HER2+ Breast Cancer & Neoadjuvant Checkpoint Inhibition

BY PETER M. GOODWIN

Adding the anti-programmed-death-ligand 1 (PD-L1) antibody atezolizumab to standard neoadjuvant treatment (with chemotherapy plus dual human epidermal growth factor receptor 2 [HER2] blockade) in patients with high-risk HER2-positive early breast cancer, did not improve pathological complete response (pCR) rates in the IMpassion050 Phase III, randomized, placebo-controlled, double-blind trial—the first to report data comparing a neoadjuvant anti-HER2-based regimen with or without a checkpoint inhibitor. But the investigators found no new safety signals from adding such “checkpoint inhibition” with atezolizumab. And they insisted that the negative finding for the endpoint of pCR did not rule out the chance of eventually finding benefits in event-free and overall survival. The lack of response (as measured by pCR) was irrespective of whether patients had tested positive for PD-L1.

“What we can say now is: We couldn’t increase the pCR rate significantly with adding a checkpoint inhibitor to anti-HER2 treatment-based chemotherapy. Hence, our median follow-up time now is [only] 16 months, so we have to wait for a longer time, because it may be the case that pCR is not the best endpoint to assess the efficacy of a checkpoint inhibitor in breast cancer,” lead author Jens Huober, MD, Head Physician of the Breast Centre at Cantonal Hospital in St. Gallen in Switzerland, told Oncology Times after presenting the study findings at the ESMO Breast Cancer Virtual Congress 2021.

Since dual HER2 blockade with pertuzumab and trastuzumab is reported to activate antibody-dependent cellular cytotoxicity (and is standard of care for patients with high-risk HER2-positive disease), the study looked at whether combining this with checkpoint inhibition might restore anti-cancer immunity even further and improve patient outcomes.

Study Details

All 454 patients in the IMpassion050 study received neoadjuvant therapy with dose-dense anthracycline and taxane-based chemotherapy in combination with pertuzumab and trastuzumab. Half of the patients (226) had atezolizumab added to their neoadjuvant regimen, while the remaining half (228) patients added a placebo.

The findings reported at ESMO compared pCR in the two groups. The study is ongoing, with analysis planned to assess the impact of the checkpoint inhibitor on clinical and survival outcomes.

To qualify for the trial, all patients needed to have had primary tumors larger than 2 centimeters, pathologic confirmation of nodal involvement, and a positive test for HER2. PD-L1 and hormone receptor (HR) status were assayed.

The overall treatment package continued for 52 weeks, at which point patients with residual disease could continue with their allocated drug (atezolizumab or placebo) together with trastuzumab and emtansine. pCR was assessed for the entire intention-to-treat (ITT) population and also for patients who had tested positive for PD-L1.

The co-primary endpoints were pCR in the ITT-positive and PD-L1-positive populations. Event-free survival (EFS), overall survival, and safety were secondary endpoints. The trial was stopped prematurely when the Independent Data Monitoring Committee judged that there had been an unfavorable risk-benefit profile with atezolizumab.

Outcomes

The results of the trial indicated the need to better investigate biological differences on the impact of PD-L1 by disease setting, noted Carmen Criscitiello, MD, PhD, Assistant Professor at the University of Milan, and Senior Physician with High Specialty in Immunotherapy in the Division of Early Drug Development at the European Institute of Oncology in Milan.

“In the metastatic setting, the benefit of adding an immune checkpoint inhibitor to chemotherapy is largely confined to the PD-L1 positive population. In the neoadjuvant setting, benefit in patients with triple-negative breast cancer has been observed in the overall population and in both PD-L1 positive and negative subgroups. In the IMpassion050 PD-L1 positive group, the pCR rate was [lower] in the experimental arm compared to the control arm—suggesting [an] opposite trend in PD-L1 negative tumors,” she said.

In the ITT population pCR was achieved by 62.4 percent of patients in the atezolizumab arm and 62.7 percent in the placebo arm. In the PD-L1 positive population pCR was achieved by 64.2 percent of the atezolizumab arm and 72.5 percent of the placebo arm.

There were higher rates of Grade 3 and 4 adverse events (AEs) in patients treated with atezolizumab: 51.8 percent compared with 43.6 percent in the placebo group. Serious AEs were also higher with atezolizumab (19.5%) compared with placebo (13.3%). Four patients in the atezolizumab group during neoadjuvant treatment died compared to no deaths in the placebo group.

Huober said the safety profile had been consistent with other combination studies with atezolizumab, with no new side effects. But although the additional immunotherapy with atezolizumab had not enhanced the pCR rate in the overall population or in any subgroup, he did not rule out a beneficial clinical effect.

“What counts for patients are event-free survival and overall survival, and we need longer follow-up for those results. In addition, there is some evidence in triple-negative breast cancer that pCR may not be the best endpoint for measuring the efficacy of immunotherapy,” he noted.

Criscitiello agreed that pCR had not proved to be a robust and validated endpoint for efficacy. She said the findings should be interpreted with caution until there were long-term results on EFS. “In triple-negative breast cancer, immune checkpoint inhibition added to standard neoadjuvant therapy [only] modestly increased pCR rate in the GeparNUEVO and KEYNOTE-522 studies. Yet, EFS was significantly improved in both studies,” she said.

Criscitiello noted that, although the benefit of adding an immune checkpoint inhibitor to chemotherapy in the metastatic setting was largely confined to the PD-L1 positive population, this had not proved to be the case in the neoadjuvant setting, where benefit with triple-negative breast cancer had been observed in the overall population—in both PD-L1 positive and negative subgroups.

“In the IMpassion050 PD-L1 positive group, the pCR rate was numerically inferior in the experimental arm compared to the control arm—an opposite trend in PD-L1 negative tumors” she said. “This indicates the need to better investigate biological differences on the impact of PD-L1 by disease setting.”

Criscitiello also noted that findings on safety needed to be examined carefully, since the regimen had been given with curative intent.

“There is a need to investigate if there is any link between atezolizumab and the treatment-related deaths,” she noted. “In the curative setting, we should be even more conservative and cautious when we look at the toxicity that may be induced by a new treatment. So far, this combination has not demonstrated an improvement in pCR rate, so the balance between risk and benefit should be carefully monitored before considering this therapeutic strategy.”

Peter M. Goodwin is a contributing writer.