Abstract 1869

Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics from a Phase 1 Study of PF-06863135, a B-cell Maturation, CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma

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Welcome to *Managing Myeloma*. I am Noopur Raje and I'm live at the 61st ASH conference in Orlando, Florida. Today I will be reviewing the results of a study titled, "Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics from a Phase 1 Study of PF-06863135, a B-cell Maturation, CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma."

The name of this is fairly complicated, but what it essentially is, is a bi-specific T-cell engager. From here on, I'm going to call it PF-3135. What this is, is a fully humanized monoclonal antibody which targets, on the one hand, BCMA, and on the other hand, it targets CD3, and it's bound to an IgG to a humanized locus through a linker and what it essentially does is the BCMA compartment goes and targets the tumor cell or the multiple myeloma cell and CD3 compartment targets the T cells, activates the T cells, brings the T cells to the tumor, and is then supposed to activate these and cause killing of the myeloma cells. So in essence, what this really is, is an off-the-shelf monoclonal antibody wherein we're using the power of immunology, the power of our own in vivo T cells. We are activating them against the tumor in this specific situation.

Now, all of you are familiar with the target which is BCMA, that stands for B-cell maturation antigen, and as a target, it is actually pretty much expressed in most multiple myeloma patients, if not all myeloma patients, and very little of this BCMA target is expressed on normal tissues; therefore, making it a really good targeted approach for all of these sort of immune strategies in this patient population.

With this first-in-human study, what we essentially wanted to do is obviously study the safety of this. We wanted to ramp up the doses of this. This was done in a classic kind of 3+3 design, which all of you are familiar with, with increasing dosing of the drug, with the idea of trying to find out what the maximum tolerated dose of 3135 is going to be, and we also wanted to come up with what the recommended phase 2 dose in clinical testing would be going forward.

So, I'm happy to say that we have actually treated 23 patients on this conjugated or the bi-specific antibody. It's given intravenously, essentially a 30-minute infusion, and as of right now we've been using it at a weekly dosing schedule. We've treated, like I said, 23 patients. The median age of these patients was about 65 years; we've gone all the way up to 82-year-old's as well, suggesting that in general, this is an extremely well-tolerated treatment.

For the first dose, given that this is a bispecific T-cell engager, we did hospitalize our patients because you do anticipate seeing, when you engage the T cells, certain toxicities, specifically like cytokine release syndrome or neurotoxicity, and that's why the first dose was given in-house so that we can observe our patients.

Most of these patients were very heavily pretreated. Their median lines of prior therapy were 11 and a lot of them, actually, this is the only probably BCMA-directed strategy which allows a prior BCMA-directed strategy, and about 21% of our patients had seen CAR-T cells before they came on to this protocol. Sixty percent of the patients to be treated were relapse multiple myeloma, 40% had refractory disease.

This, as I said, was a first-in-human dose escalation study. What we found on the study were the median duration of treatment was about four weeks; they've gotten that much. We did see some treatment-related adverse events, but most of them were grade 1 and 2. We did see cytokine release syndrome, suggesting that we were able to engage the T-cell component – that was seen in about 24% of patients. The thrombocytopenia and anemia which was seen was probably mostly disease related. We did see fevers in about 10% of patients and we do believe that the fevers were related to this bi-specific T-cell engager. Outside of that, we've not had any grade 4 or 5 treatment-related adverse events. We are continuing to ramp up the dose and we haven't reached the MTD in this.

We've looked at the pharmacokinetics and the pharmacodynamics of this agent, which was another primary aim of the study, and what we are able to show quite nicely is we were able to engage the T cells the way we wanted to and if you look at the PK of this BiTE antibody, we were able to see that the half-life of this drug is anywhere between four to eight days and, therefore, the weekly dosing of this drug.

Now again, this is an ongoing trial. So, to talk about responses, it's a little too early, and we may just be around at the dose levels where we are beginning to start seeing efficacy. Having said that, we have seen one patient who's actually had a complete response to this, we've had another patient who's had minimal response, and we've had about six patients who've had stability of disease and who've been able to continue on this and maybe their responses will deepen over time. Nine of these patients have obviously experienced disease progression, and most of these were on the very low dose levels.

So, it's too early again to talk about clinical benefit. But I think the bottom line here is this is a drug which is doing what we expected it to do. It is engaging the T cells the way we wanted it to do, and the pharmacokinetics and the pharmacodynamics of this BiTE antibody seem to be very acceptable, and we're looking forward to continuing to ramp up the dose. One of the other things that we're going to work with, with the same 3135 is to move it to a subcutaneous version in some of our patients going forward.