Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-BCMA CAR T Cell Therapy

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Welcome to *Managing Myeloma*. I'm Noopur Raje and I'm live at the 61st ASH conference in Orlando, Florida. What I will be reviewing today is the results of the study titled, "Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-BCMA CAR T Cell Therapy." This is going to be presented by one of my colleagues, Dr. Jesus Berdeja, on Monday at this meeting. And what it really is, is the next generation of CARs that we are working on.

We've already presented and now published bb2121, which is the first CAR in the context of multiple myeloma. Again, the target here is BCMA, which stands for B-cell maturation antigen, and this, as I've already said, is expressed from all multiple myeloma cells. And what we were able to demonstrate with bb2121 is we were able to produce these CARs in the majority of patients. We were able to give them back these CARs and the toxicity of this was very manageable.

So, moving forward what do you do next? And what we found with bb2121 was, on an average, people had disease control for close to a year, and we saw that the persistence of these CAR T cells was approximately six to eight months. So, bb21217 is the next generation of bb2121. And here, the modification is to try and improve on the persistence of these CAR T cells so that we have an even better response than the 12 months that you've seen with bb2121. And the way we are trying to do this is by exposing these CAR T cells in vitro, so outside of your body, to a PI3 kinase inhibitor, and that PI3 kinase inhibitor is called bb007 and therefore the name bb21217. And what this PI3 kinase inhibitor does to T cells is it enriches for a memory T-cell phenotype.

Now, all of us who do immunology know that if you have more memory T cells they hang around in the body for a lot longer, and when they hang around in the body for a lot longer we hope that we're going to see more of a persistence of these CARs and by seeing more of a persistence of these CARs, we are going to do even better than seeing that average of a one year of a disease control. So, that is basically the rationale for why we did the study and why we're using this PI3 kinase inhibitor, and what I'm going to share with you now is some of the data we have on the initial patients that we've treated with bb21217.

At this meeting, you're going to hear about 22 patients who received bb21217. Obviously, because this was a newer version of our old CAR, we had to do a pretty straightforward dose escalation here. We started at 150 million cells and have gone all the way up to 450 million cells. On an average, our patients were aged about 63 years and a lot of these – or almost all of them – were extremely heavily pretreated, with a median seven lines of therapy and they were penta-exposed. All of them exposed to bortezomib, lenalidomide, carfilzomib as well as pomalidomide, and the majority of them were also exposed to daratumumab. So, very

relapsed/refractory patient population and a lot of these patients, most of them, in fact, had high-risk cytogenetic features as well. So, in general, a pretty sick patient population that was treated with this next generation of the CAR.

As of right now, this is still early days, and we're still following patients. So, the median follow-up is not that long; it's about 23 weeks or so. But the bottom line is, the good news is, this CAR has also been just as well-tolerated as the previous one. We haven't seen a lot of very significant cytokine release syndromes. Most of it has been grade 1 and 2, and just one patient had grade 3 CRS, which was quite easy to manage with steroids as well as tocilizumab. We did have a little more in terms of neurotoxicity with bb21217. There was just one patient who developed encephalopathy on this, which was reported as a grade 3 initially and then resolved subsequently. So, we did see a slightly higher signal of neurotoxicity with this.

As far as efficacy is concerned, the follow up on this is quite short. It's still about two months or so, but we are seeing more than 83% of our patients actually showing a very nice response and we have about half these patients we've been able to test for MRD negativity and we've seen MRD negativity in this patient population. So, this is still ongoing.

The reassuring piece here is this is very similar to what we saw with bb2121, and I think a longer follow up is going to allow us to see if we actually see what we ended up wanting to see, which is persistence of that memory T cell phenotype, which hopefully will convert into a longer remission duration with this newer version of the CAR T cells.

So again, I think the importance of studies, you're going to hear a lot about CAR T cells. I think there's a lot of excitement around CAR T cells and we are all very excited about them. There's a bunch of different ones which are being presented at this meeting. The bottom line is very high efficacy and we're getting pretty good at managing toxicities. At least this one is very well-tolerated, and I think understanding what it is that causes the disease to come back is going to allow us to get even better control of myeloma. I think understanding CAR T cell technology is important. Referring patients early for these kinds of approaches will result in much, much, much better outcomes, hopefully, in the very near future.

So, again, excited about this technology and, the other piece, which I think we tend to forget is there's a lot of stuff happening in the BCMA space. So, we've finally identified a great target for myeloma, and with all of these options I think having a consultation with experts in this field will allow you to decide what BCMA-directed strategy makes the most sense, depending on the kind of disease you have.