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Exploring Efficacy & Overall Survival in the TROPiCS-02 Trial

Dr. Chalasani:
Hormone receptor-positive/HER2- breast cancer is the most common biology of among breast cancer subtypes. This biology also makes up for majority of patients with metastatic breast cancer. Currently, their five-year survival rate is around 30 percent. While targeted hormone therapy combination treatments have improved outcomes in these patients, eventually the disease becomes resistant to endocrine-based therapy, and they need to be treated with chemotherapy. Novel targeted delivery of chemotherapy is a rapidly growing field with antibody-drug conjugates, frequently referred to as ADCs, showing more efficacy on having on clinical outcomes.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about the TROPiCS-02 trial is Dr. Hope Rugo, Professor of Medicine and Director of Breast Oncology and Clinical Trial Education at the University of California San Francisco Comprehensive Cancer Center.

Dr. Rugo, thanks for being here today.

Dr. Rugo:
Thank you so much for your interest.

Dr. Chalasani:
So let's dive into this exciting trial. Can you share some background on why the TROPiCS-02 trial was started?

Dr. Rugo:
That's a great question. Sacituzumab govitecan, which was the experimental agent in TROPiCS-02, is a first-in-class Trop-2-directed antibody drug conjugate with a high drug-to-antibody ratio and the payload of SN-38, which is the active metabolite of irinotecan. This is membrane permeable so that it can leak out and kill neighboring cells, the so-called bystander effect. Sacituzumab govitecan, as you know, is approved in patients who have metastatic triple-negative breast cancer who received at least one therapy in the metastatic setting based on the ASCENT trial, which showed an improvement in progression-free and overall survival.

In the initial phase I/II trials of sacituzumab govitecan, there was a cohort evaluated to heavily pretreated hormone receptor-positive, HER2-negative metastatic disease. In those patients who all received sacituzumab given day one and day eight every three weeks, there was an impressive response rate around 30 percent and progression-free survival that was just under a year. I think, you know, this is a very durable response, and the toxicity was similar to what we'd seen in treating triple-negative breast cancer, the primary toxicity being neutropenia. So that was very encouraging data in 54 patients and led to the whole concept of further studying sacituzumab govitecan in hormone-receptor positive disease.

There's also the other background, which is that Trop-2 itself is expressed on about 80% of breast cancers regardless of subtype, and it's a transmembrane calcium signal transducer. It's been linked to worse outcome in cancer progression, so it made sense to expand the group of cancers essentially that we were testing this agent in.

Dr. Chalasani:
Great. Thank you. So, can you comment on the study design and what were its objectives?

Dr. Rugo:
Absolutely. So, sacituzumab was tested in this phase III trial in patients who had heavily pretreated hormone-receptor positive, HER2-negative metastatic breast cancer. The receptor status was determined locally, not centrally. Patients had to have received at least two but not more than four lines of chemotherapy for metastatic disease and at least one endocrine therapy, a taxane, and a CDK4/6

inhibitor in any setting.

Patients were randomized to fit into this criteria one-to-one to receive sacituzumab govitecan or treatment of physician choice, a chemotherapy option including capecitabine, vinorelbine, gemcitabine or eribulin. The primary endpoint was progression-free survival by blinded independent central review, but a key secondary endpoint was also overall survival, of course response and patient-reported outcomes and safety. And like many trials we've seen recently, this was designed with a hierarchal statistical plan. So progression-free survival is the primary endpoint needed to be significant to look at overall survival. In turn, overall survival needed to be significant in order to look at overall response. And then overall response has to be significant to look at quality of life and time to deterioration. So we had already reported progression-free survival earlier in the year in the first interim analysis and then most recently reported the second interim analysis of overall survival.

Dr. Chalasani:
Great. Thank you. Now that we have the background and the really interesting study design, can you comment on the results a little bit more?

