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Poster Pearl: Sacituzumab Govitecan for HR+/HER2- mBC Boosts PFS and OS

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:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss a poster presented at the 2023 San Antonio Breast Cancer Symposium that examined clinical outcomes by age subgroups in the phase three TROPiCS-02 study of sacituzumab/govitecan in patients with HR-positive HER2-negative metastatic breast cancer is study author Dr. Hope Rugo. She's 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, welcome to the program.

Dr. Rugo:
Thank you so much for having me.

Dr. Turck:
Let's just dive right in, Dr. Rugo. What was the objective of this post-hoc analysis, and what methods did you employ to achieve that goal?

Dr. Rugo:
Well, so for this analysis specifically, our goal was to look at the clinical outcomes by age subgroups of patients who were treated with sacituzumab/govitecan, the TROP2 ADC, versus treatment of physician choice, in which over 50 percent of the patients received the chemotherapy drug eribulin.

In patients who had metastatic HR-positive HER2-negative breast cancer who had received at least 2 but not more than 4 lines of chemotherapy for metastatic disease, the median lines of chemotherapy we've already shown in TROPiCS-02 was 3 lines. So just to clarify the patient population, because I think that's so important when we're thinking about age differentiation, patients had HR-positive disease, so they had to have received at least 1 line of endocrine therapy. But relatively unique at the time, TROPiCS-02 required that all patients had received a CDK4/6 inhibitor, which of course now is a standard.

The primary outcome of this study was progression-free survival with secondary outcomes, including the kinds of safety analyses that this poster represented, and of course overall survival. Data previously presented and published has shown that sacituzumab improved progression-free and overall survival compared to treatment of physician's choice with a statistically significant and clinically important difference favoring sacituzumab.

Dr. Turck:
And could you share any other details about the kinds of patients who were included in this analysis?

Dr. Rugo:
One of the interesting things about this trial population is that in the population as a whole, almost all patients have visceral metastases. So it tells us a lot about the natural history of this disease, and we're seeing that with CDK4/6 inhibitors and with more endocrine therapy options, more patients are starting chemotherapy with visceral metastases. And in this case, more than 90 percent of patients

had visceral metastases.

In this trial, the total number of patients who were randomized was 543, so about 270-ish patients to each arm; the majority of patients were under the age of 65. We had 73 patients who received sacituzumab and 67 patients who received treatment of physician's choice who were 65 years or older.

And just additional factors about that, there were more comorbidities. When we look at four or more pre-existing comorbidities, between 80 to 90 percent of patients who are 65 years or older fit that criteria, where it was about 75 percent in the younger women. So a modest increase, and about half as many patients had 1 to 3 comorbidities. So it's just sort of pushed towards a higher risk subgroup of patients.

Dr. Turck:
So, Dr. Rugo, now that we know more about the patients enrolled in this study, let's zero in on the results of the post-hoc analysis. Starting with efficacy, what did you find in each age subgroup?

Dr. Rugo:
Well, as we expected and as has been shown in some other trials looking at our new agents, we saw that the progression-free survival benefit was maintained in patients who were 65-years or older compared to those who were younger. And that was really encouraging. The hazard ratio for the younger population was 0.69, and the hazard ratio for the older patients was 0.59 for progression-free survival by blinded independent central review. But the median progression-free survival went from 3.5 to 6.7 months by medians in the 65 years or older group. And I think that that's clinically meaningful and important for our patients.

As I mentioned earlier, sacituzumab improved overall survival compared to treatment of physician choice in the intent to treat population with a difference that was statistically significant. When we looked at patients based on age, with the same caveats of the smaller numbers in the older age population, we saw that the results were almost identical. So the hazard ratio for the younger patients was 0.81. It was 0.8 for the women who were 65 years or older, and the median difference in overall survival was actually even greater in the older population, albeit a smaller subset of the total population with a difference of well over 4 months. So we saw a difference of about 4.8 months in the absolute difference in medians between sacituzumab and TPC in these older patients.

And then we also looked at the other endpoints that we evaluated in TROPiCS-02 in terms of overall response, clinical benefit rate, and median duration of response, and in these populations, we also saw that patients benefited more from sacituzumab than TPC in all of those three endpoints, and the odds ratios were all very favorable and similar between the two age groups. So this was really, I think, encouraging data because this efficacy data is impacted by toxicity as well. And so the fact that patients were able to get enough drug to have these clinically important improved outcomes was, I think, very important data.

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 a post-hoc analysis of the TROPiCS-02 study looking at sacituzumab/govitecan in patients with HR-positive HER2-negative metastatic breast cancer.

Well, speaking of toxicity, what can you tell us about safety? How common were treatment-emergent adverse events in each subgroup?

Dr. Rugo:
So the toxicity of sacituzumab overall is well known, with the most common toxicities being neutropenia and diarrhea, with some impact on polymorphisms in UGT1A1 similar to irinotecan, the parent compound of the payload, which is SN-38.

