Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/the-emerging-role-of-immunotherapy-in-triple-negative-breast-cancer/13750/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Emerging Role of Immunotherapy in Triple-Negative Breast Cancer

Dr. Chalasani:
Immunotherapy is starting to make its way in breast cancer, especially triple-negative breast cancer. As oncologists it's imperative that we know how to identify patients with triple-negative breast cancer who may benefit from immunotherapy. And once we identify those patients, we also need to learn and minimize immune-related adverse events that patients may experience. That's why today we'll be discussing some key studies that may be setting the stage for this new treatment for the next decade.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about immunotherapy in triple-negative breast cancer is Dr. Nan Chen, an Assistant Professor of Medicine at the University of Chicago.

Dr. Chen, welcome to the program.

Dr. Chen:
Thank you so much for having me.

Dr. Chalasani:
So, to start us off, Dr. Chen, can you share how you approach testing in a patient, whose diagnosed with metastatic triple-negative breast cancer?

Dr. Chen:
So I think probably the most important thing from an immunotherapy perspective is to make sure that we get testing for PD-L1 as soon as we can. In the past we had two drug options and, unfortunately, two different tests, and so it was somewhat of a thought of which test to send or if you had enough tissue to send both, but currently, we only have one FDA-approved immunotherapy drug in this space, which is pembrolizumab, and thus, there is an accompanying test, which is the 22C3 test, and that is what I would recommend sending on all newly diagnosed metastatic triple-negative patients.

Dr. Chalasani:
So, can you tell us what the prevalence or the incidence of the positivity or the negativity in the triple-negative breast cancer?

Dr. Chen:
Yeah, absolutely. So in the KEYNOTE-355 trial, the positivity rate, which in triple-negative breast cancer is considered a combined positive score or a CPS of above 10, was about 40 percent.

Dr. Chalasani:
Okay, great. So once the testing is complete and we have a patient with a positive PD-L1 by CPS score, how do you approach that? What is the chemotherapy backbone you choose, or do you recommend single-agent immunotherapy? How do you approach the next steps?

Dr. Chen:
So in triple-negative breast cancer, we've seen that single-agent immunotherapy doesn't really have durable responses for the vast majority of patients, and thus, we need to pair it with a chemotherapy. There are three different chemotherapy partners that we can use. We can use paclitaxel, Abraxane, or carboplatin gemcitabine. In terms of which one to use, in the study all three of them did exhibit an improvement above chemo alone, and so it really is a little bit dealer's choice. In my personal practice, I like to think about what the patient received in the early-stage setting.

Certainly, there are some patients that are diagnosed with de novo metastatic disease, but if a patient received a taxane in the early-

stage setting and relapsed within the last 6 or 12 months from receiving their chemo, then I would probably choose carbo-gem over that just because it's a new type of chemo they haven't received. If it's a de novo patient, you know, all the options are there, but I tend to choose Abraxane over paclitaxel just for side effect profile purposes.

Dr. Chalasani:
So with that being said, like you mentioned, we had two FDA-approved drugs before, but now we have one. So, can we just like dive into those studies a little bit?

Dr. Chen:
Yeah. So the IMpassion130 study was a study of the drug atezolizumab in combination with Abraxane in patients with, again, PD-L1 positive metastatic triple-negative breast cancer. That study was a positive study, and it showed an improvement in progression-free survival in patients who received atezolizumab as opposed to a placebo. The IMpassion131 study was very similar. It's the same patient population, first-line metastatic triple-negative breast cancer. Instead of using Abraxane, they used paclitaxel. In addition to being different drugs, we give steroid premedication with paclitaxel because of the risk of infusion reactions, which we wouldn't typically do with Abraxane, and so that's another—and we know that steroids may have an effect sometimes on how our immunotherapy is efficacious, so that is another difference between the two trials. The IMpassion131 trial, unfortunately, was ultimately a negative trial, and so that certainly is different compared to what we saw with the pembrolizumab data in which both of these chemotherapies showed positive results.

Dr. Chalasani:
This is something we come across in the clinical maybe not as relevant as now, but again, like you were mentioning with the correlative studies, the overlap of PD-L1 positivity because the IMpassion used the SP142 whereas this one was the CC23, you know, the CPS one, so what was the overlap of positivity by both?

Dr. Chen:
So I think this brings up a really interesting point just about PD-L1 testing in breast cancer in general. Clearly, PD-L1 as a biomarker of benefit of immunotherapy is not super robust. We have patients that are with PD-L1 positivity that don't respond well, and we have patients with PD-L1 negativity who do respond well, so this is not the best biomarker we have. To complicate that, you know, you mentioned that there were two different tests that we were using to see, you know, whether patients were positive or not, the SP142 and the 22C3. The SP142 looked exclusively at immune cells whereas the 22C3 kind of looks both at PD-L1 expression on tumor and immune cells. And so in both studies there was actually about 40 percent of patients who were PD-L1 positive in their respective tests, but there have been other studies performed that show that these are not the same patients that we are capturing. There is some overlap, but there are also some patients who will be positive on one test and negative on another, and so clearly, the way that we are looking at PD-L1 expression needs some improvement.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking to Dr. Nan Chen about the role of immunotherapy in triple-negative breast cancer.

So maybe we'll switch gears a little bit to the early-stage, triple-negative breast cancer. So Dr. Chen, can you just give us a brief overview on the KEYNOTE study, which set the stage in the early-stage triple-negative breast cancer?