Dr. Rugo:
Absolutely. So, progression-free survival was aimed for a hazard ratio of 0.7 and that was the first result we reported at ASCO 2022 and now published in the Journal of Clinical Oncology. What's interesting is that the progression-free survival showed sort of a curious pattern that we see in trials where patients are enrolled who have been heavily pretreated regardless of the class of agent. For example, we saw this also in the EMERALD trial that treated patients with an endocrine therapy who had been heavily pretreated. So in this case it was chemotherapy. What we saw was that at the time of the first scan to evaluate response, about 20 percent of patients, a little bit more in each arm had progressive disease and went off study, so that limits a little bit of our medians by Kaplan-Meier. Regardless of that fact, the median progression-free survival was significantly prolonged with sacituzumab compared to chemotherapy of physician choice, and a little under 58 percent of the patients who got chemotherapy received eribulin. The medians were four months for chemotherapy and 5.5 months for sacituzumab, a difference that was 1.5 months, but the hazard ratio was 0.66, and the P value 0.0003. We did 3 landmark analyses looking at 6, 9 and 12 months, and in each timepoint there were more patients alive and free from progression who received sacituzumab compared to chemotherapy, and notably at one year there were three times as many patients alive and free from progression who received sacituzumab. The first interim analysis of overall survival showed a numeric trend towards improvement, but it was not statistically significant.

We presented at ESMO 2022 the second interim analysis of overall survival, which will be the final formal analysis because it was significant favoring sacituzumab

At the second interim analysis, we had 100 more survival events than we had at the first interim analysis, a little bit sobering, but 390 events had occurred in the overall patient population with a median follow-up of about 12.5 months. Overall survival was significantly prolonged with sacituzumab going from 11.2 to 14.4 months, an absolute difference of 3.2 months, hazard ratio 0.79 and a P value of 0.02. We also looked at a landmark analysis at 12 months, and at 12 months just 47 percent of patients were alive with chemotherapy, and 61 percent were alive with sacituzumab, a difference of 14 percent.

Because we saw a significant improvement in overall survival, we could look at response criteria. Overall response and clinical benefit rate were significantly higher or greater in patients who received sacituzumab compared to chemotherapy, and the median duration of response was longer. And we looked at the quality of life using the EORTC QLQC-30 scales and saw a significant delay in time to deterioration in global health status, quality of life and fatigue favoring sacituzumab and a similar time to deterioration with pain.

The safety profile is similar to what we saw in ASCENT where the primary toxicity is neutropenia. There was no increase in febrile neutropenia. There was one patient death attributed to sacituzumab. That was a neutropenic colitis death.

Dr. Chalasani:
Great. That kind of segues into my question about you know, the side effects that the clinician should be concerned about and any kind of monitoring strategies you use.

Dr. Rugo:
Well, that's a really important question. The one nice thing about the new generation of antibody drug conjugates is that they don't cause neuropathy, and neuropathy can be a huge limitation for treatment long-term with chemotherapy in the metastatic setting and has a huge impact on quality of life. But neutropenia obviously can have life-threatening consequences, so now that we're treating patients earlier with triple-negative disease with sacituzumab, I'm seeing a lot less neutropenia.

So, for neutropenia, if a patient has received growth factors with their last chemotherapy, I use growth factors up front with the first cycle trying to avoid that rise in first-cycle neutropenia. I usually give a single dose of filgrastim on day 3 and then day 11 essentially after day

8 treatment. Some of my colleagues have actually used pegfilgrastim as a single dose after day 8, and that can be an effective strategy as well. I use the filgrastim, the short-acting, because often I can decrease the amount of growth factor I'm giving for patients who don't have as heavily pretreated bone marrow, but for some patients they even need more than that, particularly our older patients, and then pegfilgrastim might be a good strategy to avoid multiple visits to the infusion center in patients who have to get their injections in a cancer center, our older patients.

Diarrhea is also a toxicity from sacituzumab. So we have to tell patients about the diarrhea and make sure they have an antipropulsive agent, like loperamide, at home. And then if patients continue to have diarrhea even with counseling on use of loperamide, we actually dose-reduce, and that usually takes care of the problem fairly rapidly.

You know, some fatigue is seen with all of our treatments. And then alopecia is important to warn patients about. Alopecia did not occur in all patients, but in our practices we've seen significant hair loss in a majority of patients receiving sacituzumab.

