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Evidence-Based Treatment Decisions in Metastatic Triple-Negative Breast Cancer

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Gilead Sciences, Incorporated. Here's your host, Dr. Alexandria May.

Dr. May:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and today I'm joined by Dr. Neil Iyengar to discuss how we can better align our first-line treatment decisions in metastatic triple-negative breast cancer with emerging data and evolving guidelines. He's the Director of the Cancer Survivorship Program and Co-Director of the Breast Medical Oncology Program at Winship Cancer Institute at Emory University.

Dr. Iyengar, thanks for being here today.

Dr. Iyengar:
Thank you for having me, Dr. May. It's a pleasure.

Dr. May:
For some background, the NCCN Version 3.2026 guidelines have introduced important updates to first-line treatment in metastatic triple-negative breast cancer, including new preferred options and clearer stratification by PD-L1 status. With that in mind, Dr. Iyengar, can you walk us through what you see as the most important updates to these guidelines and what these changes mean for how first-line treatment decisions are made?

Dr. Iyengar:
Absolutely. So I think this is a general trend in the way that guidelines, and specifically NCCN guidelines, are being updated with a much more biomarker-driven approach. So specific to the first-line setting in metastatic triple-negative breast cancer, as you mentioned, we now see stratification by PD-L1 status, specifically using the CPS score, with a score of 10 or greater counting as PD-L1-positive and a score of less than 10 counting as PD-L1-negative.

And this is really driving whether or not we're combining treatment with immunotherapy in the first-line setting. It's nuanced, of course, because we have data supporting the combination of immunotherapy with some therapies, and we don't yet have phase 3 data for the combination of immunotherapy with other therapies. So we're no longer in a world of just chemotherapy as an option. So this decision based on biomarker status, and specifically PD-L1 status, is not only important for that immunotherapy decision, but it's also important for the cytotoxic partner, whether that's chemotherapy or an antibody-drug conjugate.

And finally, we also see that germline BRCA status is included in the updated NCCN guidelines to help guide first-line treatment decision-making.

Dr. May:
So for patients who are PD-L1 eligible, in light of the newer first-line options now reflected in the guidelines, how are you approaching treatment decisions, and what factors guide how you select among these therapies?

Dr. Iyengar:
I think for that population, we now know from several trials that the use of immune checkpoint inhibition, specifically pembrolizumab, is the preferred treatment approach. Now, what has evolved over time, as I mentioned earlier, is the appropriate cytotoxic partner with the immune checkpoint inhibition. Historically, based on the KEYNOTE-355 trial, this was a standard chemotherapy combination with

pembrolizumab that demonstrated improvements in both progression-free survival as well as overall survival compared to chemotherapy alone. However, we now have data from the ASCENT-04 trial that demonstrates improvement in progression-free survival for the combination of sacituzumab govitecan, an antibody-drug conjugate, with pembrolizumab versus chemotherapy with pembrolizumab.

So I would say with this update, we have sacituzumab govitecan plus pembrolizumab as a preferred option in the first-line treatment of PD-L1-positive metastatic triple-negative breast cancer.

Dr. May:
And for patients who are PD-L1 ineligible, how have the new first-line recommendations influenced your therapeutic approach?

Dr. Iyengar:
This is where we have more treatment options at the current moment. Of course, the data are rapidly evolving, but in this space, again, historically, we have standard chemotherapy options, but we've now seen at least two phase 3 clinical trials demonstrating an improvement in progression-free survival with the use of an antibody-drug conjugate versus standard chemotherapy. So we have the ASCENT 03 trial demonstrating improvement in PFS with the use of sacituzumab govitecan over standard chemotherapy, as well as the TROPION-Breast02 trial demonstrating the superiority of datopotamab deruxtecan versus standard chemotherapy for extending progression-free survival. But I will mention that in the PD-L1 ineligible population, this is where we can differentiate by germline BRCA status. And for our patients who do have germline BRCA alterations, we may want to consider a PARP inhibitor in this setting as well.

Dr. May:
Now, with multiple new preferred first-line options in metastatic triple-negative breast cancer, how do differences in trial design shape the way you interpret the evidence and select among these new therapies?

Dr. Iyengar:
I think that if we look at trial design, including eligibility criteria, this helps to guide treatment selection in the clinical setting. Certainly, PD-L1 status is critical for treatment selection, as we've discussed. But we also know that there are differences in trial design, for example, in terms of eligibility criteria. So the ASCENT-03 trial, for example, with sacituzumab govitecan included patients who had at least six months or more since their curative intent treatment, including any prior anti-PD-L1 therapy, whereas the TROPION-Breast02 trial included that population of more rapid progressors, although this tends to be a less common scenario.

Now, the other key trial design feature to keep in mind is that the ASCENT-04 and 03 trials included crossover. Sacituzumab govitecan, in the US and in several other countries, is already approved for use in triple-negative breast cancer in the second-line setting and beyond.

