Managing Myeloma

Highlights from the 2018 ESH International Conference on Multiple Myeloma

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Welcome to *Managing Myeloma.* I am Dr. Saad Usmani. Today, I would like to give an overview of key topics discussed this year at the 4th International Conference on Multiple Myeloma held in Mandelieu, France. This year's conference covered presentations focused on smoldering myeloma, frontline therapy, assessment of response, relapsed myeloma, as well as advances in immunotherapies. I would like to share a few insights from these presentations.

From the smoldering myeloma to active myeloma, that was the first session that was covered by Dr. Mateos and Dr. Ghobrial. They walked through what defines smoldering myeloma, especially with the current concept where many of us are thinking that this MGUS to active myeloma transition, as it is taking place, there are patients who either have MGUS or they have active myeloma that has not presented with symptoms yet. So, they took a deeper dive and talked about how to define high-risk smoldering myeloma. Some of the key features in clonal evolution from MGUS to smoldering myeloma where we may be able to tease out patients who have real myeloma that has not declared itself and through MGUS. They also talked about how to manage patients from a disease biology perspective looking at the pace with which the monoclonal protein and the light chains are moving, and how imaging plays a role, especially in the context of the new whole body MRIs which have better ability to look at what is going on inside the bone marrow, and then low-dose whole body CTs are able to capture bone damage and changes to the architecture much better than skeletal surveys. So, these kinds of things were explored along with clinical trials that are being done in high-risk smoldering myeloma. Both Dr. Ghobrial and Dr. Maria V. Mateos have conducted clinical trials that have been focusing on those high-risk smoldering myeloma patients. They have already presented early data at previous ASH meetings and so, they discussed some of the newer trials such as the GEM-CESAR trial and the elotuzumab, lenalidomide, dexamethasone combinations during their presentation. I think we should keep this in the context of where the field is going. We are going to see more and more of these evaluations looking at the immunome, MGUS to smoldering to active myeloma transition, genomic and epigenomic changes, and how to tease out which patients to pick for treatment, and then what would be the best treatment strategies. So be on the lookout at future meetings. This is a hot area of research and we are trying to landmark where in the spectrum of MGUS to active myeloma patients actually need to be initiated on treatment.

Then, within the frontline therapy, there was a European perspective and the US perspective given to induction regimens for both transplant eligible as well as ineligible patients. Historically, looking at the proteasome inhibitor-based triplets where they have been combined with IMiDs as well as with alkylators such as cyclophosphamide for the transplant eligible patients. Then looking at the non-alkylator based novel agent treatments comparing them to totally novel agent treatments for older patients. The field of geriatric oncology and assessment is something that is still underexplored. Sonja Zweegman helped cover some of these new geriatric assessments

that are being considered for myeloma patients. Again, knowing that an average myeloma patient at diagnosis is around the age of 69 or 70, this leaves us with the majority of myeloma patients being in the geriatric range where we are trying to figure out how their physiological age, whether it matches up or is better or worse than their chronological age. The new clinical trials that are exploring the combinations of monoclonal antibodies as well as other novel drug classes in combination with the usual three-drug regimens were discussed for the transplant eligible patients. On the forefront was the daratumumab combinations. There were also discussions about transplant ineligible clinical trial options with all oral regimens that include the novel proteasome inhibitor ixazomib with existing myeloma therapies. There was also discussion around the long-awaited data that should be coming later this year, combining monoclonal antibodies with immunomodulatory drugs and dexamethasone for all the transplant ineligible patients. There were discussions around some of these ongoing trials within the transplant space. We saw some of the IFM 2009 clinical trial data with early versus delayed stem cell transplant. Also, curious data on survival benefit in subsets of patients within the EMN02 trial which had looked at a bortezomib-based induction therapy along with maintenance strategy, and sandwiched in between were patients who had single or double stem cell transplantation. So those specific trials were discussed. There was a lot of interest in developing new strategies for high-risk myeloma patients knowing that we struggle with this group of patients. A subset analysis from the EMN02 trial which has been presented at ASH last year was revisited especially in context of tandem transplants which have, over the years, fallen out of favor but perhaps the data show curious signal in high-risk patients. We also discussed that with the plethora of novel agents and drug classes coming down the pike, especially with interest in immunotherapies and the chimeric antigen receptor (CAR) T-cell therapies whether there would be a role for tandem transplant. Allogenic stem cell transplant was also discussed in the same context with the newer cell therapies that are being developed in myeloma whether it makes sense to be pursuing clinical trials with either tandem or allogenic stem cell transplant.

