Expert Discussion: Immunotherapy in Breast Cancer – Ready for Prime Time?

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Rinnerthaler: Should PD-L1 Reflex Testing Be Standard for Every Patient with Newly Diagnosed Metastatic Triple-Negative Breast Cancer?

Müller: Given the efficacy and approval of atezolizumab for first-line therapy of triple-negative metastatic breast cancer, I believe that PD-L1 testing is a standard. If things go well, we will soon have another option for first-line treatment by using pembrolizumab and also another chemotherapy backbone apart from taxanes. Therefore, another scoring will be required with the CPS score.

Balic: For metastatic triple-negative breast cancer, PD-L1 testing should already be a standard and with the upcoming pembrolizumab approval another companion diagnostic test will have to be performed as already pointed out. There is an overlapping proportion of positivity; however, there is also a non-overlapping one, and in order to identify all candidate patients we will have to perform both tests.

Zaman: Indeed PD-L1 testing should be a standard in the first-line metastatic setting, as there is a survival benefit in the concerned population at least in the IMpassion

130 by adding atezolizumab to chemotherapy. The benefit of pembrolizumab is also dependent on PD-L1 expression.

For later lines, the role of PD-L1 expression seems less clear. There are more data supporting the predictive value of TIL.

Dieci: Combination of ICI and chemotherapy demonstrated an advantage in PFS (IMpassion 130 and Keynote 355) and OS (IMpassion 130, though not formally tested) in PD-L1+ patients. However, many PD-L1+ patients still do not benefit from this combination. Moreover, the addition of atezolizumab to paclitaxel did not improve the outcome of PD-L1+ mTNBC patients in the IMpassion 131 trial and the OS results of Keynote 355 are still awaited. At present, considering all of these data and the limited systemic treatment options for mTNBC, the eligibility for ICI + chemotherapy should be evaluated by PD-L1 testing in newly diagnosed mTNBC. Nab-paclitaxel should be preferred over paclitaxel as a chemotherapy backbone. Further biomarker research as well as updated overall survival data (Keynote 355 and IMpassion 131) are needed.

Rinnerthaler: Are Results from Different PD-L1 Immunohistochemistry Assays Interchangeable in the Metastatic Setting?

Müller: Test systems are certainly not interchangeable without extensive efforts. As we have no definition for the test system to be used with the European approval, it will be a major task for pathologists to harmonize testing. In my perception, these efforts are on the way with training programs and ring experiments in order to obtain comparable results.

Balic: As already suggested above, these results are not interchangeable, and both tests will have to be performed.

Zaman: Not currently. SP142 is positive in around 40% and seems to be the most predictive of the benefit of atezolizumab when added to nab-paclitaxel. 22C3 in CPS with a 10% cutoff identifies also around 40% of the patients as benefiting from pembrolizumab added to chemotherapy. However, it is not clear if these two 40% are the same patients.

Dieci: PD-L1 IHC assays differ in sensitivity, staining platforms, and scoring methods. Discrepancies in PD-L1 status definition have been demonstrated among SP142, 22C3, and SP263 assays in mTNBC samples from IMpassion 130 even when adopting similar cutoffs, with SP142 being the least sensitive. The benefit of atezolizumab added to nab-paclitaxel was demonstrated in all PD-L1+ subgroups based on different PD-L1 assays but it was larger in SP142/PD-L1+ patients. Unfortunately, at this stage there are no conclusive data to clearly account for the interchangeability of the results of different PD-L1 assays. Harmonization efforts in this direction are urgently needed, as well as studies aimed at integrating PD-L1 IHC with other biomarkers (i.e., TIL), to improve the accuracy of patient selection.

Rinnerthaler: What Is Your Preferred Treatment Option in the Small Subset of Newly Diagnosed Triple-Negative Breast Cancer Patients with a Germline BRCA1/2 Mutation and PD-L1 Expression Positivity?

