**Sagar Lonial, MD, FACP**
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

**Nikhil C. Munshi, MD**
Professor of Medicine
Department of Medicine
Harvard Medical School
Boston, Massachusetts

**Dr. Sagar Lonial:** Hello and welcome to *Managing Myeloma*. My name is Sagar Lonial, and I am a Professor at the Winship Cancer Institute of Emory University in Atlanta, Georgia. Today, I am speaking with Dr. Nikhil Munshi, Professor of Medicine at the Harvard Medical School in Boston, Massachusetts, and we are talking about highlights from the ESH 3rd International Conference on multiple myeloma specifically focusing on the session that Dr. Munshi chaired on biology of plasma cells. Welcome, Dr. Munshi.

**Dr. Nikhil Munshi:** Thank you very much, Dr. Lonial. It is my pleasure being here.

**Dr. Sagar Lonial:** You had a very interesting biology-based session focusing on a couple of areas of interest including immune-based therapy. So, let's start off with the initial lecture that you gave on clonality.

**Dr. Nikhil Munshi:** This biology session had two different foci of interest. One was genomics and clonality which I gave the lecture on, and then the second aspects were concerning immune-mediated killing of myeloma cells. So, as you asked, the clonality discussion was regarding how myeloma cells at the time of diagnosis have multiple clones and then they evolve further. This is an area of extreme interest because biologically speaking, these are the parts of the mechanisms which lead to development for drug resistance and eventually patients' lack of response and have a terminal outcome. So, there are a few important things to understand. These results have come out of a number of genome sequencing studies that have been done by us and by others. It has identified a few important salient points. Number one, now we know what are the various specific mutations in myeloma, and from a practical point of view, those mutations would be important as a target and we can discuss about it a little bit later. Number two, at the time of diagnosis, already there are multiple clones present, and that is why when we treat the patient and when they relapse, the relapsed disease would have a little bit different characteristic than the initial presenting features. Number three, over time, there is further evolution of the clones in myeloma leading to development of multiple newer clones with newer characteristics and newer response, or lack thereof, to the treatment we give.

**Dr. Sagar Lonial:** So, Nikhil, let me ask you a question about that, because I think when one looks at the genomic landscape of a newly diagnosed patient, particularly a patient with high-risk disease where I think the genomic instability may be higher than it is in a standard-risk myeloma patient, we talk about between 5 and 10 clones and things along those lines, but from a functional perspective, how do we know that those clones behave or respond differently to therapy?

**Dr. Nikhil Munshi:** That is a very important question. There actually are probably not 5 to 10 clones; a more recent whole genome sequencing data shows there might be 100s of clones present. But to your question, the way we know that each of these clones or some of these

clones have a differential sensitivity to treatment we give is based on what is left after the treatment. So, out of those 100s of clones, when patients respond and the myeloma disease goes down, at that point and more importantly when the patients relapse, the genomic characteristics, the mutational profile or the mutational landscape of the relapse sample is different than what we see at the time of diagnosis. So, we know that some of the clones have survived and actually grown while we are giving treatment, the others have been extinguished. We see this differential clonal response and that tells us that they have differential sensitivity to the drugs.

**Dr. Sagar Lonial:** Yes, certainly that kind of sequential data that your group has generated is very important for us to help to understand some of these questions. So, let's talk a little bit about the other talks and focus a little bit more on immunity which is certainly a huge area in oncology, but not wanting to be left out of the fun in myeloma, we have certainly take in that immune banner and try to move it forward.

**Dr. Nikhil Munshi:** I think the second area of interest in this particular session but very broadly for myeloma and even more broadly for all cancers has been immune-based therapies. There are two components to it and the two other presentations sort of touched on both the components. One is killing of the tumor cell using antibody-based therapies which was Professor Malavasi's presentation. Then, the second component of the third talk was on impact of some of the cell signaling pathways in the specific area of cell survival that can affect and sort of provide interaction of the accessory cells in the bone marrow that can make immune-based therapy not as effective. So, if we go to the first of the two immunity-based talks, Professor Malavasi's talk was targeting on CD38 as an important target. In myeloma, CD38 is an important molecule because we have one already approved antibody, daratumumab, which is effectively targeting CD38 providing significant responses by itself and even significantly higher responses when combined with an immunomodulatory drug or a proteasome inhibitor drug. So, CD38 is a very important target for us, and Professor Malavasi presented data on how the target itself is an ectoenzyme. What it would mean is that it is a receptor that the antibody sort of utilizes for its effect, but it also has a functional impact in the microenvironment to generate atmosphere that provides some level of protection to the tumor cells. He described very elegantly how this CD38 molecule and its activity lead to production of a chemical called adenosine that then affects further ability of the other immune cells to act appropriately (the NK cells and the T-cells). His data suggested that if one suppresses this adenosine molecule, one could augment the immune effects of CD38 targeting therapies. As part of his presentation, he showed that actually myeloma cells shade these vesicles that contain adenosine and contain the CD38 cell surface molecule which can then pass on this information to the next cell for them to also become less responsive. The important aspect of this is that targeting some of these functions of CD38 and the mechanism would be beneficial in augmenting immune-based responses.

