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Emerging Considerations in Triple-Negative Breast Cancer: Focus on Immunotherapy

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Dr. Mencia:
Not only is triple negative breast cancer associated with a poor prognosis and short survival, but its management has been challenging due to the significant toxicities of standard chemotherapy and a lack of proven targeted therapies. Fortunately, recent clinical trials looking at immunotherapy-based combination approaches are showing promise and are changing the standard of care for patients with TNBC.

This is CME on ReachMD, and I'm Dr. William Mencia. Joining me to discuss the potential role of immunotherapy in patients with triple negative breast cancer are Dr. Sara Hurvitz and Dr. Tiffany Traina. Dr. Hurvitz is a medical oncologist at UCLA Health's integrative breast cancer practice and high-risk breast cancer clinic, and Dr. Traina is [Clinical Director of Breast Medicine Service at the Memorial Sloan Kettering Cancer Center].

Welcome to you both.

Dr. Hurvitz:
Hi there. I'm really happy to be here. Thanks for having me.

Dr. Traina:
Hi. I'm looking forward to our time together.

Dr. Mencia:

Dr. Traina, up until now we've been defining triple negative breast cancer by what it's lacking, namely lacking the presence of HER2, estrogen receptor or progesterone receptor. However, we are seeing more and more data emerging regarding the molecular heterogeneity of these types of cancer. What can you tell us about the molecular heterogeneity of these tumors, and as we continue to learn more about this, what are the implications of these findings in terms of treatment?

Dr. Traina:
I think that's a great question. We've been defining this class of cancers based on what it's lacking, and I think what we're going to see in the coming years instead is defining advanced breast cancer by what its important driver is. So, I think, for the time being, there are really three main classifications that we consider for the discussion of what is triple-negative breast cancer. One being it's important to know a patient's germline BRCA mutation status. The second category that I think would be very important is to understand tumor somatic gene alterations that a cancer may have to explain what its drivers are, and third, an area that is still very much in research, would be to try to understand the presence of the androgen receptor in triple-negative breast cancer, as there is a small subset of TNBC which may have a very luminal signature and a hormonal expression profile associated with it. So, if we take those in order, a patient's germline BRCA mutation status is an actionable piece of information to have today, and that's as a result of two trials that have led to the FDA approval of PARP inhibitors for women with HER2-normal, germline BRCA1 or 2-associated advanced breast cancer, where we've seen progression-free survival with drugs like olaparib and talazoparib on the order of about 40-50% improved over treatment of physician's choice for women who have a triple-negative breast cancer associated with a germline BRCA1 or 2 pathogenic mutation. Outside of germline mutations, somatic tumor mutations that may be actionable include those in the PI3-kinase, AKT or PTEN pathways, and there have been two interesting phase 2 studies looking at AKT inhibitors in the first-line setting for patients with metastatic triple-negative breast cancer that have alterations in these pathways, and there are ongoing phase 3 studies looking at two of those agents, ipatasertib and capivasertib. And then, lastly, I would touch on another interesting agent that is related to NTRK mutations in basket – in a Basket Study, looking at many solid tumors, both pediatric and adult. Now, these mutations are rare in breast cancer. They account for less than a percent. However, in the study, and in a series that looked at thousands of advanced breast cancer tumors, although less than 1% have these NTRK mutations, about two-thirds of those were triple-negative breast cancers, and so I think this is yet another thing we need on our radar to understand what is the molecular driver of this breast cancer, and triple-negative breast cancer, in and of itself, is, I think, a poor definition that we will see evolve over the next few years.

Dr. Mencia:
So, to help focus our discussion, let's contextualize these concepts in the form of a typical clinical scenario. MB is a 35-year-old, African-American woman who has been diagnosed with metastatic triple negative breast cancer. She has sentinel node involvement and scans show lesions on her liver. Dr. Hurvitz, in the past we would be considering chemotherapy. But with what we know about the molecular heterogeneity of TNBC, what additional testing would you recommend?

