Transcript Details

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Clinical trial evidence that drives current guidelines for patients with CLL/SLL and MCL receiving third-line therapies

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Dr. Bhat:
This is CME on ReachMD, and I am Dr. Seema Bhat.

Dr. Abramson:
I'm Dr. Jeremy Abramson.

Dr. Bhat:
Dr. Abramson, let's talk about the clinical trial evidence that drives the current guidelines for patients with CLL/SLL and mantle cell lymphoma that are receiving third-line therapies. You can start with mantle cell lymphoma, then I'll review CLL.

Dr. Abramson:
Sure. So, we now have very appealing options in the third-line treatment setting for patients with relapsed mantle cell lymphoma. We have the noncovalent BTK inhibitor, pirtobrutinib, which was FDA approved based on the BRUIN trial. The BRUIN trial enrolled 90 patients with relapsed mantle cell lymphoma, all of whom had had prior covalent BTK inhibitors and most of whom were refractory to that treatment. These were heavily pretreated patients, who, with a median of 3 prior lines of therapy, and despite that, the overall response rate was 58% with a complete response rate of 20%. These responses could be durable in a number of patients with a median duration of response at nearly 2 years, and a median progression-free survival for the entire population of 7 months.

Other than the noncovalent BTK inhibitor, we have two approved CAR T-cell therapies in this context as well. Those are brexu-cel and liso-cel. Brexu-cel was initially approved based on the ZUMA-2 trial, which enrolled 68 patients who had previously been treated with a covalent BTK inhibitor. These patients also had a median of three prior lines of therapy and the overall and complete response rates were extremely high at 93% and 67%, respectively. These responses could be durable with a median duration of response of 28 months and the median progression-free for the entire treated population of 26 months.

Now, importantly, brexu-cel is associated with high rates of cytokine release syndrome and neurologic side effects with severe CRS occurring in 15% of patients and severe neurologic toxicity in 31% of patients, and this needs to be considered when selecting treatment for our patients.

The second CAR T-cell is liso-cel, which was approved based on the TRANSCEND mantle cell lymphoma study. This study enrolled 88 patients, again, almost all of whom had had a prior covalent BTK inhibitor. These patients also had a median of three prior lines of treatment. The overall response rate was 83% with a CR rate of 72%. The median duration of response was 16 months in this study, and the median progression-free survival was 15 months. The duration of response in PFS seem a little bit lower than reported on the ZUMA-2 study of brexu-cel, but these were different patient populations and it's hard to know whether this is a result of the CAR T-cell itself.

One thing that's most certain is that liso-cel was much better tolerated with lower rates of cytokine release syndrome and neurologic side effects. The rate of severe CRS was only 1% with liso-cel, and severe neurotoxicity occurred in only 9% of patients.

So, these are the three lines of evidence that we have to support pirtobrutinib, brexu-cel, and liso-cel as third-line or later treatment after a covalent BTK inhibitor.

Dr. Bhat, what can you tell us about CLL?

Dr. Bhat:
So, CLL patients in the third-line setting are usually dual refractory patients, which means that they have progressed on a covalent BTK inhibitor as well as on a venetoclax, which is a BCL-2 inhibitor. And we currently have two FDA approved agents for these patients. The first one is pirtobrutinib, which is a noncovalent BTK inhibitor. It was granted accelerated approval for treatment of patients with CLL or SLL who had received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. This approval was based on the BRUIN Phase 1/2 trial. The overall response rate for patients who had received a covalent BTK inhibitor previously was over 80% in the study and it was a bit higher in patients who had not received venetoclax previously.

The progression-free survival was also longer in venetoclax untreated patients compared to those who were exposed to venetoclax previously. As far as safety is concerned, pirtobrutinib was very well tolerated. Incidence of side effects of interest like hypertension was low. Hypertension was reported in 3.5% of the patients and atrial fibrillation and flutter was seen in 1.4% of the patients.

The FDA also granted accelerated approval to liso-cel for a similar population of patients with CLL/SLL. This is a CD19 directed CAR T-cell therapy and approval was based on the Phase 1/2 TRANSCEND CLL-004 study. CR rate was 20% in this study, and in patients with a CR, responses have been durable.

Well, that's all the time we have today. Thank you for a great discussion, Dr. Abramson. And thanks to our audience for listening.

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