So looking at the differences in toxicity in these patients by age can make a big difference in both our patient education and our prophylactic and management strategies. So let's do a deeper dive and look at the most common toxicities and how these might have varied by age.

So if we look at neutropenia, curiously—because this is not true with the CDK4/6 inhibitors where clearly there's more neutropenia in older patients—there was really no difference in the neutropenia based on age. So overall, any-grade neutropenia was 65 percent for sacituzumab in the younger patients and 56 percent in the older populations, again with the caveat of the smaller numbers. What about grade 3 or greater, where we actually have to treat patients with growth factors? In the younger patients, about 54 percent; in the older patients, 44 percent. So that was great. I mean, there's really no difference in neutropenia at all, so we don't have to prophylax simply because of age. We should use our strategies in prophylaxis based on prior neutropenia, avoiding delay in treatment, and then the use of growth factors in the most recent prior chemotherapy treatment.

Nausea, which is the next most common toxicity at about 60 percent any-grade in the younger patients and 56 percent in the older patients, is really not difficult to manage with sacituzumab. We use a triple-dug preventative regimen, which is incredibly effective. It's

short-lived and occasionally my patients will take a few days of very low-dose olanzapine at bedtime, which can curl that nausea that can occur in day 2 and 3 without the constipation or other toxicities of some of our other drugs. So I find nausea very easy to control and, again, very rare to be anything more than grade 1 or 2.

But the other toxicity which patients can see—they can't see neutropenia—and feel is diarrhea. So that's a really important toxicity to evaluate for our patients. In fact, diarrhea was increased in the older patient population. If we look at any grade diarrhea: 57 percent for the younger patients, 75 percent for the older patients, and then Grade 3, which is very bothersome or greater for patients, was about double in the patients 65 years or older, so 8 to 17 percent. So one of the ways that we deal with this is anti-propulsive and antidiarrheal agents. But another way we deal with it is by reducing the dose.

Dr. Turck:
Now the third aspect this post-hoc analysis focused on was quality of life. So what do we need to know about what you found there?

Dr. Rugo:
It's a really important endpoint, and these are patient-reported outcomes where we're looking at time to deterioration, or TTD, compared to treatment of physician choice. And overall, we found that in global health status quality of life that sacituzumab had a significantly longer time to deterioration compared to treatment of physician choice. When we broke it down into the different domains and looked at it by age, what we saw was that sacituzumab favored the treatment of physician choice in patients who were less than 65 for fatigue, which I think is really important for these patients. Otherwise, it was relatively similar.

If we looked at the patients in both age groups, we saw a numeric improvement in global health status quality of life in both age subgroups. And again, in the global when you combine everything, it was significant and for pain in the 65 year or older subgroup. Again, this has to do with collecting information, how long patients stay on study, etc. But I think it definitely shows that there's no worse quality of life or shorter time to deterioration with sacituzumab, and in some of these areas, sacituzumab was favored over TPC likely because of the longer time to disease progression, so important areas such as pain and fatigue.

Dr. Turck:
And if we bring all this together before we close, Dr. Rugo, what conclusions can we draw from these findings?

Dr. Rugo:
Well, I think that one conclusion is that it's really important for us to look at differences by age. I mean, this is just really important as we're dealing with patients of all age groups and wanting the best outcome for all of our patients. We saw a benefit in progression-free survival, overall survival, overall response, and clinical benefit rate with sacituzumab compared to treatment and physician choice, even though more than 50 percent of patients received eribulin or the previous gold standard in this setting, regardless of age in patients who had HR-positive HER2-negative heavily pretreated metastatic breast cancer. Older patients, as we would expect, had higher ECOG performance scores and, as I mentioned earlier, more pre-existing comorbidities. But we did see similar rates overall of treatment-emergent adverse events with a little increase in diarrhea, in particular, in our older patients. There was better efficacy in patients who received a higher relative dose intensity in our younger patients, and it wasn't really clear in the patients who were 65 years or older.

In terms of patient reported outcomes, we did see improvements, and numerically in the global health status quality of life, we saw a longer time to deterioration in the younger patients for fatigue and longer time to deterioration for pain in the older patients. So I think that we learn a lot from these analyses. We can take it back to clinic in order to provide optimal treatment for our patients, and I think that this shows a favorable risk benefit profile for sacituzumab in this patient population.

Dr. Turck:
Well, with those conclusions in mind, I want to thank my guest, Dr. Hope Rugo, for joining me to discuss the findings from a post-hoc analysis of the Phase 3 TROPiCS-02 study of sacituzumab/govitecan in patients with HR-positive HER2-negative metastatic breast cancer. Dr. Rugo, it was wonderful having you on the program.

Dr. Rugo:
Thank you very much for having me.

Announcer:
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