Clinical Updates from San Antonio:

Triple-Negative Breast Cancer – Neoadjuvant/Adjuvant Immunotherapy

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

Rohit Gosain, MD: And I am Rohit Gosain.

Rahul Gosain, MD: And we are oncology brothers. After ESMO 2022 highlights, we're thrilled to have Dr. Maryam Lustberg back with us to cover SABCS 2022. With Dr. Lustberg, we're hoping to take a deeper dive into the data recently presented on KEYNOTE-522 for the triple negative disease at this breast cancer symposium.

Dr. Lustberg, thank you so much for joining us today.

Maryam Lustberg, MD, MPH: Thank you so much for having me.

Rohit Gosain, MD: Dr. Lustberg, pembrolizumab with chemotherapy was approved last year in neoadjuvant settings for triple negative breast cancer patients. Today, we would like to focus on real-world data analysis off this regimen. Can you first walk us through the study design for KEYNOTE-522 and share the patient population you would consider utilizing this patient in?

Maryam Lustberg, MD, MPH: Yes, absolutely. KEYNOTE-522 was practice changing and it included patients with clinical Stage II or Stage III triple negative breast cancer. They were randomized 2:1 in favor of a pembrolizumab chemo-containing regimen. The chemo consisted of carboplatinum plus paclitaxel in combination with pembro for 12 weeks followed by epirubicin-cyclophosphamide administered every 3 weeks for a total of 12 weeks in combination with pembrolizumab as well, and the placebo arm contained the same chemo regimens without pembrolizumab. Patients after this 24-week regimen then continued to have surgery, and after surgery, the intervention arm continued with nine

cycles of pembrolizumab administered every 3 weeks, where the placebo group did not receive immunotherapy.

It's important to know that in the real world many of us are using doxorubicin-cyclophosphamide, the well-known AC regimen, and many of us are giving it in the dose dense fashion every 2 weeks instead of the every 3 weeks dosing that was done in the study, so you can shave off. That portion becomes 8 weeks instead of the 12 weeks, so you save about 4 weeks there.

It's important to reevaluate adrenal status with a baseline cortisol level prior to surgery for patients receiving KEYNOTE-522 because incidents of adrenal crisis have been reported for patients who went to surgery because of the pembrolizumab-induced adrenal insufficiency. So just wanted to reemphasize to check cortisol levels prior to surgery.

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Rohit Gosain, MD: Thanks for walking us through that design. And, again, to what you stated, it is very important to reiterate that PD-L1 score does not matter in neoadjuvant setting, however, it is extremely important in metastatic triple negative breast cancer patient population.

Now coming back to KEYNOTE-522, have you noted any key differences between real-world analysis and the actual study?

Maryam Lustberg, MD, MPH: Patients who enroll in clinical trials are often younger, fitter, have much less chronic medical comorbidities, so the three real-world data abstracts that were presented in San Antonio this year really show a patient population that tends to be less fit. They may have additional medical comorbidities just like the patients that the viewers may be more routinely seeing in the practice.

Rahul Gosain, MD: And, Dr. Lustberg, cytopenia continues to be a common side effects with this regimen. Any clinical pearls on how you would manage this in your practice, especially when these patients are getting weekly treatments?

Maryam Lustberg, MD, MPH: Yes. This is a really important question because with weekly regimens, obviously, we're very restricted in terms of using the long-acting growth factor agents. In the study, it's important to remind the viewers that carboplatinum dosing was given in two different regimens. It was actually left to the discretion of the treating physician. So you could either give carboplatinum in a weekly, lower AUC (area under the curve) weekly regimen versus a three-week dosing in combination with a weekly paclitaxel.

I think what we have noticed kind of as a community of breast cancer oncologists treating patients on KEYNOTE-522 is that the weekly carboplatinum dosing with the AUC of 1.5 to 2 tends to be much better tolerated in terms of cytopenias.

Now to your point, as these real-world data suggest, neutropenia rates are high, however, I think with the weekly dosing of carbo (carboplatinum), it tends to be improved. Certain patients who are otherwise doing well, because this is in the curative setting, I think many of us do make the argument that in order to try to maintain the dose intensity as much as possible, we could potentially incorporate a few days of G-CSF (granulocyte colony stimulating factor) therapy for patients that need it in order to be able deliver the doses that we need to deliver.

The second suggestion is that we are used to, in the United States, typically starting with the AC regimen, or the doxorubicin-cyclophosphamide regimen. With many of these regimens, the flip regimen, just like they did in the study, tends to work a little bit better in terms of cytopenias. So starting with a carbo-Taxol and pembro regimen first and then moving onto the anthracycline regimen where then you

could deliver in a dose dense fashion your long-acting growth factor agents. So just doing that flip tends to also help.

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Rohit Gosain, MD: Now sticking with the toxicity theme, have you seen more toxicity related with immunotherapy when combined with epirubicin or doxorubicin, especially from cardiac standpoint?

Maryam Lustberg, MD, MPH: As you know, the immune-related myocarditis and cardiomyopathies are extremely life-threatening. It's something that we need to be very vigilant about. The rates tend to be very low, and these abstracts also confirm that; that in terms of actual immune-related cardio myocarditis the rates are low, but it's important to be vigilant about it. So, obviously, baseline echo and at any suspicion of any increased cardiovascular symptoms, really having a low threshold for repeating cardiac imaging and really getting cardiology involved at the earliest onset of suspicion is important because they can be associated with high mortality.

Rohit Gosain, MD: Certainly, something to keep in mind. As we wait on long-term data, at this time, path CR (pathologic complete response) is it truly the best predictive marker?

