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CAR T in Marginal Zone Lymphoma: Insights from the TRANSCEND FL Study

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
CAR T-cell therapies have helped transform the treatment of aggressive lymphomas, but could they also change the game for slower-growing, harder-to-treat diseases like marginal zone lymphoma? New data from the TRANSCEND FL study may have the answer.

This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the latest research on CAR T-cell therapy's impact on marginal zone lymphoma is Dr. Sairah Ahmed. She's a Professor in the Department of Lymphoma and Myeloma with a co-appointment in Stem Cell Transplant at the MD Anderson Cancer Center, where she's also the CAR T Program Director in the Department of Lymphoma and Myeloma. Dr. Ahmed, welcome to the program.

Dr. Ahmed:
Thank you for having me.

Dr. Turck:
Well, if we start with some background, Dr. Ahmed, what does the therapeutic landscape for relapsed or refractory marginal zone lymphoma look like? And why is it so difficult to treat?

Dr. Ahmed:
So I'm going to answer the second question first. Marginal zone lymphoma is a rare subtype of non-Hodgkin B-cell lymphoma, and so it's often lumped into a basket of indolent lymphomas. And most of the data that we have are for trials that treat both follicular lymphoma and marginal zone lymphoma together, or there are very small trials that just treat marginal zone lymphoma. But what that tends to do is make it hard to answer specific questions about the behavior of marginal zone lymphoma.

Furthermore, there are actually three subtypes of marginal zone lymphoma, so you have nodal, extranodal, and then splenic marginal zone lymphoma. And while they are characterized as indolent lymphomas, they can often have disease courses that are much more aggressive.

And there are a few clinical parameters that can help us prognosticate if a patient is going to have a more aggressive disease course. But by and large, we don't know which patient will have a more indolent type of lymphoma, or something that's going to require multiple treatments and potentially treatment very quickly after each other.

So all that complexity leads to challenges in terms of treating patients. But even more, it makes it less attractive for the pharmaceutical industry to do standalone trials for marginal zone lymphoma, which then makes it harder to get drugs specifically for that indication.

So when we talk about the therapeutic landscape for marginal zone lymphoma, it's often therapies that are already in use for follicular lymphoma or indolent lymphoma in general. There are some specific drugs that have been studied in marginal zone lymphoma. One of them would be the class of BTK inhibitors, which is now an indication for use in relapsed/refractory marginal zone lymphoma. And then another class is PI3 kinase inhibitors. However, that particular class of drug has a side effect profile that has made it less favorable in terms of treatment options.

So the short answer is: while there are multiple therapeutic options for marginal zone lymphoma, a lot of the data that we use to treat it is

extrapolated from follicular lymphoma, and that doesn't necessarily hold true in terms of every patient's course.

Dr. Turck:
And before we get into the results, would you walk us through the design of the TRANSCEND FL study and how the marginal zone lymphoma cohort was structured?

Dr. Ahmed:
Absolutely. So the TRANSCEND FL study was for relapsed or refractory marginal zone lymphoma. The way in which patients were deemed eligible is they had to be adults aged 18 or older, they had to have measurable disease, they had to have received at least two prior lines of systemic therapy, and at least one line had to have been an anti-CD20 antibody and an alkylating agent. Or they could have also had a prior autologous hematopoietic stem cell transplant and then had relapsing disease after that. The other kind of eligibility criteria were a good performance status and adequate organ function that is similar to all CAR T trials.

Patients received standard lymphodepletion with fludarabine and cyclophosphamide with infusion of cells on day 0. And the primary endpoint was overall response rate, and then secondary endpoints were complete response, duration of response, and progression-free survival. When we look at the patients that were in this trial, about 77 patients were leukapheresed, and of those, 67 actually received liso-cel.

Dr. Turck:
Now, I'd like to zero in on the results. What were the key efficacy findings for liso-cel in the marginal zone lymphoma group?