Dr. Chen:
So KEYNOTE-522 is a phase III randomized trial looking at the addition of pembrolizumab to a chemotherapy backbone. The chemotherapy backbone that was utilized was carboplatin, paclitaxel, followed by Adriamycin and cyclophosphamide, which is a pretty standard regimen that we are using, and they either added pembrolizumab to that combination or they got a placebo. In this study, patients with PD-L1 agnostic, meaning that patients with any PD-L1 expression, whether it was negative or positive, were able to go on the study. And actually, all patients, including PD-L1-negative patients, there seemed to be a benefit, which in this study was shown to be an improvement in the rate of pathological complete response, or what that means is that at the time of surgery there was no residual cancer disease left.

Dr. Chalasani:
Great. So, can you comment on the key findings for the study?

Dr. Chen:
Absolutely. So they found a path CR rate of about 65 percent, which is impressive. Previous studies within the incorporation of carboplatin showed path CR rates of around 50, so this was a significant improvement, and this is what they found in the study as well. Patients who achieved a path CR, whether you needed immunotherapy to get you there or whether chemotherapy alone would have

been enough, have very excellent responses. 95 percent of patients at three years did not have disease recurrence. If you did not have a path CR at the time of surgery, depending on how much residual disease you had left, you know, the more residual disease you have left the higher the chances are that your cancer would recur within three years. Certainly, the patients with the most residual disease left only had, disease-free rates of maybe 65 percent or so.

Dr. Chalasani:
So, I know to start on the study the tumors could be PD-L1 status agnostic for the study, but can you comment on the subsequent exploratory correlative studies when they did look at the expression for the PD-L1 biomarker?

Dr. Chen:
So they divided patients into three groups: PD-L1 positive with a CPS score greater than 10, PD-L1 intermediate I suppose with a score that was greater than one but not quite 10 and then PD-L1 negative where they saw no expression whatsoever on their assay, and all three groups did show an improvement in their rate of pathological complete response. And so PD-L1 in this early stage setting is really —doesn't predict response to, immunotherapy at all, and so all patients with stage II or stage III triple-negative breast cancer should be getting the five-drug regimen.

Dr. Chalasani:
So let's say in the patients, currently, based on the regimen, when you see a patient and you start them on the neoadjuvant regimen and subsequently, at the time of surgery, there's a determination of PCR or no pathological CR, but both groups you would still continue the pembrolizumab in the adjuvant setting?

Dr. Chen:
In both groups, according to the trial, they did continue the pembrolizumab, and in most of my patients I will do so. Certainly, for patients who had an immune-related AE or had issues with pembrolizumab and they did have a path CR, we consider not giving it to them adjuvantly because we know that, you know, whether or not they received immunotherapy neoadjuvantly, if you achieve a path CR, you have a really, really good chance of not having this cancer recur, and so there are currently deescalation trials looking at for these patients in a randomized setting do we really need the pembro. The answer is still out on that, and I think it remains a case-by-case basis with your patient.

Dr. Chalasani:
Oh, absolutely. So, if the patients have received pembrolizumab in the neoadjuvant or the adjuvant setting and if you do see a tumor recurrence, can you comment on the biomarker testing and use of immunotherapy in that setting?

Dr. Chen:
Yeah. I think that that is a tricky situation. I think some of that depends on the length of time between when they received the initial therapy and when their recurrence were. Certainly, for patients that are recurring within less than six months, it's unlikely that the addition of pembrolizumab is going to—in the metastatic setting is going to provide the progression-free survival that we saw, you know, in the KEYNOTE-355 or in that setting. I certainly think for patients that have a longer disease-free, interval, it still is worthwhile to check PD-L1 in the metastatic tissue, and if positive, you know, the standard of care would be to give it.

The metastatic triple-negative breast cancer setting is rife with excellent clinical trials for both PD-L1 positive and PD-L1 negative patients, and I really highly suggest all patients and clinicians refer patients to get access to these great clinical trials. We certainly are interested in patients that are PD-L1 negative to see if other ways of incorporating immunotherapy can give them a better response; and in patients that are refractory to their first-line or have progressed on their first-line of immunotherapy, are there other drug combinations we can try to make their cancer more sensitive.

Dr. Chalasani:
So, as you're looking towards the future, you know, can you give us a sense of what other you think as combinations for immunotherapyor other things, you know, where the whole field is headed?

Dr. Chen:
Yeah. I think there's two areas that we need to work on. Number one, in terms of our conversation earlier, we need better biomarkers to help us figure out exactly which of these patients should be receiving these therapies and which of these patients their cancers will be treated successfully with immunotherapy. So there is a lot of correlative work being done, with each of our clinical trials to better identify predictive biomarkers in addition to PD-L1 that we can use in the clinic to help us pick these patients out.

In a therapeutic setting, I think, you know, we're really trying to combine this with just about everything. You know, part of are why chemotherapy is thought to be an effective partner is that it increases our neoantigen presentation and thus gives our immune system more things to look at. I think that there are other avenues of immunotherapy beyond PD-1 or anti-PD-L1 inhibitors. There are LAG

inhibitors and TIM inhibitors and other targets that we haven't been looking at previously but are now looking at. So, can we combine anti-PD-1 with other targets to make our immunotherapy more effective? Can we give other targeted therapies that make our immune system more active, present more neoantigens, kind of combat some of those things in the tumor microenvironment?

Dr. Chalasani:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Nan Chen, for sharing her expertise with us today. Dr. Chen, it was great speaking with you.

Dr. Chen:
Thank you so much. Thank you for the opportunity.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/projectoncology where you can be Part of the Knowledge. Thanks for listening.