Maryam Lustberg, MD, MPH: It's the best predictive marker that we have. Particularly, I think, in triple negative breast cancer, it has permitted us to really bring into use some of these novel agents, where if we had to certainly wait for long-term overall survival data, I think these agents would have been less available for our patients. So I do agree in principle that pathological complete response is an early way to screen the activity of promising agents.

However, ultimately, for us to continue to use these agents, then, of course, we need to confirm long-term safety as well as long-term disease outcomes which should include overall survival. So I think it's

good initially where we can give our patients the best treatments that we currently have available data for, but, ultimately, I do think survival data is more important than path CR, but it just needs more time for us to obtain that data.

Rohit Gosain, MD: If a patient has had, in fact, a path CR, do you think we are overtreating some of this patient population by continuing pembrolizumab for complete a year time?

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Maryam Lustberg, MD, MPH: The continuation of pembrolizumab for those additional cycles for patients who have achieved a complete path CR is how the study was designed. But you're absolutely right, multiple breast investigators are questioning whether that is needed or not. So there are actually additional studies that are being planned, including one by Alliance Clinical Trials to be led by Dr. Sara Tolaney, where patients who have had a complete path CR are randomized to continuing with pembro, as was done in KEYNOTE-522, versus not receiving anything at all.

So until we have those data, my overall approach would be that unless patients are having serious adverse events, that I would follow the regimen as was outlined in KEYNOTE-522, but it's very much possible in the next few years that landscape would very much change.

Rahul Gosain, MD: And, Dr. Lustberg, on completely different side, if a patient has residual disease, would you add capecitabine or a PARP inhibitor in a patient with germline mutation in combination with pembrolizumab?

Maryam Lustberg, MD, MPH: Wonderful question, and this is where this was not done in KEYNOTE-522. However, as a community of breast specialists, we strongly recommend that we do kind of extrapolate to other data for this very high-risk population. As we all know, patients with residual disease after

essentially a very intensive, multiagent, 24-week regimen of chemotherapy, if they have residual disease, their chances of developing distant metastatic incurable triple negative breast cancer is quite high. So I think, for that reason, many of us are for patients who do not have a germline *BRCA* alteration, and they do have residual disease, we're combining capecitabine based on the CREATE-X published data that they are getting adjuvant capecitabine in combination with pembro.

The viewers may rightfully ask, "Well do we have safety data for such a combination?" And I will share with you that those safety data do exist in the metastatic breast population, and we've been able to safely continue, you know, both capecitabine and pembro (pembrolizumab). So I do strongly recommend that at least six to eight cycles of adjuvant capecitabine are considered in this high-risk triple negative breast population with residual disease.

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For patients who do have a germline BRCA alteration, the results from the randomized OlympiAD study were so strong and associated with an overall survival advantage that, in that population, since we have a very targeted pathway, I do absolutely recommend combining olaparib with pembro in that population. I would not do all three together. We have no safety for that combination, but certainly olaparib can be safely combined with pembro so patients are getting the benefit of continuing the KEYNOTE-pembro regimen but also being prescribed the OlympiAD olaparib regimen for that approval. And the safety data for that combination also comes from previous combination studies in the metastatic breast cancer setting.

Rahul Gosain, MD: Well perfect. Thank you for sharing those thoughts. But how long would you continue capecitabine or a PARP inhibitor with hope to complete a year of pembrolizumab?

Maryam Lustberg, MD, MPH: So I would do the nine cycles of pembrolizumab per KEYNOTE-522. The CREATE-X study had capecitabine being administered for eight cycles in that standard two week on, one week regimen. In the United States population, the dose that is better tolerated is the 1000 milligram per meter squared BID (twice daily) dosing, 14 days on, 1 week off. So some patients may not be able to tolerate eight cycles, so for some of those patients, we may need to certainly dose reduce or terminate a little early. But if we were going strictly by the CREATE-X study, it would be preferable to do the eight cycles. So, roughly, the capecitabine and the pembro would go together. Roughly, the capecitabine may end a little earlier.

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In terms of the olaparib, the dosing and the duration would be per the OlympiAD study for the one-year duration, so that will extend a little beyond the duration of the pembro.

Rahul Gosain, MD: And, Dr. Lustberg, if a patient was to progress on maintenance immunotherapy, what will be your second-line treatment? Would you continue with IO and add chemotherapy if a patient was high PD-L1, or switch to another agent completely?

Maryam Lustberg, MD, MPH: Essentially, a patient who is recurring or progressing within the first year of essentially a very intensive chemotherapy immunotherapy regimen, these are our most aggressive basal types of triple negative breast cancer. And not to be super nihilistic about it, but these are the patients that actually very little agents right now actually work on.

So it's a little bit of a data-free zone. However, in my opinion, if they have recently progressed on immunotherapy, I'm not sure I necessarily would change the chemotherapy backbone in that setting. I think you're going to have differences of opinion. I think what this population would need is actually

antibody drug conjugate therapy. So I think in this situation, I think sacituzumab, or Trodelvy, would be the optimal agent, in my opinion, or a clinical trial.

I think there is an opportunity also to relook at the biomarkers, as you suggested. But in addition to the PD-L status, I think what would be most instructive would be what the HER2 status is. And if they're HER2-low, this may be also a population where we may consider trastuzumab-deruxtecan, or Enhertu.

Rohit Gosain, MD: Certainly exciting times. Dr. Lustberg, thank you so much for taking the time to discuss these real-world updates from San Antonio Breast Cancer Symposium.

To summarize, chemotherapy and immunotherapy combinations regardless of PD-L1 score remains the current standard of care for locally advanced triple negative breast cancer patients in neoadjuvant settings.

Thank you so much again, Dr. Lustberg.

Maryam Lustberg, MD, MPH: Thank you for having me and for the excellent questions.