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Time needed to complete: 56m

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How Do We Apply Evidence Supporting TROP2 Directed ADCs to the Metastatic TNBC Treatment Paradigm?

Announcer:
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Dr. Tolaney:
My name is Sara Tolaney. I'm a Breast Medical Oncologist at Dana Farber Cancer Institute. And today we're going to talk about evidence supporting TROP2-directed ADCs for metastatic triple-negative breast cancer.

So we do have a TROP2 ADC for the treatment of metastatic triple-negative disease, which is sacituzumab govitecan. This is an antibody drug conjugate that is targeting TROP2. It has a very high drug-to-antibody ratio at 8 to 1, and has a cleavable linker that is linked to SN-38, which is really the metabolite of irinotecan. So it's a topoisomerase 1 inhibitor.

This agent was studied for the treatment of metastatic triple-negative breast cancer within the ASCENT trial. This trial took patients who had had two or more lines of chemotherapy in the metastatic setting and randomized them to get sacituzumab or to get treatment of physician's choice chemotherapy, and was really designed to assess improvements in progression-free survival. The study did demonstrate that sacituzumab was associated with a better PFS compared to standard chemotherapy with a median PFS of 1.7 months for treatment of physicians choice chemo compared to 5.6 months for sacituzumab. And similarly, we also saw a significant improvement in overall survival favoring sacituzumab, going from 6.7 months to 12 months here.

So I think the important lesson here is sacituzumab, in essence, is more than doubling PFS and, in essence, doubling OS, but also shows that the chemo-control arm doesn't perform very well in pretreated triple-negative disease. We can also see that sacituzumab works very well in the second-line setting was really similar benefits in terms of PFS and OS, as we saw with the ITT population.

We do have to, however, keep in mind toxicities with sacituzumab, with the most common toxicity being neutropenia, where you see more than half of the patients have grade 3/4 neutropenia. We also see that patients can experience diarrhea, though that being mostly low grade. And important to note that patients usually do experience alopecia with this agent, so very important to inform your patients about that risk.

I will say that more than half of the patients in these trials generally do require growth factor support, so very important to utilize that as needed for neutropenia. But because sacituzumab has demonstrated such efficacy in the pretreated population, it really begs the question how sacituzumab will do in the frontline setting. And there are trials assessing this with the ASCENT-03, looking at the PD-L1 negative population comparing sacituzumab to treatment of physician's choice chemotherapy and the upfront setting. And then also for the PD-L1 positive metastatic triple-negative patients comparing sacituzumab to pembo to chemo/pembo, and these trials are currently enrolling.

There is however, another TROP2 ADC that is in development, which is datopotamab deruxtecan, or Dato-DXd. This targets TROP2 and has a topoisomerase 1 payload, as well this is deruxtecan, and as a drug-to-antibody ratio of 4 to 1. And what we saw was that in

pretreated metastatic triple-negative disease Dato-DXd was associated with about a 30% response rate, so very robust efficacy in pretreated patients. This agent is given once every 3 weeks and does not cause neutropenia and diarrhea, but rather does cause stomatitis and nausea. This agent is being studied currently in the upfront setting in a phase 3 study comparing Dato-DXd to treatment of physician's choice chemotherapy, and the study is enrolling.

So right now, we do have sacituzumab govitecan approved for the treatment of second-line and beyond metastatic triple-negative disease but it is now being looked at in the upfront setting. And we do have Dato-DXd also being studied in the upfront setting. So I think more to come for these ADCs, and likely we're to see these ADCs move into a first-line setting over the years to come.

Thank you very much.

Announcer:
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