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Released: 02/05/2025
Valid until: 02/05/2026
Time needed to complete: 15 Minutes

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Virtual Tumor Board: Maximizing the Potential of Immuno-Oncology in Early TNBC Through Personalized Care

Announcer:
Welcome to CME on ReachMD. This activity, titled “Virtual Tumor Board: Maximizing the Potential of Immuno-Oncology in Early TNBC Through Personalized Care” is provided by TotalCME.

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Dr. McArthur:
Hello. My name is Heather McArthur, and I'm the clinical director of the Breast Cancer Program at UT Southwestern in Dallas, Texas. And I’m joined today by my friend and colleague, Dr. Margaret, or Maggie, Gatti-Mays. She's associate professor at Ohio State University. And today we're talking about immunotherapy for early-stage triple-negative breast cancer.

So welcome, Dr. Gatti-Mays. And let’s start with a case.It’s a 32-year-old woman who palpated a mass in her left breast. She underwent imaging studies that revealed a 3-cm tumor in the left upper outer quadrant with no distant metastases on staging scans.An ultrasound-guided biopsy confirmed grade 3 node-negative triple-negative breast cancer with a Ki-67 of 50%.

Because of her young age and the triple-negative diagnosis, she went for genetic counseling and underwent testing with no deleterious mutations identified. She has excellent functional status and no contraindications to chemotherapy or immune therapy. She’s truly in perfect health.

So it’s a stage 2, so T2, N0, M0, triple-negative breast cancer. The FDA has approved the treatment of pembrolizumab together with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab for, quote/unquote, high-risk disease.

In your mind, Dr. Gatti-Mays, would this woman meet criteria for high-risk disease and why?

Dr. Gatti-Mays:
So in my opinion, yes, she would absolutely meet criteria for a high-risk breast cancer. In the KEYNOTE-522 clinical trial, in which patients with stage 2 and 3 were eligible for trial, patients with tumors that were greater than 2 cm and/or if there was involvement of a lymph node would have been eligible for that regimen. And so based upon that, I think she meets the high-risk definition and I would favor treating her with the KEYNOTE-522 regimen with neoadjuvant pembrolizumab and chemotherapy.

Dr. McArthur:
Just curious, what are you doing with your T1c N0 tumors? So 1.9 cm, let's say, node-negative tumor. Is that high risk in your mind?

Dr. Gatti-Mays:
So I think in those patients that have T1c tumors, especially when node negative, it often becomes a discussion with the patient and

consideration of other patient factors. Also, when thinking of T1c status of, really, 1.0 to 1.9 or 2.0 cm, I think sometimes for me it depends on how close they are to that cutoff. In that situation that you just mentioned of about 1.9 cm, I think with this younger patient, I probably would talk to her potentially about using the KEYNOTE-522 regimen as well. The NeoPACT clinical trial, which is not approved for current therapy, but in that clinical trial in which pembrolizumab was used along with docetaxel and carboplatin, they allowed for some smaller tumors. And so I think, again, we do see that in these tumors that probably are around 2 cm, that there would be the benefit to chemo and immunotherapy, and I would consider that patient high risk.

Dr. McArthur:
And do you have an age cutoff? So there can be a bimodal distribution of triple-negative breast cancer, and so an 80-year-old with a 2.5-cm node-negative tumor, is that someone who you're thinking about KEYNOTE-522 as well?

Dr. Gatti-Mays:
I tend to think of not just their numerical age but their physiologic age. I think, obviously, that's important when considering what's best for the patient. I do think just with how rigorous the KEYNOTE-522 regimen is sometimes, especially in patients over the age of 70, considering various factors for that patient. I think in an 80-something-year-old patient I would be a little bit hesitant to do it unless it was a very robust 80-year-old with great physiologic age. But I do think as we start to get into the elderly population, that benefit of chemotherapy does tend to be a little bit lower, and obviously the risks of toxicity are higher.

Dr. McArthur:
And I agree with you. The risk of recurrence, the peak risk of recurrence is within the first 2 to 3 years after early-stage diagnosis. So for someone who has good performance status and no major comorbid conditions, I think given the high risk within such an early period of time, I think that's reasonable. And just as a reminder, in KEYNOTE-522, we did actually enroll patients in their 80s. So that was at the upper limit of the baseline characteristics.

So we talked a little bit about the FDA approval for high-risk triple-negative breast cancer.What can you tell us about the NCCN guidance for chemoimmunotherapy in this setting?