Dr. Hurvitz:
Yes, clearly, for this 35-year-old woman, I think that she deserves to have both BRCA1 and 2 germline testing performed as well as have her tumor-immune cells tested for PD-L1 expression. This is because we have the availability now of two targeted agents for these situations respectively. PARP inhibitors, if she's a carrier of a germline BRCA mutation, and atezolizumab in combination with taxane if she is found to have tumor-immune cell positivity for PD-L1. So, all of my patients in the front-line setting with triple-negative metastatic breast cancer will have both of these tests done. In terms of PD-L1 testing, it's a little bit complicated and it bears taking a bit of time to explain that when we send out the tumor test, we need to make sure that we are requesting tumor immune cell PD-L1 expression, using the SP142 assay. This is important because I've seen patients in my practice who've been told by their oncologist, you don't have tumor PD-L1 positivity, so you're not a candidate for atezolizumab, but they didn't have the tumor immune cells tested, it was just the tumor or a different antibody was used. And so, I think we have to make sure that the lab we are using utilizes the correct probe and also is testing the tumor immune cells so that we don't miss patients who might be a good candidate for immune therapy. The other point I'd bring up is that PD-L1 testing I'm doing not only in the frontline patients but also later-line patients. Now, atezolizumab was evaluated in the Impassion 130 study in the front-line settings. So, if we're following the

way the clinical trial was done, we would use atezolizumab in the front-line setting. That said, there are a number of clinical trials ongoing for patients who have tumor immune cells showing PD-L1 positivity or tumor positivity, so I do think that testing our patients and knowing what their tumor is like is important as we are putting together our plans for treatment, not only now but in the future.

Dr. Traina:
And there is some differential PD-L1 expression in sight of metastatic disease where organs like lymph nodes, soft tissue, breast, appear to have higher PD-L1 expression, but in organs such as the liver may have much lower representation of PD-L1 positivity. Also, it's difficult, if not impossible, to do the PD-L1 testing on a fine needle aspirate or a bone biopsy. So, being aware of that may also help guide what location we would biopsy for PD-L1 testing.

Dr. Hurvitz:
I think those are great points that you've brought up, Tiffany, and I think it's also a really exciting time because we're now beginning to see new data emerge in the curative setting. The KEYNOTE-173 trial was a six-cohort neoadjuvant study where patients received pembrolizumab with a variety of different chemotherapy combinations, either taxane alone followed by anthracycline, or taxane platinum followed by anthracycline-based therapy, and a pathologic complete response rate in that study was around 60%. Of course, as we've seen in multiple neoadjuvant trials of triple-negative breast cancer, those patients who achieved a pathologic complete response had the best event-free survival. And then, most recently, at ESMO 2019, the results of the KEYNOTE-522 trial were presented by Dr. Schmid, showing that the addition of pembrolizumab to taxane platinum followed by AC or EC neoadjuvant chemotherapy led to a significantly improved pathologic complete response rate compared to those who did not have immune therapy. What is surprising is in contrast to the data in IMpassion in the metastatic setting where the benefit was pretty much exclusively seen in those with tumor PD-L1 positive expression, in the KEYNOTE-522 with pembrolizumab, the benefits, or the objective response rate improvement was seen regardless of whether the tumor was PD-L1 positive. So, this brings up a question. Should we, or will we, be using pembrolizumab for those patients regardless of PD-L1 expression, and will there be a regulatory approval of this agent in the curative setting soon? The event-free survival were too early to show a difference, but it was trending in the right direction, so I'm personally very intrigued by these data but also hope that we will have biomarkers that will help inform where these agents should be used. I'm not yet convinced that it should be every patient with triple-negative breast cancer, but it might be for some of these immune checkpoint inhibitors.