There were lots of discussion on how to best approach early relapse disease management. We have several different clinical trial options available and there was robust discussion. I think there were 2 or 3 different sessions where there was discussions around how to pick regimens, how to pick one triplet from the other and for what subsets of patients, the distinction between slow biochemical relapse as well as a rapid clinical relapse. Discussions around what choices do we have for the high-risk early relapse patients and how to make the best in terms of depth of response. In that light, minimal residual disease data from the CASTOR and POLLUX trials was discussed with longer follow-up as well as in context of standard versus high-risk disease. There was also discussion around patients who may be PI or IMiD refractory, which would be the right options for them. Discussions around salvage chemotherapy and transplant were also discussed.

The talks on late relapses and newer drug classes highlighted selinexor, which is an exportin-1 inhibitor. This drug is making its way towards regulatory approval as single agent and there are several combination clinical trials being looked at in the early as well as late relapse setting. Combinations with bortezomib, carfilzomib, immunomodulatory drugs, and even with daratumumab which is anti-CD38 monoclonal antibody are being examined in clinical trials. There was a lot of excitement about venetoclax. There are combination clinical trials as well as single-agent clinical trials with venetoclax that are waiting to mature. We already have published data with single-agent activities, especially in the context of translocation 11;14 disease, as well as some guiding post on which patients within translocation 11;14 disease may benefit the most

and what combinations make sense. There are a big host of immunotherapies that are coming down the pike in myeloma. There was a session that was led by Dr. Ken Anderson where I spoke about the monoclonal antibodies. Dr. Jesus Berdeja updated us on the state-of-the art with the different CAR T-cell trials, and then Dr. Anderson wrapped the session up bringing all of those elements together.

Within my talk, I went through the history of monoclonal antibody development in myeloma, looking at the strategies that have failed in the past, looking at IL-6 receptor as well as IL-6 specific monoclonal antibodies that were evaluated in the early 2000s that did not show any clinical activity on their own in myeloma or in combination with other drug classes that were available at that point. There were clinical trials that were done to target against DKK1 to really focus on bone disease and reverse the bone damage that is done in specific subtypes of hyperdiploidy myeloma. Our first real success of single-agent activity was with daratumumab, which is an anti-CD38 monoclonal antibody. Shortly thereafter, we had an approval of elotuzumab with lenalidomide and dexamethasone in early relapsed myeloma. Even though elotuzumab did not have single-agent activity, it appears to partner well with immunomodulatory drugs.

There was also discussion around the monoclonal antibodies that are still in clinical development. Isatuximab is an anti-CD38 monoclonal antibody which is a little behind daratumumab in clinical development, but it too has good clinical activity as a single agent and in combination with immunomodulatory drugs. We are waiting for some of the pivotal phase 3 trials to mature for that particular option. Isatuximab is distinct from daratumumab since it targets a different epitope, so hypothetically, if a patient fails one anti-CD38 monoclonal antibody they may be responding to second monoclonal antibody. We do not have clinical data to back up that claim just yet.

Then, my talk went into a discussion around antibody drug conjugates that are in development in myeloma. Perhaps the one that is farthest along in development is the GSK compound 916 which targets BCMA. We had a first look of that compound a little over a year ago with single-agent activity in a small subset of patients. I believe the phase 1 trial had a small expansion of the MTD dose with 9 patients, and 6 of those 9 patients had a PR or better response which got all of us excited. Since then, the 916 compound has had further patients treated on that particular trial and there are some larger phase 3 trials that are moving forward with that compound. I have to say that one concern in terms of AE and SAEs that we had with the GSK compound was the ocular toxicity that was observed. Although it is reversable, it becomes a specific issue for patients and there appears to be a known mechanism for this. It is thought to be a reversable process, but patients do require ophthalmic evaluations quite frequently and this is something, from a development standpoint, we will have to look at different schedules of treatment as well as different potential dosings as we combine this drug with other mechanisms of actions for myeloma, but it is certainly very potent.

The next drug class that I talked about were bispecific monoclonal antibodies. Currently, we have bispecific monoclonal antibodies that are targeting BCMA, GPRC5D, and SLAMF7 I believe is also coming along. The concept of bispecific monoclonal antibody actually dates back to the late 1960s. The idea was that if you can engineer an antibody that attacks the cancer cell and on one of the arms attacks the CD3 on surface of T-cells, it can bring together the T-cell with the cancer cell and let the T-cell take the cancer cell out. Earlier this year, we have seen

some data presented showing clinical activity with AMG 420 which is a continuous infusion bispecific monoclonoal antibody targeting BCMA. There are several others that are in clinical development. The main message we are getting about BCMA is that it is a very good myeloma target. Now, we are trying to figure out what are the best ways of treating it, whether it is ADCs bispecifics or CAR T-cell therapies.

Speaking of CAR T-cell therapies, my talk was followed by a talk from Dr. Jesus Berdeja who updated us on the state-of-the-art with the CAR T-cell therapies. The first part of his talk was more informational about what CAR T-cell are, what is the difference between first-, second-, third-generations and subsequent generations of CAR T. He highlighted the BCMA CAR T data that has been already presented and published by the NCI group, the UPenn group, and then highlighted the Bluebird bb2121 data that were presented earlier this year at ASCO by Dr. Noopur Raje, and some data from the Nanjing Biolegend LCAR BCMA CAR T-cell. The latter company, Nanjing Biolegend, has now been bought by Janssen and further development of the BCMA CAR T is being done by Janssen. I would not be surprised if we see some clinical activity data from the early phase trials, perhaps in a year from now. With bb2121, almost all patients had the optimal cell dose of more than 150 million CAR T-cell showed disease response, but perhaps, the best responses were seen with the higher cell doses closer to 450 million CAR T-cell given. In terms of progression-free survival, Dr. Berdeja shared that patients who got the BCMA CAR T had roughly 11.5 to 12 months of PFS benefit which is almost three times better than any other single-agent mechanism of action that we have in relapsed/refractory patients. These were patients who were beyond fifth median prior lines of treatment. They were patients who were refractory to pomalidomide, carfilzomib, as well as daratumumab in this BCMA CAR T experience. So, there were some of us that did not share the enthusiasm. They were expecting more from the CAR T, perhaps with the curative intent in mind, but in general, I think, these results are very impressive and early. The CAR T are still a younger technology compared to others, so we have to just stay tuned and wait for more data to emerge.

The last and perhaps the best talk of the conference was Dr. Ken Anderson that brought around the concept of not simply looking at the myeloma cell biology but also the bone marrow microenvironment along with immune repertoire. It would be a three-pronged approach if we are to cure or have a long-term disease control from myeloma when patients are diagnosed, and he covered parts of the talks that Jesus and I had. Conceptually, he highlighted why it is important to go after the immune repertoire, why the same disease biology may behave differently in different patients. He also highlighted some of the newer mechanisms of actions that are being developed such as Protex. He also talked about some of the newer ways in which you can modulate the immune system beyond the checkpoint inhibition of PD-1/PD-L1 pathway and overall, brought the whole context of the meeting together in that one particular talk.

With that in mind, I would like to conclude the summary that I have given for the ESH Meeting. Thank you for viewing this activity.