Editorial Commentary

Updates on the preoperative immunotherapy for triple-negative breast cancer

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Introduction

Triple negative breast cancer (TNBC) has been a challenging disease to treat compared with other breast cancer subtypes due to its aggressive biological feature and the absence of actionable targeted therapy (1).

Even with the use of poly-chemotherapy in either neoadjuvant or adjuvant setting, 5-year disease-free survival rate is only around 70%, while 5-year overall survival (OS) rate is merely 77% with TNBC (2,3). These figures highlight the persistent need for novel therapies to improve long-term outcomes.

In recent decades, several novel agents have been investigated with the goal of improving the prognosis of early-stage TNBC. However, only few of these therapies have entered clinical practice, including the recent approval of olaparib for high-risk BRCA mutated TNBC patients in the adjuvant setting (4).

However, the recent emergence of neo-adjuvant immunotherapy has changed the treatment landscape for triple-negative breast cancer.

Pre-operative immunotherapy in early TNBC

There are several randomized trials assessing programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1) agent in combination with neoadjuvant chemotherapy with three of these trials showing an improvement in pathological complete response (pCR) rate with the addition of immunotherapy.

I-SPY2, a phase II study, evaluated the inclusion of pembrolizumab in neoadjuvant chemotherapy for high-risk early breast cancer. The study randomly assigned participants to receive weekly paclitaxel either with or without pembrolizumab, followed by AC (doxorubicin and cyclophosphamide). In the TNBC subgroup, the pembrolizumab arm demonstrated a higher pCR rate compared to the standard treatment arm (60% *vs.* 22%) (5).

The phase III IMpassion031 trial demonstrated that incorporating atezolizumab into neoadjuvant weekly nab-paclitaxel followed by AC significantly increased pCR rate from 41% to 58% (6). As secondary endpoint, the median event-free survival (EFS) was not reached in both arms with a hazard ratio of 0.76 [95% confidence interval (CI): 0.40–1.44].

The NeoTRIP trial, on the other hand, did not show a statistically significant improvement in pCR rate when atezolizumab was added to neoadjuvant nab-paclitaxel and carboplatin (48.6% *vs.* 44.4%, P=0.48) (7).

In the GeparNuevo study, 174 patients received neoadjuvant weekly nab-paclitaxel followed by EC (epirubicin and cyclophosphamide) and were randomly assigned to the addition of durvalumab versus placebo; patients did not resume adjuvant durvalumab after surgery. While the addition of durvalumab numerically increased pCR rates in all patients, this did not reach statistical significance (8). In a subsequent analysis conducted at a median follow-up of 42 months, it was observed that the

inclusion of durvalumab enhanced the 3-year invasive disease-free survival (iDFS) from 76.9% to 84.9% [hazard ratio (HR): 0.54, P=0.0559] and OS from 83.1% to 95.1% (HR: 0.26, P=0.0076) (9). While these findings were promising, it is important to note that the trial was not powered to detect survival differences and therefore the results need to be interpreted with caution.

Neoadjuvant pembrolizumab with chemotherapy in early TNBC

Although a number of trials explored the effects of incorporating immunotherapy agents to neoadjuvant chemotherapy on pCR rates in TNBC, only the KEYNOTE-522 trial has mature EFS results leading to the international regulatory approval of pembrolizumab in this setting.

KEYNOTE-522 is a randomized phase III trial enrolling 1,174 patients with previously untreated stage II /III TNBC evaluating pembrolizumab or placebo in combination with neoadjuvant chemotherapy comprised of carboplatin with paclitaxel followed by AC or EC. Pembrolizumab was also administered for adjuvant treatment, independent of pathologic response to neoadjuvant therapy. The trial demonstrated that the addition of pembrolizumab increased the overall pCR rate from 51.2% to 64.8% (P=0.00055) and improvements in pCR rates were seen regardless of PD-L1 expression (10). The fourth planned interim analysis demonstrated a statistically significant improvement in EFS in patients treated with pembrolizumab (84.5% *vs.* 76.8%, HR: 0.63) (4). Patients who achieved a pCR after neoadjuvant therapy experienced a very favorable outcome regardless of whether pembrolizumab was utilized, with a 3-year EFS rate of 94.4% compared to 92.5%. By contrast, in patients who did not achieve pCR, there was a benefit from the addition of pembrolizumab: 3-year EFS rates were 67.4% in the pembrolizumab arm and 56.8% in the placebo arm. While there was also a numerical improvement in OS, the data is still immature.