Dr. Mencia:
Dr. Hurvitz, you mentioned KEYNOTE-522 earlier, and you've both brought up IMpassion 130, and the possibilities of using immunotherapy regardless of PD-L1 status. So if we add some additional parameters to our patient's tumor, and we make MB's TNBC PD-L1 negative. Based on what we know today, how would you approach treatment planning if her tumor was PD-L1 negative?

Dr. Hurvitz:
This is a really good question to ask because the only data that we have to support the use of immune therapy as standard of care in metastatic triple-negative breast cancer comes from the IMpassion 130 study, and in that clinical trial, the progression-free survival trended toward a benefit in the intent-to-treat population, but was statistically significant only in the PD-L1 positive population. Moreover, while the overall survival did not show a statistically significant improvement in the intent-to-treat population, the P-value was about 0.07, and the benefit with atezolizumab was only around two months. In the PD-L1 positive population, you now see a highly statistically significant improvement in overall survival on the order of seven months. So, I think if my patient is tested and her tumor is clearly PD-L1 negative, I would not recommend atezolizumab for her. Although this is a therapy that is tolerated reasonably well, there are serious adverse events that are immune related that need to be considered, and so I wouldn't use this in an off-label approach in a patient without PD-L1 expression. Instead, I would, again, look for BRCA- or 2 mutation in this young woman with triple-negative breast cancer and offer her a PARP inhibitor if she has a germ-line mutation. I would consider doing Next generation sequencing to look for the rarer mutations, microsatellite instability, or mismatch repair deficiency, which would indicate that a drug such as pembrolizumab might be useful. PIK3CA mutation, if I saw that, I would be interested in referring her for a clinical trial of the PI3-kinase inhibitor, and as Tiffany mentioned earlier, NTRK mutation, which is rare, but if it's seen, we now have the ability of a

targeted agent. So, clinical trials would be my approach to move forward, and sometimes we can't find a clinical trial for our patient, in which case I would utilize chemotherapy.

Dr. Mencia:
Let's come back to our patient, MB. Dr. Traina, let's change the parameters of this case one more time, and in this scenario let's say that her tumor is both BRCA and PL-L1 positive? What factors would you take into consideration in determining first-line therapy and how would you recommend sequencing therapy appropriately here between the PARP inhibitors and immunotherapy?

Dr. Traina:
That's a fantastic conundrum to have, to have more than one biomarker with a targeted therapy that's predicted to be of benefit. The short answer is we don't know just yet. What we can glean from the IMpassion data is that there were about 7% of patients that had both co-expression of PD-L1 and either a BRCA1 or BRCA2 mutation, and in the IMpassion trial, BRCA alteration had no predictive value for the addition of atezolizumab. So, clearly, the benefit of atezo comes from having PD-L1 positive expression by SP142. So, what we're faced with is data from IMpassion that would suggest using a checkpoint inhibitor in the first-line setting might have an overall survival advantage in the PD-L1 positive subset. Recall Sarah just mentioned that the overall survival difference – the magnitude was about seven months, although that did not have the statistical power to show significance. On the other hand, we have data from the OlympiAD and EMBRACA trials showing a benefit from PARP inhibitors in the setting of medium progression-free survival prolongation. There was a presentation at AACR a year ago by Mark Robson showing in the subset of patients on the OlympiAD study who were treated with olaparib in the first-line setting, there appeared to be an overall survival advantage. So, we're stuck with balancing compelling evidence to use both of these agents in the first-line setting, and what I'd love to see shortly are the results of trials looking at the combination of PARP inhibitors and checkpoint inhibitors. So, rather than needing to choose one over the other, perhaps we'll see the greatest benefit coming from these doublets in a chemotherapy-free approach. Today, though, with the data we have, I think this is a very personalized discussion.

Dr. Mencia:
Those are great messages for our audience to keep in mind as we wrap up our discussion today, and I'd like to thank my guests, Drs. Sara Hurvitz and Tiffany Traina for helping us better understand the emerging role of immunotherapies in triple negative breast cancer.

It was great speaking with both of you today.

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