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Treating mTNBC: A Safety Analysis of Sacituzumab Govitecan

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss a study published in *NPJ Breast Cancer* that details the safety analysis from the phase 3 ASCENT trial focusing on sacituzumab govitecan in metastatic triple-negative breast cancer is Dr. Hope Rugo. In addition to being an author of the study, Dr. Rugo is a Professor of Medicine and the Winterhof Distinguished Professor of Breast Oncology at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, where she's also the Director of Breast Oncology and Clinical Trials Education.

Dr. Rugo, thanks for being here today.

Dr. Rugo:
Thanks for having me.

Dr. Turck:
So if we start with some background, Dr. Rugo, would you tell us about sacituzumab and how it works to treat patients with metastatic triple-negative breast cancer?

Dr. Rugo:
Absolutely. Sacituzumab is a first-in-class TROP2 ADC that carries SN-38 topoisomerase 1 inhibitor as a payload. SN-38 is the active metabolite of irinotecan, and the drug-to-antibody ratio for the antibody of TROP2 to the payload is about 7 and a half.

Sacituzumab was first studied in an umbrella trial looking at different malignancies, but in that phase 1 and then expanded phase 2 trial, there were 108 patients with previously treated metastatic triple-negative breast cancer with an overall response rate of 33 percent and a good PFS of 5.5 months. So based on that, the phase 3 ASCENT trial was conducted, which randomized about 529 patients who had received a median of 4 lines of prior therapy. This was counted from beginning of treatment, even the early stage, so about 3 lines of therapy in the metastatic setting. The trial had no upper limit for the number of lines of therapy. And these patients were randomized to get sacituzumab or single-agent treatment of physician choice, including eribulin, vinorelbine, gemcitabine, or capecitabine, but more than 50 percent received eribulin in the TPC arm.

So the trial showed a significant improvement in progression-free survival, going from 1.7 to 5.6 months, with the hazard ratio of 0.41. Highly statistically significant. And also, a remarkable improvement in overall survival going from 6.7 to 12.1 months, with a hazard ratio of .48. Again, highly statistically significant. And this data then led to regulatory approval around the world for sacituzumab govitecan in patients with pretreated metastatic triple-negative breast cancer.

A subsequent analysis looked at patients who were treated to a relapse on their early-stage therapy, and the benefit was seen in that trial population as well. So the drug can be used earlier in patients with highly resistant disease, and it's generally, I would say, the second-line standard of care for patients with triple-negative breast cancer, with trials ongoing looking at sacituzumab in the first-line setting as well.

The adverse events from sacituzumab include neutropenia, diarrhea, and, to a low degree, anemia and febrile neutropenia. So we were very interested in looking at this in more detail, which is the subject of this paper.

Dr. Turck:
Well, speaking of that, I was wondering if we could zero in on the details of the safety analysis you conducted. What did this detailed analysis entail from a methodology standpoint?

Dr. Rugo:
So one of the important areas that we looked at here, and I think is important for any study where we're looking at our new treatments, is the time course of the most common adverse events that impact our patients. So one of the areas of methodology was to evaluate the time course; what was the median time to the event, so when did it happen? And what was the median duration of the event? Which is also really important; are these events that take forever to get better, like pneumonitis, or is it something that resolves very rapidly?

We also wanted to know the total incidence, of course, by grade of neutropenia and diarrhea. We wanted to understand the use of growth factors so that we could help people understand what growth factors could do for them in terms of managing the neutropenia and avoiding complications. And then we wanted to look at safety in older patients as well as efficacy by dose reductions and interruptions.

And then lastly, an area of great interest of mine is trying to understand individual risk. And so we were able to look at a smaller cohort of patients who had UGT1A1 polymorphism data available to try and understand what the impact was of UGT1A1 polymorphisms on the specific toxicities that we're looking at.

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. Hope Rugo about the safety analysis from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer.

So if we turn our attention to the results, Dr. Rugo, what were the key findings of your safety analysis?

Dr. Rugo:
What we note is that neutropenia was more common—and we had reported that previously—in patients who were receiving sacituzumab than those that were receiving treatment of physician choice. And you know, that makes perfect sense because some of the patients received drugs that don't cause as much neutropenia. And then diarrhea, also, was more frequent in the patients receiving sacituzumab.