Dr. Ahmed:
Absolutely. So in terms of patients treated, about 45 percent of them were over the age of 65, and about 15 percent of them were over the age of 75. This was a population that was relapsed/refractory, with high-risk features such as progression within 24 months, prior transplant, and refractory to last systemic therapy. And the overall response rate was quite high at 95 percent with a complete response rate of 62 percent.

Dr. Turck:
Now, building on those efficacy results, what do the 24-month follow-up data suggest about the durability of response in this population?

Dr. Ahmed:
So the data that has been presented is with a 24-month duration of response. And so certainly, it is a shorter time period, but there will be more data coming out. However, it's quite favorable at that 24-month time period.

So the duration of response was 88 percent at 24 months. And for patients that were in a complete response, the duration of response was 89 percent. And for those patients who had a partial response, it was 89 percent as well. For progression-free survival, similarly, the median has not been reached, but the 24-month PFS was 85 percent, 90 percent for patients who were in complete response, and 90 percent for patients who were in partial response, with an overall survival at 24 months of 90 percent for the whole cohort. And for patients who were either in a complete response or a partial response, it was both 95 percent.

And I think one of the things that's quite different from other aggressive lymphomas is that those patients who attained a partial response still had excellent duration of responses. And so there's still that plateau. And potentially with longer follow-up, we may see that those patients do similarly well as patients who attain a complete response.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Sairah Ahmed about data from the TRANSCEND FL study that focused on the impact of CAR T-cell therapy on marginal zone lymphoma.

Now, if we look at this from a safety perspective, Dr. Ahmed, how did liso-cel perform in this cohort, particularly in regards to cytokine release syndrome and neurologic events?

Dr. Ahmed:
So for this patient population, the CRS of any grade was about 76 percent, but the vast majority of that was grade 1, with only 4 percent grade 3 CRS noted. The median time to onset and resolution for CRS was about 4 days, and most patients were treated with corticosteroids and tocilizumab.

For neurotoxicity, any grade neurotoxicity was 33 percent. Again, most of that was low-grade—grade 1 or grade 2—with only 4 percent of grade 3 events. And the median time to onset and resolution was, again, about 8.5 days for onset and 8 days for resolution.

I think the thing to keep in mind is that this is very similar to what we have seen in the past with liso-cel, so there's not a lot of deviation or new safety signals to be seen in this patient cohort.

The other interesting part of this particular trial is the other adverse events of special interest. So beyond CRS and ICANS, the grades of cytopenia, secondary malignancy, and infection are all quite important, again, with an indolent disease subtype that is being treated with CAR T-cell therapy.

All grade 3 cytopenias recovered to grade 2 by the time of data cutoff. And the incidence of second primary malignancy and infection was not different than what was seen in other datasets.

The B-cell aplasia and hypogammaglobulinemia was, again, almost seen universally. However, the resolution was seen around the time of 24 months. And so that's very similar to the adverse events that we've seen published for liso-cel in indolent lymphoma as well as in aggressive lymphomas.

Dr. Turck:
So then given all these findings, where do you see liso-cel fitting into the broader CAR T landscape for marginal zone lymphoma?

Dr. Ahmed:
I think particularly when we talk about relapsed/refractory marginal zone lymphoma, CAR T-cell therapy as a therapeutic option and 4-1BB constructs both have a safety profile that is well placed to be able to treat these patients. And certainly the outcomes, although with short follow-up, seem to show significant improvement over other types of treatment that we would potentially give patients in this line of therapy.

Again, I think the thing that strikes me most about the TRANSCEND data is that this is an older patient population, and so we worry about toxicity. And in this dataset, we really haven't seen significant therapy-related toxicity with liso-cel.

Dr. Turck:
Well, as those final comments bring us to the end of today's program, I want to thank my guest, Dr. Sairah Ahmed, for joining me to discuss the evolving role of CAR T-cell therapy in marginal zone lymphoma care based on data from the TRANSCEND FL study. Dr. Ahmed, it was great having you on the program.

Dr. Ahmed:
Thank you so much.

Announcer:
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