Dr. Gatti-Mays:
Sure. So I think in terms of, again, kind of figuring out these higher-risk patient populations, it's very similar in terms of the size criteria. And so in these patients, again, kind of using the T2 criteria as the cutoff and/or node positivity would favor using the chemo and immunotherapy.

Dr. McArthur:
So we pointed out that we typically treat people who have stage 2 or 3 triple-negative breast cancer with some exceptions, depending on our definition of high risk. And as a reminder, in the KEYNOTE-522 study, 1,174 patients were enrolled and randomized 2:1 to receive chemotherapy with either pembrolizumab or placebo as concurrent therapy. And then, for those assigned to receive pembrolizumab, they continued to receive pembrolizumab in the adjuvant setting to complete a total 1 year.

It's a lot of chemotherapy that's administered in the regimen, and that was a very intentional decision because we didn't want people to question the results, stating that suboptimal therapy was being administered, so that was a very intentional decision to include carboplatin together with paclitaxel and then anthracycline with cyclophosphamide. The study, notably, was originally designed for a pathologic complete response primary endpoint, and during the course of the study, a decision was made to expand the study to allow for a co-primary endpoint of event-free survival, and that ended up being really a critical decision. It wouldn't have led to the FDA approval. And I'll just say that at that first analysis that we saw from this study, the addition of pembrolizumab to neoadjuvant chemotherapy improved pathologic complete rates by 14%. And it was agnostic of PD-L1 status, so you don't need to test for PD-L1 in this setting because it's beneficial for both the PD-L1-positive and PD-L1-negative subsets.

That 14% improvement did diminish over time with subsequent analyses to 9% at the next analysis and then 7.5% at the following analysis. So the FDA waited to see event-free survival data before they allowed the approval of the regimen. And we've since seen some pretty exciting follow-up from the study with event-free survival improvements at 5 years of 9% and at 5 years an overall survival advantage of 4.9%.So really solidifying this regimen as an important standard of care, a life-extending, life-improving standard of care for our high-risk patients.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Heather McArthur, and here with me today is Dr. Margaret Gatti-Mays. We're discussing the use of immune therapy for the perioperative treatment of early-stage triple-negative breast cancer.

We've had a number of other studies, Dr. Gatti-Mays reported, in this neoadjuvant space that have not led to FDA approvals. We've seen IMPASSION-031 looking at neoadjuvant chemotherapy plus or minus atezolizumab. We, just last week, saw results from the

GeparDouze study, which for me was a little disappointing. Interested to hear your view. And so I don't think that we're going to see a shift away from KEYNOTE-522 unless we see a different strategy in the neoadjuvant setting in the form of TROPION-Breast04.

So do you want to just provide a little color to how you're thinking about how the other studies performed in this space and what you're anticipating from the TROPION-Breast04 study, potentially?

Dr. Gatti-Mays:
Sure. So, Dr. McArthur, I absolutely agree. I mean, I think it has been very interesting, obviously, seeing the KEYNOTE-522 study be so encouraging, so positive, especially as we kind of tend to get further out from the initial trial and see more of the follow-up data, really seeing kind of that persistent benefit. I do think, as you mentioned, there's been several clinical trials that have been in this space, including some of the ones that you've mentioned, NeoTrip-PD-1, ETCTN10013, and several ISPY arms. And while there's been kind of some persistence in terms of the immunotherapy checkpoint inhibitor that's used, so a lot mostly focusing on PD-1, there's been variations in the chemotherapy backbone, in specifically how it's given. And so I do think in a tumor like breast cancer that we typically consider immunologically cold or maybe not as responsive, it's that combination, I think, the synergy, which really proves to lead to that clinical benefit. And so I think I agree with you. I think KEYNOTE-522, while it's a lot of chemo, we've seen that it's effective.

I am very excited to see TROPION-Breast04 results out in a couple of years. In that, datopotamab deruxtecan with durvalumab is given for 8 cycles in the neoadjuvant setting, and so I think very exciting to potentially shift away, maybe, from cytotoxic chemotherapies to some more of these antibody-drug conjugates, and potentially that may change the landscape.

But unless that trial, I think, is overwhelmingly positive, I think we'll be with KEYNOTE-522 for quite some time. And again, for good reason.

Dr. McArthur:
I'm the global PI for the TROPION-Breast04 study, and again, that's a study looking at antibody-drug conjugate Dato-DXd with durva going head-to-head against KEYNOTE-522, with the hope that it improves upon efficacy and maybe mitigates toxicity by doing away with the conventional chemotherapy backbone. So more to come on that.