Müller: Although this is a very small minority of patients, we had many thoughts about the best sequencing of treatment in this setting and my conclusion so far is that we do not know for sure. I would discuss both options of a PARP inhibitor and a checkpoint inhibitor as the first treatment with the patient as I would interpret the approval of atezolizumab for first-line treatment as first-line chemotherapy.

Balic: The answer to this question can only be very subjective. Although the data suggest using the combination of nab-paclitaxel and atezolizumab first, for se-

lected patients I would prefer to start with a PARP inhibitor. There is no evidence for any of the sequences, and the decision has to be discussed with the patient and shared. Probably this concrete question will remain unanswered.

Zaman: Checkpoint inhibitor plus chemotherapy seems to me to have a higher priority because of the survival benefit in IMpassion 130. Therefore, I would use it as the first line. The response to chemotherapy is also more predictable in the first line than the response to PARP inhibitors, with some patients doing well but others not at all (it is a clinical impression).

Dieci: There is no data to support one strategy over another (olaparib first followed by atezolizumab + nab-paclitaxel – approved in patients not previously exposed to chemotherapy for PDL1+ mTNBC – vs. atezolizumab + nab-paclitaxel followed by olaparib). Atezolizumab + nab-paclitaxel has demonstrated an OS advantage in the first-line setting. Olaparib was associated with an OS improvement versus treatment of the physician's choice in the subgroup of patients who did not receive previous chemotherapy for metastatic breast cancer in the OlympiAD trial. Considering the evident differences in treatment invasiveness and tolerability, I would discuss carefully the two options with the patient.

Rinnerthaler: Can an Immune Checkpoint Inhibitor plus Chemotherapy Combination Be Considered as a Standard Neoadjuvant Therapy in Early Triple-Negative Breast Cancer Patients? If Not, What Further Results from Clinical Trials Should Be Awaited to Conclude on the Role of Immunotherapy in This Setting?

Müller: So far, we in our center do not use checkpoint inhibitors in neoadjuvant therapy of early breast cancer outside clinical trials. Although trial results presented last year are encouraging, I would like to see an improvement in not only pCR but also in DFI survival or even OS.

Balic: The FDA has approved the use of pembrolizumab, but the EMA is awaiting further outcome data. Generally it is advisable to wait for a longer follow-up for iDFS and OS; however, in a high-risk node-positive patient at a young age I would consider introducing the addition of pembrolizumab in the treatment.

Zaman: Yes, we currently use it in stage II and higher, based on the results in terms of pathological complete response. However, in the longer term, additional positive data in terms of outcomes and safety are absolutely needed.

Dieci: At this stage I would not consider ICI + chemotherapy as standard in the neoadjuvant setting for all

TNBC patients. I would certainly consider this combination for higher-risk patients. Survival data are eagerly awaited. Moreover, ongoing studies using immunotherapy in the postneoadjuvant setting for patients not achieving a pCR (A-BRAVE NCT02926196 and S1418/BR006 NCT02954874) will contribute to define the optimal strategy to integrate immunotherapy for TNBC patients undergoing neoadjuvant chemotherapy.

Rinnerthaler: What Role Will Tumor-Infiltrating Lymphocytes and PD-L1 Expression Play in Immunotherapy Treatment Selection in Early Triple-Negative Breast Cancer Patients?

Müller: So far, no uniform conclusions can be drawn from the data I have seen. One could assume that in early breast cancer PD-L1 expression or TIL is a more dynamic marker that might be useful to explore during treatment or that other markers will help to identify patients with more (or less) benefit from checkpoint inhibitor therapies.

Balic: With all our knowledge so far, TIL and PD-L1 expression and their routine reporting may add to selection of patients with a higher likelihood of a response and better outcomes, but not for determination of the treatment.

