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How Durable Is the Benefit Seen With CAR T-cell Therapy in Multiple Myeloma?

Announcer:
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Dr. Cohen:
Hello, my name is Adam Cohen from the University of Pennsylvania in Philadelphia. Today I'll be discussing the topic How Durable Is the Benefit Seen With CAR T-cell Therapy in Multiple Myeloma?

We know that BCMA directed CAR T-cells can induce very high response rates, even in highly refractory myeloma patients. On the left, you can see data from the KarMMa study looking at Ide-cel with an overall response rate of 73% in 128 treated patients, including 33% achieving a complete response or better. Responses were even higher in the subset that received the highest dose of Ide-cel, 450 million cells, with an overall response rate of 81% and CR rate of 39% in this subset. On the right, you can see data from the CARTITUDE-1 study, testing the Cilta-cel CAR T products. The overall response rate here was 98% in 97 highly refractory patients, with a remarkable 83% of patients achieving a stringent CR or better. The question is, however, how durable are these responses?

So here, we see the response duration to Ide-cel in the KarMMa study. On the left, you can see response duration broken down by dose of CAR T-cells, showing that the highest response duration, 11.3 months, was seen in the patients who received the 450 million dose. On the right, you can see the Duration of Response According to Best Response. You can see that patients who only achieved a partial response had short response duration of only 4.5 months. Very good partial response patients had a median response duration of 10.4 months, and those who achieved the CR or better, roughly 1/3 of the patients, had a median response duration of 19 months at the time of this data cut off. While this is fairly impressive, you can see, however, that there continue to be relapses even in the CR patients who have had ongoing CR for a year or even 18 months. This is in contradistinction to what's seen after CAR T-cell therapy in diseases like DLBCL and ALL, where patients who have had a durable complete remission, 12 months or more, very rarely seem to relapse.

This slide shows the persistence of the CAR T-cells in patients receiving Ida-cel as well as the incidence of anti-CAR antibody development. You can see that CAR Transgene peaks in the first month, and then there's a gradual decline with most patients having undetectable CAR levels by six months or beyond. This seems to correlate with the emergence of a high frequency of anti-CAR antibodies. 44% of patients at six months up to almost 2/3 of patients at 12 months. This also seemed to correlate with the likelihood of response to re-treatment with Ida-cel. Of 16 patients who were positive for anti-CAR antibodies, none of them responded after Ide-cel reinfusion, whereas, of those who were anti-CAR antibody negative, six out of 12 or 50% responded. However, these responses tended to be short-lived with median PFS of only two to three months.

Here, we see progression-free survival in the latest update of the CARTITUDE-1 study with Cilta-cel. With a median follow up of close to 28 months, the median progression-free survival had not been reached, and 27 month PFS rate was estimated at 55% for all patients and 64% for the CR patients. On the right, you can see the progression-free survival for patients who had persistent MRD negativity lasting for more than six months or 12 months. This was fairly impressive. And the 27 month PFS rate was 79% for patients who had

sustained MRD negativity for 12 months or greater. However, even in this situation, you can see that they're starting to now be a number of patients relapsing beyond two years, suggesting that even in these patients w

ho achieve very deep responses that they're unlikely to be cured at least in this heavily refractory setting.

Now looking at predictors of shorter duration of response in PFS with Cilta-cel, you can see at some of the common high-risk features that we know are associated with poor outcome in myeloma, namely high-risk sighted genetics and high ISS stage, higher tumor burden, and particularly the presence of extramedullary plasmacytomas at baseline where the median duration of response was only about 13 months.

So to conclude, Ida-cel and Cilta-cel have very high response rates in highly refractory myeloma patients and are currently a FDA approved for patients with four or more prior lines of therapy who have been exposed to a proteasome inhibitor, IMiD, and CD38 antibody. The median duration of response to Ide-cel in the KarMMa study was 10.7 months. The median duration of response of Cilta-cel in the CARTITUDE-1 study was not reached with the median follow up of about 28 months. There are now ongoing studies exploring the use of both of these BCMA CAR T-cell products in earlier lines of therapy where patients may have healthier T-cells and less refractory disease burden to try to see if we may be able to extend the duration of response even further and perhaps start to cure a subset of our patients. Thank you very much for your attention.

Announcer:
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