**Dr. Sagar Lonial:** It is amazing the very early activity of certainly daratumumab and other CD38 targeted approaches has been pretty impressive in combination with some of our great agents and alone. If you can tweak the system a little bit more, it would be even more impressive whether through regulation of adenosine or upregulation of CD38 expression through ATRA or other things along those lines. It seems like we have just only scratched the surface.

**Dr. Nikhil Munshi:** Absolutely. I think CD38 is a great target of other antibodies in development, and anything that makes its efficacy better would be a significant advance in this area.

**Dr. Sagar Lonial:** The last lecture then really focused on intracellular signaling as a mechanism of resistance to immune therapy.

**Dr. Nikhil Munshi:** That is correct. It was also a very elegant presentation by Professor Mutis from Amsterdam that he has studied the cross talk between the plasma cells or myeloma cells and the bone marrow stromal cells and endothelial cells, the microenvironment itself including the extracellular matrix, to understand the signaling that may be initiated by this interaction and how it can lead to anti-apoptotic effects in the myeloma cells to protect against immune-based therapy-mediated cell killing. So, this interaction actually protects myeloma cells from being killed by the immune cells itself and that includes both T-cell and NK cell effects. His cell signaling studies in these settings showed that surviving one of the anti-apoptotic related molecules drives this effect. And if one develops a surviving targeting therapeutic modality, it can improve the efficacy of some of the immune therapies, and by itself also, targeting surviving could be important in myeloma. So, it was another angle of how bone marrow niche protects myeloma cells and how one can develop methods or treatments to overcome this protective effect.

**Dr. Sagar Lonial:** There have been, if I recall, and I do not remember now off the top of my head, but there have been surviving inhibitors that have been tested in myeloma. I do not remember that they had great activity.

**Dr. Nikhil Munshi:** You are very right. There were surviving targeting drugs, small molecules, which have been tested, and our group has also looked at it a number of years ago. By itself and biology-wise, it was interesting. The surviving is one of the anti-apoptotic agents that can be targeted and has a functional role. Its main evaluation originally had happened for surviving by itself and its effect, and it was underwhelming results, and that is why the molecule has not gone into clinical studies. The angle that probably this presentation brings about is that maybe surviving by itself is not the great target, but when you look at it in the context of bone marrow microenvironment and specifically ability of the immune cell-mediated killing, that inhibiting surviving may have some greater role. So, by itself not so great and probably does not have much future, but in the context of this discussion, one should probably revisit and see if there is any role in inhibiting surviving.

**Dr. Sagar Lonial:** Interesting, so as one begins to put each of these three important biology-based lectures together, what are sort of some take-home messages for the practicing clinician?

**Dr. Nikhil Munshi:** So, I think I would summarize the take-home messages in three things, and those three things represent the three talks in some ways. So, the first one is this important aspect of clonal heterogeneity and clonal evolution, and there was also a discussion in that talk that I presented that even treatment that we use can impact how the clones develop. Moving forward, I think we have to keep in mind that myeloma evolves and the myeloma we start treatment with and myeloma at the time of relapse may have different features. So, we do need to repeat some of the genomic studies that we did at diagnosis, but now at the relapse, we need to repeat it to see if it has changed. Number two in the same talk; it is important to know that certain mutations can be targeted today with the available drugs. There are ongoing studies for it. For example, we can have a BRAF inhibitor, we can have a MEK inhibitor to target Ras mutations and we have an IDH targeting drug, etc. So, some of the mutations can be targeted and can be utilized. Number two, CD38 is a very important target, and further improvement and

refinement in CD38 targeting antibodies will be beneficial, and the take-home message is that there are a number of studies ongoing to improve upon that. And then finally, the third point about the third presentation was that immune treatments are very, very important. We know that drugs like pembrolizumab with lenalidomide provides 75+% response rate in a relapsed/refractory patient, and there are CAR-T studies ongoing that has a great promise, but then, there are mechanisms which prevent these immune treatments from working very well and there is a better understanding to now inhibit those mechanisms to improve the immune-mediated killing.

**Dr. Sagar Lonial:** Yes, certainly very exciting and with not just CAR-T cells but now immunoconjugates and the bispecific antibodies coming down the road as well, I think one of the real challenges is how do we put our standard drugs together in combinations with many of these immune-based therapies either in combination or sequences that allows them to be maximally effective?

**Dr. Nikhil Munshi:** I think that is a task for us and a good problem that with all these good treatments we have to be careful that we combine them to get synergistic effect but at the same time not use it in a way that one drug may in fact end up countering the other drug. So far, we have not faced that problem tremendously, but I think with many more drugs available, we have to now realize which would synergize and what sequential fashion that we can use them in so that we can optimize the activity, especially bringing in the immune component which probably is the next important frontier in myeloma that may lead to curative outcome. Its utilization at the earlier time point, but very importantly for maintenance would be important next steps in our making it better, and the presentation in the session focusing on something of this fundamental biology but with the view of its clinical application is going to be contributing tremendously to achieve those next lines of questions.

**Dr. Sagar Lonial:** All right, that sounds very good and thank you Dr. Munshi for the highlights you provided today and thank you all for joining us. For additional resources, please view the other educational activities on ManagingMyeloma.com.

**Dr. Nikhil Munshi:** Thank you very much Dr. Lonial. It was pleasure presenting this.