It's an increasingly complicated world that we live in, Dr. Gatti-Mays. Four different chemotherapeutics to talk about now with our newly diagnosed patients who, of course, are frightened. And now we have to talk about immune therapy.We're a little bit spoiled here. I have a lot of protected time for my new visits to spend time talking through a lot of these issues with my patients. I have APPs in my practice who also sometimes do some of the toxicity profile discussions, and then I have a patient-facing pharmacist in my clinical group as well. So I'm a little bit spoiled in that regard.

How are you approaching shared decision-making in this increasingly complicated space?

Dr. Gatti-Mays:
Sure. So I think, just as you said, I really do feel like with this complicated regimen, it needs to be a multipronged approach with a multidisciplinary kind of support. In most of the new patient visits, when we're talking about this chemotherapy regimen, I think a lot of patients are overwhelmed, obviously, at the initial diagnosis of a breast cancer, and then talking about all of these agents, I think it's even more overwhelming. And so just making sure that talking to the patient using, obviously, terms that are appropriate for lay patients to understand in terms of the reason why we're using this and the ways in which we give the medications. I do think the counseling by the pharmacy team, and by the nurses as well, becomes very important to not only help communicate appropriately with the patients, but I think to reiterate a lot of what was said during that initial visit when the patient's overwhelmed.

Dr. McArthur:
I agree with all of that, Dr. Gatti-Mays.

And just as a reminder, in the KEYNOTE-522 experience, about 99% of patients treated with the chemotherapy/pembrolizumab combination had any-grade adverse events. So adverse events are common.The majority of the treatment-related adverse events were ascribed to the chemotherapy backbone, and it's a chemotherapy backbone that I think most providers are familiar with and feel comfortable managing. It's the added layer of the immune-related adverse events that takes a little bit more education with our patients and with our colleagues, including those in the emergency department, for example. Immune-related adverse events, the most common is hypothyroidism, so low thyroid in about 15%, hyperthyroidism in about 5%. But any body system can be affected, pituitary, adrenals, lungs, colon, etc., fortunately with an incidence rate of 3% or lower. But it does require very good communication and a low threshold for early intervention with steroids for all of the non-thyroid toxicities, and then thyroid-directed medications for the thyroid-mediated immune-related adverse events. And it also requires education, because although the majority of events occur in the neoadjuvant phase when immune therapy is being co-administered with chemotherapy, there have been case reports of delayed immune-related

adverse events, even a year after last exposure. And that's why this is not just a medical oncology challenge. Those patients might be following up with their surgeon or their radiation oncologist, and so we collectively have to have a low threshold for considering immune-related adverse events, even when a patient is off therapy.

So that's the overview of the incidence of immune-related adverse events. Dr. Gatti-Mays, what's your approach to treating immune-related adverse events?

Dr. Gatti-Mays:
So I think one of the key things with immune-related toxicities is really early identification and starting management.And so making sure that patients who are on pembrolizumab, I generally check their thyroid function periodically. Typically, every 6 to 9 weeks on therapy, making sure that prior to surgery they receive a random cortisol level to make sure that there's no signs of adrenal insufficiency. But really, making sure that you're attuned to these types of autoimmune reactions, making sure you know where the latest resources are.

Both NCCN Guidelines and ASCO are very appropriate, as are the Society for Immunotherapy of Cancer clinical practice guidelines. And so I think just being aware that these occur and making sure that you know where the resources are and engaging consultants early if needed.

Dr. McArthur:
We have incorporated the labs into our order sets for immune regimens, and that's been extremely helpful to prevent people from just forgetting to order them. And the point that you make about identifying adrenal issues prior to surgery is critically important because, of course, adrenal insufficiency identified during the course of surgery could be devastating. So thank you for those excellent recommendations.

Well, I really enjoyed this conversation, Dr. Gatti-Mays. But before we wrap up, can you share your one take-home message with our audience today?

Dr. Gatti-Mays:
Sure. I think in patients that have high-risk triple-negative breast cancer, using KEYNOTE-522 regimen with chemo and immunotherapy is very appropriate and is recommended, given the fact that we see improved pathologic complete responses with the addition of pembrolizumab to chemotherapy, improved 3-year event-free survival, and improved overall survival. And this benefit is seen in all patients irrespective of PD-L1 status.

Dr. McArthur:
Outstanding. Thank you so much. That’s all the time that we have for today, so I want to thank our audience for listening and thank you, Dr. Gatti-Mays, for joining me and for sharing your valuable insights. It was truly great speaking with you today. Thank you so much.

Dr. Gatti-Mays:
Thank you.

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