In terms of safety, pembrolizumab resulted in an incidence of immune-related adverse events (irAEs) in 33.5% of patients, with 12.9% of them being grade 3–4. Specifically, hypothyroidism was observed in 15.1% of patients, hyperthyroidism in 5.2%, and adrenal insufficiency in 2.6%.

These compelling results led to a rapid practice changing and the Food and Drug Administration (FDA) approval of pembrolizumab for early-stage TNBC on July 26, 2021. China's National Medical Products Administration (NMPA) has also granted approval for the combined use of pembrolizumab and chemotherapy as a neoadjuvant treatment for high-risk early TNBC expressing high PD-L1 [combined positive score (CPS) ≥20] on Nov 10, 2022. But based on the improvements in both pCR rates and EFS were seen regardless of PD-L1 expression in the Keynote 522 trial, PD-L1 testing may not be necessary before administration (4,10).

Controversies in preoperative pembrolizumab

Although the KEYNOTE-522 study has resulted in changes in clinical practice, there are still several important questions that have not been addressed.

In KEYNOTE-522, the chemotherapy backbone included paclitaxel and carboplatin, followed by AC or EC. This combination has been thought to be relatively toxic and requires additional consideration to balance with patient's quality of life. Although several sets of data have shown that incorporating carboplatin into an anthracycline and taxane combined chemo-regimen in early stage TNBC is associated with an improvement in outcomes it is unclear whether all four chemotherapeutic drugs are needed when pembrolizumab in used in the neoadjuvant setting (11-15). The phase II NeoPACT trial evaluated 109 TNBC patients receiving six cycles of neoadjuvant carboplatin and docetaxel with pembrolizumab and produced a 58% pCR rate using this anthracycline free regimen (16).

It is also uncertain that if it is necessary for all patients to receive both neoadjuvant and adjuvant pembrolizumab to attain a benefit in EFS. Based on the exploratory analysis of EFS by pCR status, it was indicated that patients who achieved pCR experienced similarly favorable outcomes in terms of EFS in both treatment arms.

This suggests that pembrolizumab could be omitted in the adjuvant setting in patients with pCR. The ongoing OptimICE-PCR study aims to address this question by randomizing patients who have received neoadjuvant chemotherapy plus pembrolizumab and achieved a pCR to either undergo 1 year of adjuvant pembrolizumab or be observed without further treatment. The primary objective of the study is to assess whether observation is noninferior to 1 year of pembrolizumab in this setting.

Keynote-522 only Enrolled patients with stage II–III TNBC. However, data suggests that the risk of recurrence in stage I TNBC can be substantial. Can we extrapolate the results from Keynote-522 to treat certain patients with

stage I TNBC? Can we consider giving a shorter duration of chemotherapy in these patients, possibly with a taxane and carboplatin (17) in combination with pembrolizumab and depending on clinical and pathologic response add an anthracycline?

Finally, the optimal adjuvant regimen in patients that do not achieve a pCR after neoadjuvant pembrolizumab is still unclear. Currently, Olaparib and capecitabine are used in the adjuvant setting but there is no data on their combination with pembrolizumab (3,18). Based on the safety data of these two combinations as well as the synergism seen in trials in the metastatic setting of PARP inhibitors with immunotherapy and chemotherapy one can consider these combinations in clinical practice. However, this use of pembrolizumab cannot be considered standard of care (19,20).

Conclusions

Preoperative pembrolizumab combined with chemotherapy is a major breakthrough in treating patients with high-risk early TNBC. As with every significant scientific advancement, the results of KEYNOTE-522 also give rise to a number of important questions.

Further work is needed to investigate optimal chemotherapy backbone and duration of pembrolizumab. Research is also needed to explore the selection of patients based on biomarkers. These efforts will ultimately result in optimal tailored treatments that maximize oncologic benefit of immunotherapy for early TNBC.

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