So we looked at the median time to onset of the first event of grade 3 or greater neutropenia; it was 21 days for the sacituzumab arm compared to 14 days for treatment of physician choice. And that actually makes sense because the protocol required that your neutrophil count was 1.5 on day 1 of each cycle to try and avoid the issue of febrile neutropenia. So a lot of patients would come in at day 1 of a cycle, we didn't give prophylactic growth factors in the trial, and their neutrophil count would be below 1.5. However, once we started using prophylactic growth factors, that issue resolved. And in clinical practice, we use an ANC of 1,000 in order to make a go/no-go decision at both day 1 and day 8.

The median duration of an individual episode of grade 3 or greater neutropenia was about 6 days. Overall, what was the incidence? Any-grade was 63 percent for sacituzumab, and in the first treatment cycle, we saw more of it, so 43 percent in the treatment of physician choice arm, and of grade 3 or greater in the first cycle was 28 percent. So it does, I think, really emphasize the importance of understanding risk factors for our patients so that we can prophylax appropriately. Febrile neutropenia occurred in just 4 percent of patients, but I think that's largely avoidable by using growth factors.

So what about diarrhea? Diarrhea was also more frequent in patients who received sacituzumab, but median time to onset was 19 days so this occurs in the first cycle. The median duration for an individual episode was about 5 days, and so that's important to keep in mind. This happens in the first cycle and generally resolves fairly quickly, which is a good thing.

The overall grade, like all-grade diarrhea, was 59 percent, so about 60 percent of patients get some grade or other diarrhea, 10 percent grade 3. So of those patients, I guess you could think about 50 percent of patients getting fairly easy-to-manage diarrhea. You just need to make sure when they get their first dose, they have an anti-propulsive medication in their pocket and that they have a low threshold for taking medication.

Dr. Turck:
So just to recap, what would you say were the biggest takeaways as far as how we can best monitor and manage adverse effects associated with sacituzumab?

Dr. Rugo:
Well, I think that what's really important for our patients is education, and it's education of the patients and education of our staff, so that patients know when to call in, when to take their medications—those are two really important things—and what side effects to look out

for. Managing these side effects is really critical. So I always tell patients, “Side effects are primarily low neutrophils, so you might need growth factors at some point.” I found as I'm treating patients earlier in the course of therapy, I give growth factors later in the course treatment because their bone marrows are healthier. And then, diarrheal medication. I won't treat a patient unless they have loperamide in hand.

And I think the issue about the polymorphisms is intriguing. So, you know, there are patient populations who will be at higher risk for diarrhea. In those patients, there's consideration in the future for studying whether or not those patients should be starting at a lower dose; it’s hard to know, but certainly dose reduction for diarrhea that can't be managed with medications or is higher grade or longer lasting is an important strategy as well.

Dr. Turck:
And lastly, Dr. Rugo, are there any other key lessons or conclusions we should take away from these findings?

Dr. Rugo:
So in addition to the summary I just mentioned, two areas that we were able to look at in this paper I think are helpful. We looked at the impact of age as well as UGT1A1 polymorphisms, and the low-metabolizing polymorphisms mean that SN-38, the payload of the antibody drug conjugate, hangs around for longer. Basically, the safety profile was manageable in patients who were 65 years or older, where additional data has shown that efficacy was maintained in these patients with triple-negative breast cancer who are older. And we saw the same key adverse events, but it was very manageable.

The patients with UGT1A1 poor-metabolizing phenotype—and we looked at star-28, so patients who are homozygous for star-28—had higher rates of neutropenia, febrile neutropenia, anemia, and diarrhea. And so it's important to keep in mind that these patients need to be monitored closely and that dose reductions may be an important strategy for managing the toxicity in these patients who are poor metabolizers based on UGT1A1 polymorphisms.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Hope Rugo, for joining me to discuss the safety analysis from the phase 3 ASCENT trial focusing on sacituzumab govitecan in metastatic triple-negative breast cancer. Dr. Rugo, thanks for being here today.

Dr. Rugo:
Thank you so much again for having me and for talking about these important issues.

Announcer:
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