Zaman: In the metastatic setting, TIL are not in the decision algorithm for first-line treatment. They could be useful for selecting a patient for monotherapy with a checkpoint inhibitor in later lines in the metastatic setting. However, PD-L1 expression appears as essential to select patients for a combination of chemotherapy and checkpoint inhibitor. SP142 for atezolizumab and CPS for pembrolizumab. In the neoadjuvant setting, currently neither TIL nor PD-L1 seems necessary when selecting patients for the addition of a checkpoint inhibitor to chemotherapy in TNBC.

Dieci: TIL and PD-L1 identify TNBC patients who are more likely to achieve a pCR after neoadjuvant chemotherapy, but they do not specifically predict the efficacy of ICI added to cytotoxic treatment. The integrated evaluation of these biomarkers could identify subgroups of patients with very “hot” tumors that could benefit from an ICI-based deescalated neoadjuvant treatment strategy. Dynamic on-treatment assessment of TIL and PD-L1 could be explored in clinical trials testing priming strategies to turn a cold tumor into a hot one.

Rinnerthaler: In Your Opinion, What Is the Role of the Cytotoxic Backbone of a Neoadjuvant Immune Checkpoint Inhibitor plus Chemotherapy Combination in Early Triple-Negative Breast Cancer Patients?

Müller: All major trials so far have used a chemotherapy backbone in a more conventional dosing and schedule, with almost all also using anthracyclines. If the upcoming results of checkpoint inhibitors also prove an improved outcome, it might be possible to reduce the cytotoxic treatment intensity for some patients.

Balic: So far the immune checkpoint trials in the neoadjuvant setting suggest that only addition of an immune checkpoint to an effective chemotherapy combination, including anthracyclines and taxanes (and preferably carboplatinum in high-risk patients) provides both immunostimulatory and also efficient treatment options. So far, there is no room for deescalation of the chemotherapy for triple-negative patients.

Zaman: The cytotoxic backbone seems to play an important role. There seems to be no difference between solvent-based paclitaxel and nab-paclitaxel in the opposite to the metastatic setting. The TONIC and NeoTRIPaPDL1 studies suggested a significant role for the anthracyclines, which probably have to be part of the regimen.

Dieci: I believe that the chemotherapy backbone plays an important role in this setting. Many cytotoxic drugs can elicit an immune response through different mechanisms. Anthracyclines are able to induce an immunogenic cell death, which seems to be particularly relevant in this setting. In my opinion, the lack of anthracyclines in the neoadjuvant backbone of the NeoTRIP study is one of the main reasons for negative results. Both taxanes and anthracyclines should be included. As for the taxane backbone, the use of paclitaxel in Keynote 522 did not preclude the trial's positive results in terms of pCR improvement.

Conflict of Interest Statement

Gabriel Rinnerthaler has done consulting for or had an advisory role in Roche and MSD. He is also on the speakers' bureau of Bristol-Myers Squibb and Roche and received research funding from Roche and travel, accommodations, and expenses from Roche and Bristol-Myers Squibb.

Volkmar Müller received: speaker honoraria from Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Pfizer, MSD, Novartis, Roche, Teva, and Seattle Genetics; consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Tesaro, Seattle Genetics, and Nektar; institutional research support from Novartis, Roche, Seattle Genetics, and Genentech; and travel grants from Roche, Pfizer, and Daiichi Sankyo.

Marija Balic has received personal fees and consulting fees from Amgen, AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer, Roche, and Samsung.

Khalil Zaman has received consulting fees from or participated in the advisory boards of AstraZeneca, Daiichi, Exact Science, Lilly, MSD Merck, Mylan, Novartis, Pfizer, and Roche. Khalil Zaman has also received: travel and accommodation support from AstraZeneca, Daiichi, Pfizer, Roche, Pierre Fabre, and Vifor; unrestricted funding for organization of scientific events from AstraZeneca, Daiichi, Eisai, Exact Science, Lilly, MSD, Mylan, Novartis, Pfizer, Roche, and Synlab, and research funding from Roche.

Maria Vittoria Dieci received personal fees for consultancy/advisory roles from Eli Lilly, Novartis, Pfizer, Genomic Health, and Celgene.

Chair

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