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Clinical Implications of Current Guidelines on First-Line Immunotherapy and PARP Inhibitors for TNBC

Announcer:
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Dr. Schmid:
This is CME on ReachMD. I'm Dr. Peter Schmid. In this brief lecture today, I'll talk about the use of immune therapy and PARP inhibitors as first-line treatment for triple-negative breast cancer, according to current guidelines.

Triple-negative breast cancer is a difficult-to-treat subtype of breast cancer. It's a very heterogeneous disease. In fact, we can argue, is there one type of triple-negative breast cancer? There are many studies and classifications that show us that there are different subtypes of triple-negative breast cancer based on different biological behavior. Clinically, we are trying to bring this down to one clinical strategy. The clinical decisions, of course, also depend on the presentation of patients with metastatic breast cancer, and this includes the pretreatment, which is currently changing very much with the adoption of more intensive chemotherapy, but also the adoption of immune therapy for the treatment of early triple-negative breast cancer.

Chemotherapy remains the mainstay of therapy for metastatic triple-negative breast cancer, but new agents have become increasingly important over recent years, including immune therapy, which I'm talking about today, PARP inhibitors, but also, antibody-drug conjugates, which are currently becoming standard of care in subsequent and second- or third-line settings.

In the first-line setting for patients with metastatic triple-negative breast cancer, we currently use two critical biomarkers to guide our treatments decision. One is PD-L1, and PD-L1 is used to select patients for immune therapy. And the other one is genetic testing looking for germline BRCA1 or BRCA2 mutations to see whether patients may possibly benefit from PARP inhibitor therapy.

In patients who are PD-L1 positive, PD-L1 positive is defined as a CPS score of 10 or higher using the 22C3 assay. In a patient with this positive PD-L1 score, the current guidelines recommend, very clearly, first-line chemotherapy with either a taxane or gemcitabine/carboplatin in combination with the immune checkpoint inhibitor pembrolizumab. This was based on the result of the KEYNOTE-355 trial, a randomized phase 3 trial that looked into improving the outcome of patients in first-line metastatic triple-negative breast cancer with the addition of pembrolizumab to standard chemotherapy. It demonstrated a significant and meaningful improvement in progression-free survival with a hazard rate of 0.65, improving the median progression-free survival from around 5.6 months with chemotherapy alone to around 9.7 months with chemotherapy immune therapy, so 4 months' delta.

We saw that the benefit was almost exclusively seen in patients with a CPS 10, so high PD-L1 expression, whereas patients with lower PD-L1 score or PD-L1-negative tumors did not derive a benefit. And the benefit in progression-free survival also translated into a significant improvement in overall survival with a hazard ratio of 0.73 and a nearly 9-month survival benefit, which was, importantly, one of the first times we achieved an improved survival in patients with metastatic triple-negative breast cancer. So, therefore, treatment

with chemotherapy, either platinum or paclitaxel, has become the standard of care for patients with PD-L1-positive tumors, with the addition of pembrolizumab.

In patients with PD-L1-negative tumors, we have to decide whether patients have a BRCA germline mutation or not. If patients have a BRCA germline mutation, they could be considered for first-line treatment with a PARP inhibitor. The two PARP inhibitors currently guideline-recommended, olaparib and talazoparib, they showed very similar results in two phase 3 trials. The phase 3 trials were slightly mixed bags, included patients all with BRCA1 and BRCA2 germline mutations, but with ER-positive or triple-negative metastatic disease in the first-, second-, or third-line setting.

In a very convincing way, they show very similar results, demonstrating an improvement of progression-free survival with a hazard ratio from 0.54-0.58. What is always impressive with PARP inhibitors are the high response rates, which in the first-line setting are in the 60% range. And the treatments are associated with the medium PFS of around 7 to 9 months.

These studies have failed to show an overall survival benefit, although we see in the cohort of patients who received PARP inhibitor in a first-line setting, possibly a survival signal. In patients who don't have PD-L1-positive tumors and don't carry BRCA1 or BRCA2 germline mutations, chemotherapy remains the standard of care as per guidelines. We would usually consider taxanes or carboplatin, but depending on the pretreatment and depending on the disease and treatment-free interval, we sometimes have to choose other chemotherapy regimens as well, for example, capecitabine or eribulin, and possibly, in the future, antibody-drug conjugates with the first-line randomized trials currently ongoing.

Unfortunately, our time is up. Thank you very much for watching.

Announcer:
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