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Exploring the Treatment Landscape for Triple-Negative Breast Cancer

Dr. Chalasani:

Patients with triple-negative breast cancer face an uphill and often recurring battle, and as physicians, we're always searching for the most effective treatments. That's why today we'll speak with the lead investigator of one of the latest studies exploring the new treatment option for these patients.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about the ASCENT trial and sacituzumab govitecan treatment in metastatic triple-negative breast cancer patients is Dr. Aditya Bardia, an Associate Professor of Medicine at Harvard Medical School and a medical oncologist and Director of Breast Cancer Research at the Massachusetts General Hospital.

Dr. Bardia, thanks for joining me today.

Dr. Bardia:

Thank you for having me.

Dr. Chalasani:

To start, Dr. Bardia, can you give us some background and the ASCENT trial and the treatment with sacituzumab govitecan? What were some of your key clinical trial results?

Dr. Bardia:

So the ASCENT trial evaluated sacituzumab govitecan in patients with pretreated metastatic triple-negative breast cancer. If you look at the current landscape, the recommendation is to consider chemo with/without immunotherapy as first-line treatment for metastatic TNBC, but then patients have disease progression, and the standard options include eribulin or Navelbine or capecitabine, but the median progression-free survival is usually around 2 months or so with these standard options, so there's a need for better therapies.

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate. As a reminder, Trop-2 is overexpressed in majority of triple-negative breast cancers, other subsets as well, and so this antibody-drug conjugate, targets Trop-2 and has SN-38, the active metabolite of irinotecan as the payload, so the idea is to deliver higher doses of chemo preferentially to the tumor cells as compared to the normal cells so you have better efficacy to toxicity ratio. In a phase I/phase II trial with this agent clinical activity with response rate of more than 30 percent was seen in pretreated patients with metastatic TNBC. So the ASCENT trial compared sacituzumab govitecan, was the standard of care chemotherapy, eribulin, Navelbine, gemcitabine and capecitabine in pretreated patients with metastatic TNBC. In terms of the study results, the study met its primary endpoint. It showed that patients who received sacituzumab govitecan had almost doubling of their progression-free survival as well as doubling of overall survival as compared to standard chemotherapy.

So it's been a practice-changing study and led to the approval of sacituzumab govitecan, for patients with pretreated metastatic triple-negative breast cancer. And as per FDA label, patients should have received one line of therapy in the metastatic setting, so it could be a second-line and plus option for patients with metastatic TNBC.

Dr. Chalasani:

Great. Thank you. So, given that it is a Trop-2-directed antibody-drug conjugate, would you recommend Trop-2 testing prior to deciding the use of sacituzumab?

Dr. Bardia:

That's a great question. The drug targets Trop-2, so one would expect that the expression of Trop-2 would impact responses, and this is

partly true. If we look at the ASCENT trial, patients who had tumors with high Trop-2 expression, the response rate was higher as compared to patients who had tumors with low Trop-2 expression. However, even in patients who had low Trop-2 expression, the response rate, the progression-free survival was better with sacituzumab govitecan as compared to standard of care endocrine therapy, so that is why Trop-2 expression is not recommended in terms of routine clinical practice because it will not impact your clinical decision-making. Even in patients with low Trop-2, this agent is better than standard of care endocrine therapy, so we do not recommend testing Trop-2, for therapy selection, at least at this time.

Dr. Chalasani:

So, following up on that, if there are higher responses based on the Trop-2 expression on the tumor, have you seen in the ASCENT trial or other studies with sacituzumab any change in the adverse events based on the expression, or is that something to worry about when you're talking to patients?

Dr. Bardia:

So, in general, Trop-2 is overexpressed in tumor cells, not so much in normal cells, so we've not really seen a correlation between Trop-2 expression and the adverse event profile. The common side effects include myelosuppression, diarrhea, as well as alopecia. We have seen some correlation between UGT1A1 polymorphisms and the incidence of adverse events, and the rationale is that the drug has SN-38 payload, which is metabolized by UGT1A1, so if there's polymorphism in the UGT1A1, it can have higher levels of SN-38, which can contribute to the side effect profile. And you do see some correlation between UGT1A1 polymorphisms and incidence of certain adverse events like neutropenia and febrile neutropenia.

Dr. Chalasani:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I am speaking with Dr. Aditya Bardia about oral selective estrogen receptor degrader as a treatment option for patients with hormone receptor-positive HER2-negative metastatic breast cancer.

Can you just give a sense of how often or what is the frequency of dose reductions which were needed on the study and also in your practice?

Dr. Bardia:

Yeah. The number one side effect with this agent is myelosuppression neutropenia, including high incidence of grade 3/grade 4 neutropenia, which can usually be managed by dose holds and if need be dose interruptions. I would say about one-third of patients need dose holds interruptions with sacituzumab govitecan. We did subset analyses looking at patients who had dose reductions versus not and the impact on outcomes and we could see that even with dose reduction there was no negative impact in terms of outcomes. And I think it's about the right dose for the patient, not necessarily the highest dose, so clinically, I would feel very comfortable reducing a dose if a patient has a lot of adverse events.

Dr. Chalasani:

So, currently, based on its approval, you did mention earlier that it's approved as a second line, but if a patient comes in who was on neoadjuvant and completed the adjuvant treatments, is there a scenario where you would use it earlier, if they have disease progression or metastatic disease earlier?

Dr. Bardia:

Yeah. So we can look at a scenario of patient who receives neoadjuvant treatment, has residual disease, then gets capecitabine and then soon thereafter has disease recurrence. So, technically, that would be one line. As per FDA label, you need one line of therapy in the metastatic setting as well. So, for a patient like this, I would consider chemo with/without immunotherapy as the first line for metastatic TNBC. If the tumor has PD-L1 expression, consider the use of pembrolizumab. But then after that when the patient has disease progression, one could consider sacituzumab govitecan in the second line and plus setting.

Now, how about the first-line setting? That is something that's being investigated in clinical trials, the ASCENT 03 and ASCENT 04. These are clinical studies looking at sacituzumab govitecan with/without immunotherapy as first-line therapy for patients with metastatic TNBC.

Dr. Chalasani:

Great. So, given that sacituzumab govitecan did change the practice with, you know, really good, responses and durable responses, in patients with triple-negative, how do you see the future for antibody-drug conjugates to play in triple-negative breast cancer?

Dr. Bardia:

There's a lot of interest in antibody-drug conjugates, interest in looking at antibody-drug conjugates in the first-line metastatic TNBC

setting but also neoadjuvant/adjuvant to prevent disease recurrence: sacituzumab govitecan in the example of Trop-2 ADC. There's another ADC that has received a lot of attention. It's called datopotamab deruxtecan, or Dato-DXd, which is a Trop-2-directed ADC, and also interest in HER2 ADCs with bystander effect, which can target these so-called low HER2 tumors, ER+ as well as TNBC, with an agent like trastuzumab deruxtecan, so interest in ADCs. And the whole idea is to deliver higher doses of payload preferentially to tumor cells than normal cells so we can further improve on not just the efficacy but also have a better toxicity profile.

Dr. Chalasani:

Well, with those final thoughts in mind, I want to thank my guest, Dr. Aditya Bardia, for joining me today and sharing his expertise on ASCENT trial and insights as a treatment option for patients with triple-negative breast cancer. Dr. Bardia, it was great having you on the program today.

I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/projectoncology, where you can Be a Part of the Knowledge. Thanks for listening.