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

New Findings on Triple-Negative Breast Cancer Treatments

Announcer:
You're listening to a special focus on breast cancer from *Advances in Women's Health,* sponsored by Lilly.

Dr. Birnholz:
Coming to you from the European Society for Medical Oncology's Annual Congress in Barcelona, Spain, this is ReachMD. I'm Dr. Matt Birnholz. Joining me is Dr. Giuseppe Curigliano, Associate Professor of Medical Oncology at the University of Milan. Dr. Curigliano has been a true pioneer in early drug development research for breast cancer, serving as principal or co-investigator in several phase I and II clinical trials for biological, cytotoxic and immune modulator agents and will be applying some of those insights he has gained from these experiences towards today's topic on triple-negative breast cancer.

Dr. Curigliano, welcome to you.

Dr. Curigliano:
(Italian accent) So, good morning to everyone. It's my pleasure to be here and to discuss with you about news from ESMO 2019 on triple-negative breast cancer. As you will know, we are going to list in a few days to the data from the KEYNOTE-199 and the KEYNOTE-522 that are respectively 1 trial in the metastatic setting for triple-negative breast cancer and another trial in the neoadjuvant setting. So the real question is that: Does immunotherapy is really practice-changing and breakthrough in the context of triple-negative breast cancer? We have for sure 1 drug already approved, atezolizumab in combination with nab-paclitaxel for first-line, PD-L1, triple-negative metastatic breast cancer, and what we know from this trial is that in PD-L1-positive, so in a subpopulation of triple-negative, you have an improvement in progression-free survival and in overall survival, and these data have been confirmed in ASCO 2019.

Dr. Birnholz:
But much more dramatic in the overall survival category, is that right?

Dr. Curigliano:
Much more dramatic in overall survival category but just in the PD-L1 patient population that are 41% of triple-negative breast cancer. The question is whether pembrolizumab will replicate or not this data. You know, data will be presented in 2 days. What we know is that from the press release that is already available is that pembrolizumab improved survival in PD-L1-positive triple-negative breast cancer. As you know, the KEYNOTE-119 was a prospective randomized trial comparing pembrolizumab monotherapy versus chemotherapy of investigator choice, so in this trial we have a different way of drug development in which the immune checkpoint is used alone. And it's not surprising for me to know that we will see the benefit just in the PD-L1-positive population from the pembro monotherapy, because if we look at the previous data, it was quite clear that immune checkpoint as monotherapy can work just in highly selected population that can be PD-L1-positive or tumor-infiltrating lymphocyte positive.

But we will have also data from another trial. That is the KEYNOTE-522. This is a prospective randomized trial comparing chemotherapy in the neoadjuvant setting plus or minus pembrolizumab, so immune checkpoint plus chemotherapy, and the data are quite surprising because the addition of pembrolizumab increase the rate of pathological complete response from 48 to 58%, so there is really something new that is potentially practice-changing—because, as you know, Food and Drug Administration, if you demonstrate that the addition of an experimental agent increase PCR in the setting of triple-negative, this can potentially lead to the approval of this agent.

The surprise for me in this neoadjuvant setting is that the improvement is independent of the PD-L1 expression, so we have 2 different settings, the metastatic one and the neoadjuvant one, in which the benefit of pembrolizumab is not concentrated only in the PD-L1

population, specifically in the neoadjuvant setting.

Dr. Birnholz:
Now, Dr. Curigliano, does that imply that we have a gap in our knowledge base regarding the predicted biomarkers or the biology of triple-negative breast cancer to understand why that percentage difference exists independent of PD-L1?

Dr. Curigliano:
This is a huge gap. I completely agree with you. I don't know if, in the case of neoadjuvant trial, I am quite sure that chemotherapy that is given together with pembrolizumab may be willing to use a lot of immunogenic cell death with a lot of tumor-infiltrating lymphocytes that were coming in the tumor bed following exposure to chemotherapy, and since PD-L1 has been assessed at baseline, maybe we should check following exposure to chemotherapy to see if tumors becoming PD-L1-positive will derive much more benefit in terms of response rate.

I don't believe we should give immunotherapy to any patient in triple-negative breast cancer. I believe we need to better identify those patients who will derive more benefit, and those patients are patients harboring tumors that are more immunogenic, so tumor-infiltrating lymphocytes, TL-positive*5:32 or PD-L1-positive.

But another point of discussion, the most important endpoint in the neoadjuvant trial is not pathological complete response. I would like to see long-term effect of immunotherapy in this population of patients and to see if we have an overall survival benefit, because any immunotherapy approach has been designed to prevent cancer recurrence, not to increase response rate, so that's why the real endpoint for any trial in the early breast cancer setting should be overall survival. This is my message.

