Clinical Updates from San Antonio:

HER2- Advanced Breast Cancer – Heavily Pretreated Patients

Rahul Gosain, MD: Good evening, everyone. I am Rahul Gosain.

Rohit Gosain, MD: And I'm Rohit Gosain.

Rahul Gosain, MD: And we are Oncology Brothers. Today we would like to welcome our friend, mentor, patient advocate, and importantly, a renowned breast medical oncologist, Dr. Stephanie Graff, where Dr. Graff will focus on clinically relevant studies presented at SABCS 2022.

The first study looks at low-dose tamoxifen. Then the other two studies will look at the data for elacestrant and capivasertib, and, then last, sacituzumab as we eagerly await its approval in hormone receptor-positive breast cancer patients. Without further ado, let us welcome Dr. Graff.

Stephanie Graff, MD, FACP: Thanks so much for having me. I think that's an overly generous introduction. I'm excited to be here talking about this with you guys.

Rohit Gosain, MD: Thank you so much for joining us, Dr. Graff. Let us start off with our first study, TAM-01 or babytam. Looking at low-dose tamoxifen in noninvasive breast cancer patients. Can you please walk us through the study and its findings.

Stephanie Graff, MD, FACP: Yeah, I think first the babytam, I call it babytam – you can call it low-dose tam or TAM-01. Babytam was a trial that was accrued outside of the US, and patients were randomized to 5 milligrams of tamoxifen versus placebo. Obviously, the standard is 20 milligrams, so this was a nontraditional trial, which is part of why it was outside of the US. And patients were either eligible if they had ductal carcinoma in situ that was estrogen

receptor-positive or a high-risk breast lesion, which was defined as atypical ductal hyperplasia or lobular carcinoma in situ.

And just over 50% of the patients, I think 70% of the patients had ductal carcinoma in situ, so it's very easy to take this data and apply it to a DCIS patient population. And what we saw was that patients that got babytam, as compared to tamoxifen, had a significant reduction in the rate of breast events, which included both local recurrences, same side ipsilateral breast events, contralateral new breast events, including second events of ductal carcinoma in situ, as well as invasive events.

And all of those reductions are exactly why patients take these medicines. But perhaps more strikingly compared to the historical situation with tamoxifen, the side effects were much better tolerated. Patients had less hot flashes. The rate of the scary things that we think about with tamoxifen was a little bit lower than what's been reported.

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And so back in 2018, when we got the initial follow-up, which was the five-year follow-up on this study, both the ASCO, American Society of Clinical Oncology, and the United States Preventative Task Force – USPSTF – I always struggle to get those letters out – went ahead and recommended adding it to their preventative guidelines; and the NCCN said that it was a reasonable consideration if patients were either unwilling to take regular tam (tamoxifen) or unable to tolerate regular tam.

And so now this is the 10-year follow-up, and all of those benefits persist, which I think means that we can all feel really comfortable offering this in our regular practice. Now I still recommend 20 because the data's a little bit stronger. But just like that NCCN guideline that if

somebody doesn't tolerate it or had a lot of side effects, I think the threshold to drop down to the 5-milligram dosing is very reasonable.

Rohit Gosain, MD: Now, diving into our second important study, EMERALD, a Phase III study looking at an oral selective estrogen receptor degrader, commonly known as SERDs; can you please walk us through this study and its recent updates.

Stephanie Graff, MD, FACP: Yes, so the EMERALD study was a Phase III trial using elacestrant; and elacestrant is one of the new-generation SERDs. It's oral and so it's competing with fulvestrant. So patients were randomized to either elacestrant or fulvestrant, and we've seen in trial after trial that after progression on a CDK4/6 inhibitor, fulvestrant just isn't getting really long durable responses. And you, of course, see that in your clinical practice all the time.

So, trying to do better than fulvestrant has been an exciting next step. These patients that were enrolled in the EMERALD study, not all of them had previously had a CDK4/6 inhibitor. About 70% had previously had a CDK4/6 inhibitor. And so they updated this result by looking at the number of patients that had, how they had progressed based on the length of time that they had taken a CDK4/6 inhibitor at the time of progression.

And what they're trying to tease out is who was still hormone sensitive, and how do the CDK4/6 inhibitors change our endocrine resistance? And so they ended up just using timepoints. Six months of CDK4/6 inhibitor, 12 months of CDK4/6 inhibitor, 18 months of CDK4/6 inhibitors. And what we saw was that with all of those, the duration of response to elacestrant got longer and longer.