So the trials were designed with an ethical trial design which provided sacituzumab govitecan to patients after they came off of the study treatment if they were enrolled in the control arm. This is important because it was ethically the right thing to do in the conduct of these trials, but from a scientific perspective, it really makes it difficult to interpret longer-term endpoints like overall survival, for example. So I think that when we are looking at those types of endpoints in the ASCENT trials, we need to be very cognizant of that crossover trial design and look to the primary endpoint—progression-free survival—and some of the surrogates of longer-term outcomes, like duration of response as well as progression-free survival 2, or PFS2.

In addition to that, the control arms in the various trials also differ. For example, in the ASCENT trials—03 and 04—the control arm included the possibility of giving doublet chemotherapy with carboplatin platinum-based doublet chemotherapy, which we know can have a significant response rate. And, in fact, about half of patients in the control arm for both trials, ASCENT-03 and 04, received doublet chemotherapy, whereas in the TROPION-Breast02 trial, only single-agent chemotherapy was allowed. So this is going to have an impact on the delta difference in response rates between the intervention arm, the antibody-drug conjugate, versus the standard chemotherapy arm with the ASCENT trials allowing doublet chemotherapy and the TROPION-Breast02 only allowing single-agent chemotherapy.

Ultimately, I think this is important to keep in mind for treatment selection because these trial design differences did impact several of the endpoints.

Dr. May:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Neil Iyengar about how we can incorporate emerging data and guideline updates into the first-line treatment of metastatic triple-negative breast cancer.

So Dr. Iyengar, how should community oncologists think about incorporating these treatment options into practice today?

Dr. Iyengar:
I think it's important that, of course, we stay up-to-date with our practice. And so in this landscape of rapidly emerging new data and

therapeutics, we're pushed to rapidly adapt our clinical practice. Fortunately, we've been using many of these biomarkers already. PD-L1 status is not a new concept in breast cancer. And so I think it is important that practicing oncologists are implementing a biomarker-driven approach. We need to be obtaining tissue samples and biopsies at the time of metastatic diagnosis and testing for PD-L1 status. This is typically done through immunohistochemistry. There are some commercial panels that are available that are primarily known for next-generation sequencing but also do immunohistochemistry, which you can actually expedite or request expedited results. So this is important testing to be doing upfront. Of course, germline genetic testing is also critical to do for treatment selection with regard to the PARP inhibitor choice. So that's where I would start—making sure that we're implementing biomarker testing to drive treatment decision-making.

And then ultimately, we're in a place right now where we actually have treatment options to discuss with our patients with triple-negative breast cancer. This is an area where we've typically had limited treatment options, so it's really wonderful to be able to have different treatment options where we can use some practical features in addition to the biomarker-driven approach to guide treatment selection.

For example, the different therapeutic options, of course, have different adverse effect profiles. We need to use prophylaxis—eye drops and mouthwash—for datopotamab deruxtecan. We need to use growth factor—G-CSF—for sacituzumab govitecan, and oftentimes diarrhea management needs to be implemented there as well. So there are differences in AE profiles. There are differences in prophylactic measures that may practically impact the choice for our patients.

There are differences in schedule. Sacituzumab govitecan is given on a day one, day eight basis every 21 days, whereas datopotamab deruxtecan is given every three weeks. So these have practical implications for treatment selection, and I think we're at a place now where we as oncologists can look at the preferred agent from an efficacy standpoint, but perhaps even more so from the standpoint of tolerability for our patients given their prior responses or reactions to treatment for breast cancer, as well as practical measures in terms of choosing a treatment that works for our patient.

Dr. May:
As we approach the end of our program, Dr. Iyengar, what are the most important practical takeaways for community oncologists making first-line treatment decisions in metastatic triple-negative breast cancer?

Dr. Iyengar:
I think one of the largest challenges right now is, how do we rapidly implement into our clinical workflows all of the new data that are coming out so quickly? It seems that when we implement a new strategy in clinical practice, we are now all of a sudden having to change that approach because there's a new data set that has been released.

So my advice there, and what I think is really critical is that the biomarker-driven approach is something that is likely here to stay for the long term. So I think it is a good investment upfront to change our clinical workflows, if it's not been done already, to use biomarker testing in the upfront setting and to implement this in an efficient way.We are going to have even more options coming down the pipeline in the first-line setting for all biomarker categories. And so starting off by implementing biomarker testing, I think, is going to be critical.

And secondarily, I would say training all of our clinical team—the nurses and the PharmDs, many of whom are involved in the day-to-day management of adverse effects—because the AE profiles, as we've been discussing, are really quite distinct between these treatment options.

And being proactive is going to make the implementation and tolerability of these treatments far superior than trying to be reactive.

So ultimately, I would say implement a biomarker testing strategy upfront that will serve us well now and in the future, and continued training for AE management, not only for ourselves as oncologists, but for all of our staff.

Dr. May:
With those key takeaways in mind, I want to thank my guest, Dr. Neil Iyengar, for joining me to explore what the emerging evidence and guideline updates mean for the first-line treatment of metastatic triple-negative breast cancer.

Dr. Iyengar, it was great having you on the program.

Dr. Iyengar:
Thank you for having me.

Announcer:
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