Editorial Commentary

Tislelizumab: an effective treatment option for early-stage triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is adding to the woes of the growing burden of breast cancer (BC) globally and BC became the most common cancer type among women in China (1,2). TNBC accounts for 15–20% of the newly diagnosed BC cases and is characterized by the lack of estrogen and progesterone receptors as well as the absence of human epidermal growth factor receptor 2 overexpression (3). TNBC can be majorly categorized as basal-like and claudin-low and is highly heterogeneous at the tumor level, which governs its malignancy and the responses to the treatment (3,4).

Owing to the lack of effective treatment options, TNBC remains a clinical challenge. TNBC has a high tumor mutational burden and immunogenicity among other BC subtypes. