ASCO Highlights from Noopur Raje, MD

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I am Noopur Raje from Massachusetts General Hospital Cancer Center. I am here in Chicago at the ASCO Meeting and I'm going to talk to you about part of the myeloma session we had yesterday, focusing mainly on immuno-oncology. I presented our clinical trial with bb2121 which is a CAR T-cell product, so I will start out with that. What we did was an updated data analysis of a first-in-human phase 1 clinical trial which included about 43 patients; including both the dose escalation as well as the expansion phase of this clinical trial. There were a couple of questions we had before going into this clinical trial; one is whether circulating BCMA levels matter in patients, as pre-clinical data suggested that they did not. We also looked at receptor density of BCMA on tumor cells, and again at least pre-clinically the suggestion was that it did not matter whether or not you have high or low BCMA level expression for efficacy of such a product. The bb2121 product is a CAR T-cell product constructed, or generated, from autologous lymphocytes (autologous T-cells), which are then manipulated wherein a viral vector is used to recognize humanized BCMA. It also has a costimulatory domain like most of the CAR T-cells such as CD3-zeta. In addition, we used 4-1BB and, in our opinion, this seems to be a good strategy in terms of both T-cell expansion as well as toxicity. With that in mind, we went ahead with this first-in-human study. We did a classic dose-escalation trial design. We started off with 50 million cells in patients and went all the way up to 800 million cells. Patients were lymphodepleted with cyclophosphamide and fludarabine, and this was followed by giving back the CAR T-cell infusion. I think what was absolutely striking here were a couple of things: one is we saw very little in the way of toxicity. We did see some cytokine release syndrome which was seen in about 70% of patients, but most of that CRS was grade 1 and 2 and very easy to manage. We had a few patients who had a higher-grade CRS, but again completely reversed with the use of tocilizumab. The other highlight of this trial was the fact that we did not really use a whole lot of tocilizumab. It was certainly not mandated in the study and we ended up using it only in about, I think, nine patients. Again, the use of steroids for all of these issues was also quite low. The other toxicity worth remembering and worth considering is neurotoxicity, which has been reported with CAR T-cell approaches. I think the good news with this particular clinical trial was we saw neurotoxicity in about 30% of patients, with really only one grade 4 neurotoxicity which we described in detail at ASH, and that reverted and reversed completely. From a toxicity signal standpoint, this bb2121 product was actually quite well-tolerated. In terms of efficacy and in terms of dose expansion, we did two things: we included patients with low BCMA expression, and we mandated that these patients had received daratumumab. When we looked at the efficacy, we saw a very high response rate in all patients, in excess of 90%. There are some patients with responses that are still ongoing at the lower doses because that was the cohort which was most recently accrued, and we just do not have all that data. In terms of efficacy and response rates, again, very high. In terms of durability of response, also what has been reported for the first time at this ASCO is that we had a median progression-free survival for these very heavily pre-treated patients of approximately

11.8 months. If we looked at patients who achieved bone marrow clearance or MRD negativity within the bone marrow, their progression-free survival was as high as 17.8 months. Certainly, patients are relapsing, so you do not see a plateauing of the curve; nonetheless, trying to put the data in perspective, given this heavily pre-treated patient population, I do not think we have seen this kind of an efficacy in end-stage myeloma to date. I think the other very reassuring feature here was the tolerability of these CAR T-cell products.

We also had other cellular therapy approaches which were presented at this session; one of them was presented by my colleague, Nina Shah, from UCSF, although most of the work which she presented was done at MD Anderson. I think it is an interesting way of thinking about cellular therapy here wherein Dr. Shah used allogeneic cord blood cells, and out of those cord blood cells got natural killer (NK) cells as a therapeutic modality for myeloma. NK cells are a great target in myeloma and we have been thinking about using this target in myeloma for a long time. In fact, when we use immunomodulatory drugs in myeloma like lenalidomide and pomalidomide, pre-clinically we have shown increased levels of NK cell activity, and that goes hand in hand with efficacy. There are certain monoclonal antibodies, which all of you are familiar with, such as elotuzumab, which targets NK cells and activates NK cells. There is certainly interest in the NK cells field in the context of myeloma. What Dr. Shah did very nicely in this study was took these patients who had relapsed, gave them high-dose melphalan and an autologous stem cell transplant, followed by these NK cell infusions. What the data very nicely showed us are that these NK cells stuck around for about eight days or so, and just the fact that this kind of approach was a feasible approach using an allogeneic product was very encouraging. I think a lot more work needs to be done in this field, and the biggest challenge in this NK cell field is how long these NK cells will persist. Based on her data, it was about a week or so of NK cell persistence. I think over the next couple of years, we will begin to learn and understand how we can further activate these NK cells and how they can stay on in our system for longer so that they have a therapeutic benefit.

We also talked about, interestingly enough, a couple of trials, the KEYNOTE trials, which I think the whole myeloma community has been waiting for a very long time. The KEYNOTE trials are two large randomized trials, one in the upfront setting and one in the relapsed/refractory setting. The upfront setting was lenalidomide in combination with pembrolizumab and dexamethasone, versus len-dex alone. In the relapsed setting, the KEYNOTE trial was pomalidomide with pembrolizumab and dex, versus pom-dex. Everybody is aware that these trials were cut short and had to be terminated early which was in the middle of last year. At this year's ASCO Meeting the FDA collated the data from both of these clinical trials and showed us that PD-1 checkpoint blocker in combination with the IMiD results in a slightly higher mortality from the combination. I think this was a very instructive session because what was presented yesterday was the fact that most of the mortality was related to toxicity, and it was toxicity from immune-related adverse events (IRAEs) which typically do not occur immediately and can take four to five weeks to occur. To me, this was a teaching moment wherein we learn how to use these drugs better. The good news is, because it was all toxicity-related, I think we have to try and understand and appreciate these drugs better; understand as to how to manage the toxicity of these drugs better. Our hope is that we can still try and work with these drugs in the future because they do work for a subset of myeloma patients and they can be very, very effective in those folks.

Abstracts:

Raje N, Berdeja J, Lin Y, et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. ASCO 2018. Abstract 8007.
https://meetinglibrary.asco.org/record/160693/abstract

Shah N, Mehta R, Li L, et al. Phase II study of ex vivo expanded cord blood natural killer cells for multiple myeloma. ASCO 2018. Abstract 8006.
https://meetinglibrary.asco.org/record/160689/abstract

Krauss A, Mulkey F, Shen YL, et al. FDA analysis of pembrolizumab trials in multiple myeloma: Immune related adverse events (irAEs) and response. ASCO 2018. Abstract 8008.
https://meetinglibrary.asco.org/record/160685/abstract