Dr. Chalasani:
Great. Thank you. That was so insightful and, you know, just very practical information for our audience too.

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Hope Rugo about the TROPiCS-02 trial for hormone receptor-positive/HER2- breast cancer.

So one thing, Dr. Rugo, especially with the DESTINY studies coming in and with the T-DXd getting approved, if you were to translate TROPiCS-02 study results into a clinical practice, could you comment a bit about the use of one ADC after another and how would you kind of strategize those?

Dr. Rugo:
Absolutely. Of course, that's the big topic on everybody's minds now.

So the question is where do we use now we have a wealth of riches in an area where we really were our wealth of riches was focused on endocrine therapy and targeted agents prior to this point. I think that in patients who have hormone-receptor positive, HER2-low disease, T-DXd is the standard of care in the second-line setting improving progression-free and overall survival. In patients who have HER2-zero disease, we would use sacituzumab and maybe move it up to the, you know, right after the second line or in some cases in the right patient in the second line, uh, rather than waiting until the third line to start the drug. In patients who have hormone-receptor positive, HER2-low disease who received T-DXd we're very interested in the sequential efficacy of sacituzumab, and I think I've already had several patients receive sequential drug. And one of my colleagues said we should try something else in between so they're not back-to-back, and other people have asked about the rationale of sequential treatment, but I think that what's important to keep in mind is the antibodies are quite different that are the delivery mechanism of the payload, the toxin that's attached to the antibody drug conjugate, and the payloads, although they are both topoisomerase inhibitors, they very different drugs. Once you've given sacituzumab to a patient with HER2-zero disease, we know, based on recent published data, that the tumor might become HER2-low over time. Then I would consider using trastuzumab deruxtecan in sequence after sacituzumab with an intervening agent or not.

In triple-negative breast cancer, it's a little bit harder because we have a big phase III trial with the ASCENT trial, so I tend to lean on giving sacituzumab first, but I would use T-DXd in sequence if patients have HER2-low, triple-negative breast cancer.

Dr. Chalasani:
Great. Thank you. So, as we look into the future with all these novel therapies, what do you believe might be the next steps for research about these ADCs? And where do we go from here?

Dr. Rugo:
Well, of course there's a million studies going on now, and they're in some ways going to step on each other's toes so, but, you know, we want the best for our patients, so as long as we can put all this data together, we're going to be really a massive step forward. So there's DESTINY-Breast06, which is testing trastuzumab deruxtecan against chemotherapy of physician choice in the first-line hormone-receptor positive setting. Sacituzumab is being studied in the first-line setting in triple-negative breast cancer both with and without pembrolizumab depending on PD-L1 status, and trastuzumab deruxtecan is also being studied in combination with immunotherapy. There is data from the BEGONIA trial from a single arm with under 30 patients. And then sacituzumab will be tested in a first-line trial in hormone-receptor positive breast cancer. And there are two ongoing phase III trials with datopotamab deruxtecan, a Trop-2 antibody drug conjugate, same toxin, but a new Trop-2 antibody, and that's being studied in the second- and third-line setting in hormone-receptor positive disease and in the first-line setting in triple-negative breast cancer with a small cohort of patients who don't have access to PD-L1 inhibitors who can join on to the trial.

There are neoadjuvant and postneoadjuvant trials that are either planned or ongoing with both of the ADCs that have approval in one

setting or another, sacituzumab and trastuzumab deruxtecan, and it will be fascinating to see how these drugs work.

So you can just hear from that alone which really hasn't even delved into the world of HER2-positive disease that there are a huge number of trials ongoing, and really what we're looking to is to move these agents earlier in the course of therapy; and, of course, our ultimate goal is to cure more women with breast cancer.

Dr. Chalasani:
Great. Thank you. Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Hope Rugo, for sharing her insights on the TROPiCS-02 trial for hormone-receptor positive, HER2-negative breast cancer. Dr. Rugo, thanks for this great discussion today.

Dr. Rugo:
Thank you for inviting me and for your great questions.

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