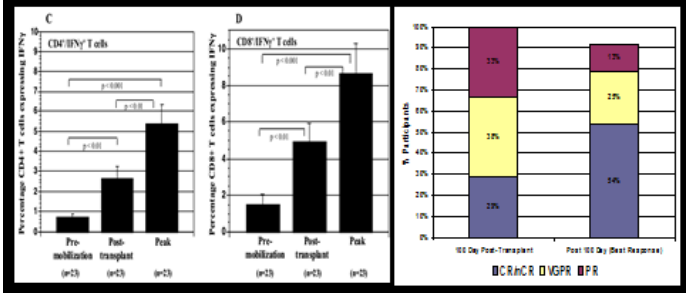
Munshi: Yeah, so the antibodies are really now in progress, and we will have one very soon and a second one very soon, too. But the other aspect of immunotherapy is to really do vaccination. And also, we are beginning to do what is called "adaptive immunotherapy," where we produce cells and inject them—immune cells. [12,17] In regards to vaccination, there are a number of studies happening. One of the studies, for example, is myeloma cell dendritic cell fusion, and then those few cells are given as a vaccine. [18,19]

Background: Immunotherapy in Conjunction with Stem Cell Transplant

- Autologous transplant for myeloma offers an ideal platform for consolidative immunotherapy
  - Patients achieve minimal disease state but transplant is not curative
  - Transplant mediated cytoreduction minimizes immunosuppression
- Enhanced response to immunotherapy post-transplant in animal models
  - Depletion of regulatory T cells during the period of post-transplant lymphopoietic reconstitution
  - Expansion of tumor reactive clones

Rosenblatt J et al. *Blood* 2013;19(13):3640-8.

Background: MM/DC Vaccination following Autologous PBSCT for Myeloma



Rosenblatt et al, CCR 3013

CT-011 is not US FDA approved for the treatment of multiple myeloma.

Rosenblatt J, et al. *Blood*. [ASH Annual Meeting] 2012;120(21):abstract 578.
Rosenblatt J et al. *Clinical Cancer Res*. 2013;19(13):3640-8.

Blockade of PD-1 in Conjunction With the Dendritic Cell/Myeloma Vaccines Following Stem Cell Transplantation

Clinical Trial Design

- CT-011 humanized PD-1 antibody
- Myeloma patients post-transplant receive
  - Cohort 1: CT-011 alone
  - Cohort 2: CT-011 in combination with dendritic cell/myeloma fusion vaccine
- Primary Objective: Immune response
- Secondary Objectives: Toxicity, Clinical effect

Rosenblatt J et al. *Clinical Cancer Res* 2013;19(13):3640-8.
Clinicaltrials.gov ClinicalTrials.gov Identifier: NCT01067287

It is now combined with lenalidomide. [20] It has been combined with checkpoint inhibitors, and in the preliminary results, it shows exciting results. [21] So, now, there is a randomized study about to start where patients will get traditional maintenance versus vaccination and then evaluate if vaccination provides better benefit. That is what we are hoping. There are peptide-based vaccinations, so there are a number of targets for peptides from MAGE-3, MAGE-C1 (CT-7), NY-ESO-1, CS-1, XBP-1, CD138, and others, and there are peptide-based vaccinations which are being utilized, again, with lenalidomide with checkpoint inhibitors, and they are being utilized in the early stage smoldering myeloma to see if they can prevent progression [NCT01718899; NCT02240537].[12] They are also being tried posttransplant, which has been an exciting area to see if we can vaccinate the patient after transplant and get immune response that prevents progression. And I think that is an exciting area for development [NCT01995708; NCT00458653; NCT01067287]. The second way that is important in this very new area is the CAR T-cells. Here at EHA, and also at ASCO and multiple other places, there are now very exciting studies where patients' T-cells are genetically modified to introduce some genes that can make the immune cells identify cancer cells, so those modified cells go to myeloma cells to kill them. And there have been excellent results in leukemia. With 90% response, we believe a number of patients are getting cured. [22] And so, now, similar technology is being tried in myeloma. [23] There are a number of targets. There are CD-19 CAR T-cells which have been given to a few patients—with very interesting results NCT02135406. [24] There are NKG2D CAR T-cells, and these target myeloma cells in certain ways, which is ongoing [NCT02203825]. There is BCMA [NCT02215967] and CD138 [NCT01886976] of the CAR T-cells all in development. They are early, but because of the leukemia efficacy, there is great excitement, and they are becoming important treatment.

Lonial: And so, it is exciting with the idea that you have got new immune targeted approaches. We are able to measure depth of response better than we ever could before. The future is bright.

Munshi: Our future is exceedingly bright. We can detect the minimum disease, and then, with immunology or immune methods, we get rid of the minimum disease—and I think we are almost there for the cure.

Lonial: Alright, great. Well, thank you for your time, and we look forward to more information at ASH coming up.

Munshi: Pleasure being here, and I think more good news is to come.

Lonial: Thank you.

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