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Can I Expect Better Outcomes With Ciltacabtagene Autoleucel Therapy Compared to Other Treatment Options in the Triple-Class Refractory Myeloma Patient?

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Dr. Cohen:
Hello, my name is Adam Cohen from University of Pennsylvania, and today I'll be discussing the topic, Can I Expect Better Outcomes with Ciltacabtagene Autoleucel Therapy Compared to Other Treatment Options in the Triple-Class Refractory Myeloma Patient?

We know that once patients become refractory to a proteasome inhibitor, IMiD and CD38 antibody, the so-called triple class refractory patient, that outcomes unfortunately are poor. On the left you see data from the retrospective multicenter MAMMOTH study, in which 275 patients, 80% of whom were triple class refractory, were treated with doctors choice of a relapse refractory myeloma regimen. Regardless of the regimen chosen, the overall response to next line therapy was roughly 30 to 35%, with median PFS between three to four months. Median overall survival is shown in the graph on the left, and unfortunately was fairly poor with median survival of 9.2 months for patients who were triple or quad refractory and less than six months for patients who are penta-refractory. On the right you can see data from the more recent locomotion study. This was a prospective multicenter study. 248 patients enrolled, 74% triple class refractory, who observed prospectively after receiving, again doctor's choice, of any available relapse refractory regimen. Overall response rate was 30%, median PFS 4.6 months and median survival of about 12 months in this study. We're fortunate to have two additional novel drugs that have been recently approved for triple class refractory myeloma. On the left, you can see data from the DREAMM-2 study, which tested the novel anti-BCMA antibody drug conjugate Belantamab. At the 2.5 milligram per kilogram dose, given IV every three weeks, the overall response rate was 31%, with median PFS of 2.8 months. Patients achieved a remission, these could be fairly durable with median duration of response of 11 months. And the median overall survival was 13.7 months. On the right you see data from the Selinexor/Dex registration study. Selinexor is a novel oral XPO-1 inhibitor and was combined with dexamethasone in this single arm study. Again, in triple class refractory patients. The overall response rate was 26%, median progression free survival of 3.7 months, and median overall survival of eight to nine months. Thus, while these are nice additions to our armamentarium and provide additional options, there clearly still needs to be additional therapies that get higher response rates and perhaps more durable remissions for this hard-to-treat patient population.

Ciltacabtagene Autoleucel, or Cilta-cel is an autologous BCMA targeted CAR T-cell product. The structure of the CAR is shown on the left. This is somewhat unique in that it has two distinct BCMA binding domains which confers higher avidity to the target. It has a 41BB co-stimulatory domain and a typical CD3 Zeta signaling domain. CARTITUDE-2 was a single arm multicenter phase 1/2 registration study exploring the use of Cilta-cel in patients who had had at least three prior lines of therapy or were double refractory to PI in IMiD. All patients did, however, have to be exposed to PI IMiD and CD38 antibody and had to have progressive myeloma at time of entry. On the right you can see the study schema, patients underwent apheresis, bridging therapy as needed and then received standard cytoxan

and fludarabine conditioning followed by a single infusion of Cilta-cel at a target dose of 0.75 times 10 to the sixth CAR+ T-cells per kilogram, that then were assessed for safety and efficacy thereafter.

Here, you can see the latest efficacy data now with roughly two years of follow up. Patients had a median of six prior lines of therapy and 88% were triple class refractory. Overall response rate was 98% in the 97 patients who received Cilta-cel with a remarkable 82.5% achieving a stringent complete response. Two-year progression-free survival was roughly 60% with median PFS not reached at the time of data cut off, with two year PFS of 71% in the patients achieving CR or better. The overall survival was estimated at 74% at two years, with median overall survival not reached. So, you can see this represents a significant improvement over the historic response rates, PFS and overall survivals that I just described previously.

In terms of safety, the most common toxicities included hematologic toxicities. 95% of patients had grade 3/4 neutropenia and 60 to 70% had grade 3/4 anemia as expected following lympho-depleting chemotherapy and CAR T-cell treatment. The majority of patients recovered to grade two or less with regard to their cytopenias by month two though a subset of patients still had ongoing high-grade cytopenias even beyond this. Cytokine Release Syndrome was seen in 95% of patients. The median time to onset of CRS is seven days with Cilta-cel, which is somewhat delayed compared to other CAR-T products and the median duration of CRS was four days. Fortunately, the vast majority, 94% of patients who had CRS, had grades one and two and high-grade CRS was fairly rare. Neurotoxicity was seen in 20.6% of patients, including 10% who had grade three or higher. This included 16% who had typical ICANs, roughly with onset around the timing of CRS or shortly thereafter. Most of these were low grade. There were 12% of patients who developed other neurotoxicities often with later onset after resolution of classic ICANs and this included six patients who developed a Parkinsonian-like movement to neurocognitive disorder that unfortunately was not reversible in a subset of patients.

So, in conclusion, Cilta-cel has very high response rates and good durability of response in patients with highly refractory myeloma and is now FDA-approved for patients after four or more prior lines including PI IMiDs and CD38 antibodies. I do believe it represents a new standard of care treatment option for triple-class refractory myeloma. There are a number of ongoing studies using Cilta-cel in less heavily pretreated populations as shown here, including the CARTITUDE-4 randomized study which has completed accrual comparing Cilta-cel to standard of care options in patients with one to three prior lines of therapy and we eagerly await the results of all of these studies to see if moving Cilta-cel up earlier will perhaps lead to even more durable remissions in our patients. Thank you very much for your attention.

Announcer:
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