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Case Consult: First-Line Treatment in Metastatic TNBC Ineligible for Immunotherapy

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Dr. Cortés:
Dear friends and dear colleagues, welcome. This is CE with GLC. I'm Dr. Javier Cortés.

Dr. Traina:
And hi there, I'm Dr. Tiffany Traina. So let's start our discussion today with a case. This is a 25-year-old young woman with a germline BRCA1 mutation, and she was diagnosed with a left breast triple-negative breast cancer, ER 0, PR 0, HER2 0, that actually had inflammatory features, so clinically T4N3 disease. And she received neoadjuvant KEYNOTE-522 and went on to bilateral mastectomy and had a very complex closure and a lymphovenous bypass at the time, and unfortunately had a significant amount of residual disease, multifocal 2- to 3-mm disease in a tumor bed greater than 8 cm, and 7 positive lymph nodes out of 20 removed.

So she went on to complete post-mastectomy radiation. She continued her adjuvant pembrolizumab, and she started adjuvant olaparib after radiation was complete.

And unfortunately, about 3 months after beginning her olaparib, she developed progressive back pain and a persistent cough that just was worsening over time. And a CAT scan at the time showed really suspicious lesions for metastatic disease to the bone, to the liver, and a large mediastinal mass that was actually causing airway compression and driving the cough.

Biopsy of that mediastinal adenopathy confirmed triple-negative breast cancer that was HER2 0, and PD-L1 testing was negative with a CPS of less than 10. So she had rather urgent radiation to the large mediastinal mass that was causing her airway compression, and following that she began datopotamab deruxtecan with denosumab for her bone metastases.

So I'm wondering, Dr. Cortés, if you could share, how do you decide whether a patient might be eligible for immunotherapy or checkpoint inhibitor?

Dr. Cortés:
Thanks, Tiffany. I think that we have obvious answers here and some others that may be a little bit controversial, of course. If a patient has a tumor which does not express PD-L1, these are tumors that, to the best of our knowledge today, seem not to benefit from immunotherapy. We discovered, we showed in the KEYNOTE-355 that when the expression was 10 according to the CPS score or higher, these patients benefited from pembrolizumab-based therapy.

However, when these tumors were in the range of 1 to 9 and, of course, lower than 1, these tumors did not benefit from PD-1. So I think that the cutoff of CPS 10 or more, I think, is reasonable to first discriminate who might benefit from pembrolizumab or not. Of course, patients who have comorbidities or specific contraindication for immunotherapy, obviously these patients are not being able to receive either pembro or atezolizumab.

But there is a third situation where, in my opinion, could be much more difficult. What happens to those patients who either received immune checkpoint inhibitors in the early breast cancer, as the patient you commented on, or those patients who did receive chemotherapy and they have a very, very short treatment-free interval, let's say lower than 6 months? These patients were not included in the KEYNOTE-355, and these patients were included in IMpassion132 with atezolizumab, and this trial failed to demonstrate an improvement. So we don't have any data suggesting that in this patient population immunotherapy might help.

So I think that these 3 situations, a situation where immune checkpoint inhibitors maybe are not adequate. And I want to maybe add something here. I don't know, Tiffany, how you foresee, how would you treat a patient who received immunotherapy according to the KEYNOTE-522 and experienced progressive disease later, let's say 1 to 3 years? Do you think that makes sense to revisit immunotherapy there? Or because they received or should receive pembrolizumab, we don't have more data afterwards? So I don't know if you can add any comments here.

Dr. Traina:
Right. Terrific. I agree with your comments around scenarios 1, 2, and 3 of use of checkpoint inhibitor. In this case that you're describing, with a long disease-free interval in a patient that had a PD-L1-positive tumor, in the absence of data that there would not be benefit, I'm inclined to rechallenge, because historically these patients in the first-line setting have done quite poorly with metastatic triple-negative breast cancer, so I would be inclined to re-challenge with such a long disease-free interval.

This is where I'm hoping real-world evidence will be able to inform some of these decisions while we await prospective trials. We've seen TROPION-Breast02, ASCENT-03, ASCENT-04—all of these trials were conducted at a time when there were very few patients progressing following KEYNOTE-522, and so it's hard to draw any conclusions from those current first-line metastatic trials that are reporting out that are really so practice changing. So in the absence of prospective data and real-world data, I think we're just trying to use our best judgment possible.

Dr. Cortés:
I could not agree more with you, Tiffany.

So, unfortunately, we don't have much time, but I want to ask you something, Dr. Traina. Tiffany, how do you select first-line therapy for patients who are not candidates for immunotherapy?

Dr. Traina:
Yeah, wonderful and very timely question, as we're seeing many trials report out here and change guidelines and FDA approvals for first-line treatment. I think that from both TROPION-Breast02 and ASCENT-03 we have seen that antibody-drug conjugates against TROP2 are really superior to traditional chemotherapy. So for the most part I think that our choice in the first-line setting is going to be an ADC.

And then factors that I consider are things like overall survival, progression-free survival, and really response rate, right? Having high response rates from antibody-drug conjugates in patients that have a large burden of symptoms coming from their cancer argues all the more to use the antibody-drug conjugate over traditional chemotherapy, and we can get into data in some of the conversations we have a little bit later.

So, obviously, efficacy balanced by toxicity, and what are patient preferences? What are our treatment goals here? Logistics around scheduling. I would love to see that my patients are spending less time in the doctor's office, less time in an infusion unit, less time traveling back and forth to clinics where, in many parts of the country and globally, patients travel hours to get to their infusion site.

So I think it is a balance of high efficacy, choosing those agents that will prolong survival, reduce symptom burden from disease, have high quality of life that we're seeing in patient-reported outcomes, and really engaging our patients in that decision-making.

Dr. Cortés:
I couldn't agree more. I think that you made very important comments, and you started with something which is critical, is that in general, for the great majority of our patients, ADCs should be considered as the optimal approach. Of course, we can never say 100%, 0%, but for sure, for the great majority, we have 2 great drugs today, hopefully early into the market, that will help us through this patient.

And you also agree there are different toxicity profiles among them. The schedule, preference by the patient, of course, always very, very important. Sometimes we forget that they should make the final decision with all the data on their hands, and also the time in the hospital is very important.

And unfortunately, that's something that we have said before, is that many patients will be unable to receive a subsequent line of

therapy. That's why the better, the earlier.

And I would like to finish with maybe one comment that is also important. We need more follow-up. It is the tail of the Kaplan-Meier curves, which mean that we have always median PFS, but there are a number of patients, maybe 20%, 25%, 30%, I don't know, that can survive very long with the great drugs we are starting to have.

So I think that all these aspects highlight the role of antibody-drug conjugates, and this is great. We need more. We need better drugs. We need to understand the combinations, maybe in the future combining those drugs with immune checkpoint inhibitors. I don't know, but certainly that's something that is terrific.

I don't know if you want to add maybe a final comment, Tiffany?

Dr. Traina:
Happy to. I think it's such an exciting time for us and for our patients with advanced triple-negative breast cancer that we have these terrific options, and we're seeing ADCs finally move up earlier into the treatment landscape.

Dr. Cortés:
Dr. Traina, Tiffany, it has been a great pleasure being with you today. With that, I think that our time is up. We hope this quick case review is helpful. Thank you very much for listening.

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