I-SPY 2 Trial Explores Immune Checkpoint Plus PARP Inhibitors in Breast Cancer

BY CATLIN NALLEY

Durvalumab in combination with olaparib and paclitaxel demonstrated a significant improvement in pathologic complete response (pCR) compared to chemotherapy among women with stage II/III high-risk, HER2-negative breast cancer, according to findings from the I-SPY 2 trial.

The results, which were presented at the 2020 AACR Virtual Annual Meeting, also showed that improvement was seen in both the HR-positive (HR+) and triple-negative breast cancer (TNBC) subsets (Abstract CT011).

I-SPY 2 Methodology

This was a multi-center, phase II response adaptive randomized trial with multiple concurrent experimental arms and a shared standard-of-care chemotherapy control. The primary endpoint was pCR. Women with tumors ≥ 2.5 cm were eligible for screening, HER2- patients were eligible for treatment; women with HR+ disease were required to have MammaPrint high molecular profile.

“There is biological and pre-clinical rationale to combine immune checkpoint inhibitors and PARP inhibitors and expect synergy between the two classes of agents,” noted study author Lajos Pusztai, MD, DPhil, of Yale Cancer Center, during his presentation. “The goal of this arm of the I-SPY trial was to estimate if the combination of durvalumab, olaparib, and paclitaxel neoadjuvant would increase pCR rate compared to chemotherapy alone in HER2-negative, stage II-III breast cancers.”

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In the experimental arm, patients received durvalumab 1,500 mg every 4 weeks for three treatments, olaparib 100 mg twice daily through weeks 1-11 concurrent with paclitaxel 80 mg/m² weekly x 12 followed by doxorubicin/cyclophosphamide for four treatments.

“The control arm was weekly paclitaxel x 12 followed by doxorubicin/cyclophosphamide x 4,” the study authors reported. “All patients undergo serial MRI imaging and imaging response at 3 and 12 weeks combined with accumulating pCR data used to estimate, and continuously update, predicted pCR rate for the trial arm.”

Key Findings

Between May 2018 and June 2019, 73 patients received durvalumab plus olaparib and paclitaxel, including 21 HR- and 52 HR+ tumors. In the control group, there were 299 patients with HER2- tumors.

“Durvalumab plus olaparib increased the estimated pCR from 20 percent to 37 percent when all HER2- cancers were considered together,” reported Pusztai. “In the triple-negative subset, pCR rates increased from 27 to 47 percent and then in the HR+/HER2- it increased from 14 to 28 percent.”

An exploratory analysis of the TNBC cohort showed that, according to Pusztai, low CD3/CD8 gene signature ratio, high macrophage/Tc-Class 2 ratio, and high proliferation signature were associated with higher pCR in the experimental arm.

As of March 15, 2020, adverse events were reported for 43 patients in the experimental arm and 215 patients in the control arm. The researchers observed no unexpected toxicities.

Fifty-eight percent of patients in the experimental arm had grade 3-4 adverse events compared to 41 percent in the control. “Overall, 19 percent of patients in the durvalumab plus olaparib experienced immune-related grade 3 adverse events compared to 1.6 percent in the control,” Pusztai noted. These events included colitis, adrenal insufficiency, pneumonitis, and pancreatitis.

“Durvalumab plus olaparib concurrent with weekly paclitaxel increased pCR rates in all three biomarker subsets where it was studied,” Pusztai stated. “The estimated probability that the experimental arm is superior to chemotherapy alone is greater than 98 percent in all subsets.

“Immune-rich cancers showed high pCR rates in all subtypes and in both treatment arms,” he added. “However, exploratory analysis suggests several potential predictive markers of durvalumab/olaparib benefit over chemotherapy alone.”

Expert Commentary

Commenting on the study, Pamela Munster, MD, UCSF Helen Diller Family Comprehensive Cancer Center, emphasized, “the addition of durvalumab and olaparib shows a benefit in all HER2- tumors with a similar magnitude of benefit in both the HR- as well as the HR+ subtypes.”

In terms of the toxicity of adding this combination to a standard-of-care neoadjuvant regimen, she noted that there appears to be about a 10 percent excess in grade 3 and higher immune-related toxicity, which is similar to other studies.

“However, with regard to toxicity expected with a PARP inhibitor, it appears that the data may be incomplete,” Munster said. “Most studies with PARP inhibitors suggest an excess of anemia and many patients requiring transfusion, but for this study anemia and fatigue rates for the drug triplet is actually less than observed with paclitaxel alone.

“And, in the absence of a clear delineation of the contribution of olaparib, some weight should be given to the financial burden of adding both durvalumab and olaparib to a preoperative regimen,” she added. So, is combined immune checkpoint and PARP inhibition in early-stage breast cancer ready for use?

“What we learned today from Dr. Pusztai’s presentation is that there may be promising activity of olaparib and durvalumab in addition to paclitaxel,” Munster noted. “This combination may be of particular interest among the subgroup of women with tumors expressing ultra-high MammaPrint.

“Placing this trial in context with other studies, the contribution of PARP inhibitors to immunotherapy in early-stage breast cancer remains uncertain,” she continued. “Thus, we should await confirmatory randomized studies that are stratified for PD-L1 expression and BRCA mutation and HRD status before using combined immune checkpoint inhibitors and PARP inhibitors in early-stage breast cancers.”

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