So for patients that were only on CDK4/6 inhibitors for 6 months, they were on elacestrant for 2.7. For patients that were on CDK4/6 inhibitor for 12 months, they stayed on elacestrant for

3.7 months. And for patients that had been on CDK4/6 inhibitor for 18 months, they ended up being able to stay on elacestrant for 5.4 months; and that compares to patients that received fulvestrant who in the 6- and 12-month arms were both only on for 1.9 months, and in the 18-month arm were on for 3.3 months. So in every definition, elacestrant outperformed fulvestrant. But the more duration of benefit you got from a CDK4/6 inhibitor, the more duration of benefit you got from elacestrant.

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Rohit Gosain, MD: Exciting times with these new SERDs continue to change the paradigm here. What are the common toxicity one should keep in mind when treating patients with elacestrant?

Stephanie Graff, MD, FACP: So, unfortunately, elacestrant does have quite a bit of GI toxicity, in particular nausea, which is something that I think is going to be a barrier. Because, I mean, again, comparing to fulvestrant, we know that fulvestrant is very well tolerated. I mean, yes, it's a shot, which nobody loves; and you have to physically come into the office for it. But compared to potentially having nausea, even disruptive nausea or nausea that needs additional medicines, that's not great for our patients either.

So, I think I still am interested to see in the SERD space what power these medicines bring when they're combined with CDK4/6 inhibitors, which is I think where we're going. As monotherapy, they're just not this earth-shattering, standing ovation sort of conference moment that we're all always waiting for.

And the other thing that I'll mention is there was a poster presentation that looked at all the SERDs. It actually was very elegant, compared about ten SERDs to how well they target ESR1

(estrogen receptor 1) mutations, which are, obviously, something that we're thinking about when we're thinking about patients that are endocrine resistant.

And elacestrant didn't perform very well, actually, in an ESR1 mutation population, particularly in the Y537 mutation population, which is that, you know, "bad" ESR1 mutation that we all think about. And so it'll be interesting to see what happens. Elacestrant is out ahead of the pack just in terms of timeline, but I'm still sort of waiting to see all of the other SERDs develop and also see what happens in the approval landscape about how these drugs start to come out of the gate.

Rahul Gosain, MD: And Dr. Graff, as we were hoping for more combination studies, this is a good segue into the next study, a combination study for AKT inhibitor with an approved SERD, fulvestrant, CAPitello-291.

Stephanie Graff, MD, FACP: Yes.

Rahul Gosain, MD: Can you please walk us through this study and its findings.

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Stephanie Graff, MD, FACP: Yes. So capivasertib is an AKT inhibitor, and it is from the Phase III CAPitello-291 trial. It combines patients with capivasertib in combination with fulvestrant versus placebo and fulvestrant, and it took patients with hormone receptor-positive metastatic breast cancer and randomized them 1:1. The overall survival data is still not mature, but those curves are divided and separating. And the progression-free survival was statistically significant with the fulvestrant arm having a progression-free survival of 3.6 months and the capivasertib arm having a progression-free survival of 7.2 months.

You know, I think there's a lot of questions about what will happen with this drug and how it combines with other agents. Capivasertib also causes GI toxicity though. Shockingly, the rate of Grade 1 diarrhea was 70%. The rate of Grade 3 diarrhea was only 9%. I don't know that 9% deserves an only in front of it, and about 20% of patients also developed a rash on the drug. So it does also have some significant toxicities to contend with. This was a trial that will, you know, they'll continue to follow for some additional maturity; but I think that we can expect to continue to see more out of this drug.

Rohit Gosain, MD: If a patient with PIK3CA mutation, do you foresee us using capivasertib, or do you think alpelisib will remain, in fact, the standard of care?

Stephanie Graff, MD, FACP: I think that we don't have an approval yet, so right now we still have alpelisib as our standard of care.

You know, I think that we need to be careful about selecting based on the genomics that were included in the trials and making sure that we're very carefully matching because, I mean, each of these, although they're acting on that same pathway, had very subtle differences in terms of which medicines were included, or which mutations were included. And that's what I would say is that we should be very data-driven in how we select patients for their drugs.

Rohit Gosain, MD: Certainly. Thank you for that.

Now if a patient has, in fact, exhausted their endocrine treatment options and have gone through a few lines of chemotherapy as well, considering their next line and option, we have exciting data from TROPiCS-2 for sacituzumab govitecan. Dr. Graff, can you please share your thoughts on the recent data presented on the overall survival for the study?