Dr. Birnholz:
Yes, that's a very powerful message. But let's jump from there then. Where do we need to go from here to that point to be able to make that leap towards improving overall survival, especially for patients with triple-negative breast cancer, metastatic, very late, not responsive to many therapies obviously? How do we get there? And what kind of hurdles or obstacles do we need to bypass in order to get to that point?

Dr. Curigliano:
We know already that atezolizumab and now paclitaxel increase survival in PD-L1-positive, so the real question is how to test PD-L1. So we need to harmonize the tests that are available up to now because testing with pembrolizumab is completely different of testing with atezolizumab. So, in atezolizumab trial, the PD-L1 expression was assessed on tumor-infiltrating lymphocytes. In the pembrolizumab trial, they used the so-called CPS score in which PD-L1 is tested and assessed on macrophages, on tumor-infiltrating lymphocytes, on tumor cells.

So, in order to answer to your question, we need to enrich the population to better identify those patients who will derive more benefit from an immune checkpoint approach. So, from now, to increase really in a sensitive way survival, what we need is the better selection of the patients.

Dr. Birnholz:
And is that something that you see in the near-term horizon, or is that a long way off?

Dr. Curigliano:
No, it's not a long way. I believe from now to 3 years we'll harmonize the weight of selecting the patients, generating what I call an immunogram. So, I believe you don't have to select just according to PD-L1 expression, but you can match expression of gene signatures that will upregulate the immune response, the (inaudible)*8:16 factors related to the host, like the microbiome, so there is a lot of research ongoing in the field of immunotherapy, and this research, of course, will cover also breast cancer.

Dr. Birnholz:
It seems like a remarkable amount of coordination would be needed to create or harness an effective immunogram that is able to capture as many predictive biomarkers as possible. What types of biomarkers... You were alluding to that. What types of biomarkers should be included to make an effective immunogram from your vantage point right now?

Dr. Curigliano:
So, tumor mutational burden and microsatellite instability, (inaudible)*8:55 expiration of LDH, numbers of tumor-infiltrating lymphocytes in the context of the tumor bed, expression or not of gene signatures that upregulate the immune system and, of course, factors related to the host, so type of microbiome that the patient has—we know that we have some microbiome that are more immunogenic in respect to others—the performance status of the patient, the number of lines of treatment that they received, so it's a multidimensional immunogram, but we can for sure select the optimal patient.

Dr. Birnholz:
Looking at this year's congress, is there anything that you are particularly excited about beyond the KEYNOTE trial data that's coming out, from your colleagues or from others that you know, other research efforts? What has gotten you really excited this year?

Dr. Curigliano:
So, 2 things, I believe. First, data in ovarian cancer, in BRCA-mutated ovarian cancer in which following chemotherapy standard of care, patients have been randomized to receive as maintenance treatment or bevacizumab alone or bevacizumab plus PARP inhibitors. And it's quite surprising to know that the addition of bevacizumab to a PARP inhibitor may increase progression-free survival, so there is a new hope for patients with ovarian cancer with the use of this targeted therapy, that is the PARP inhibitor olaparib, in a very well-selected population, that is the BRCA-mutated population.

And the second data I believe are related to cholangiocarcinoma, the gallbladder carcinoma. We don't have nothing for these patients. We have just chemotherapy. And knowing that there is a targeted agent, that is ivosidenib, against the IDH1-mutated patients—so again a selection according to a specific molecular alteration—and the use of this targeted agent that will improve progression-free survival I believe is a new hope for patients.

So, what I am learning now from this ESMO is that we are going to have a disease segmentation for any type of tumors. So, the approach for cancer treatment in the future will not be based on the organ of region but will be based to an agnostic approach related to the presence or not of a specific molecular alteration, so if you have that specific alteration, you will give that specific agent, maximizing the benefit, minimizing the toxicity, and saving a lot of money also because we have 1 agent for a specific mutation.

Dr. Birnholz:
Well, Dr. Curigliano, I would keep you here for another 20 minutes if I had my choice, my druthers, but you are a busy person. I very much want to thank my guest, Dr. Giuseppe Curigliano, for joining me to talk about the latest research in treatment developments at ESMO for triple-negative breast cancer as well as insights on what's coming ahead in the future horizons for this cancer subtype.

Dr. Curigliano, thank you so much for being here.

Dr. Curigliano:
Thank you to you. Have a nice day and enjoy the meeting.

Dr. Birnholz:
To access this and other episodes covering innovations in breast cancer treatment, visit ReachMD.com where you can Be Part of the Knowledge. For ReachMD, I'm Dr. Matt Birnholz. Thank you for listening.

Announcer:
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