Stephanie Graff, MD, FACP: Yeah, I think that the TROPiCS-2 data is, you know, so we got a TROPiCS-2 update that was an update from what we had seen at ASCO 2022. And the TROPiCS-2 data looked at patients with hormone receptor-positive breast cancer who had received at least a prior CDK4/6 inhibitor and a prior taxane. Patients were eligible if they had had two to four prior lines of chemotherapy in the metastatic setting. So this, again, is a pretty heavily pretreated patient population.

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And then they were randomized to receive sacituzumab or treatment of physician's choice, which could include eribulin, vinorelbine, capecitabine, or gemcitabine. And this update gave us the overall survival which showed a difference between treatment of physicians' choice at 11.2 months and sacituzumab govitecan at 14.4 months, which is a hazard ratio of 0.79.

I feel like on the heels of the trastuzumab deruxtecan story, that a lot of people are disappointed with that result. But I would say that hormone receptor-positive metastatic breast cancer, as it is now, hormone, endocrine therapy resistant, and at least in second-line or beyond chemotherapy just isn't going to get this amazing, robust response in the same way that a mixed population earlier phase treatment population might. And so, you know, anything that advances us forward in terms of overall survival is a win for patients.

Sacituzumab govitecan in the hormone receptor-positive population has the same toxicity that we all are well familiar with in the triple-negative population, including things like myelosuppression and diarrhea, that obviously we have to watch for really carefully.

Sacituzumab govitecan, again, you all know, is a Trop2 antibody-drug conjugate. They did also update us at this meeting on the differences based on response to level of Trop2 in the biopsy

specimen; and there is no difference, which is what we've seen in countless sacituzumab or Trop2 trials across the board. So I lovingly call this “imprecision medicine,” when we have a target, and the target doesn't matter, which is really sort of what's happening with sacituzumab. But it just seems like a really smart way to deliver chemotherapy to a population of patients with high-risk disease.

Rahul Gosain, MD: And honestly, Dr. Graff, I think it's a blessing in disguise, given there's so much discordance we're seeing in HER2. Now in the community, if we start chasing Trop2 at the levels, I really think we'll be struggling a lot. So from the community oncology perspective, I'm glad that we saw benefit all across.

Stephanie Graff, MD, FACP: Yeah, I agree. I completely agree.

Rahul Gosain, MD: You brought up some side effects, myelosuppression, GI toxicity, and you said it's approved in triple-negative breast cancer. It's also approved in bladder cancer. Can you share some of the clinical pearls that you use in your clinic to manage this toxicity?

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Stephanie Graff, MD, FACP: So with sacituzumab govitecan, I mean I think that dose reduction and dose hold is going to be your friends; and I would not be afraid to use them. I like to point out to people that in the package insert, the dose reduction of sacituzumab govitecan is dramatic. It's a 25% dose reduction for your first dose reduction. And a further 25% dose reduction, so a total of a 50% dose reduction with your second dose reduction, and I feel like when I went through my fellowship and training, that often we were doing 10 and 15% dose reductions. And so it feels like every time I do the math and dose reduce someone, I'm like, "Oh, that's a big drop in their dose." And it's the right way to do it.

So don't be afraid of dose reducing. I think that just really spending time on the front side to educate the patient about the side effects and toxicities and monitoring for them is important. I mean, often what I will tell patients is just how important that early alerting me to the diarrhea is so that I know that it's happening and get the patient in early. If they have diarrhea in your infusion center, you would manage it acutely, but at home, they would just be taking Imodium (loperamide). You don't want your patients to get dehydrated because that's only going to kind of accelerate your set of problems.

And I find that patients sometimes feel like diarrhea is somehow good. Like they're "getting" it out of their system. Right, I hear all sorts of crazy things from my patients. So I always take the time to say, "It is not okay with me. If you're having diarrhea, you have to call," so that they know that that's something that we as their medical oncologists want to hear about.

Rohit Gosain, MD: Well thanks for all those tips and tricks for managing these patients. This field continues to change by the minute. Exciting data. We saw from babytam as well as story of oral SERDs is still evolving. We are eagerly waiting on more mature data on AKT inhibitors. And then, of course, we will be looking out for sacituzumab approval.

Dr. Graff, thank you so much for taking the time to go over all these clinically relevant studies from San Antonio Breast Cancer Symposium with us today.

Stephanie Graff, MD, FACP: Thanks for having me.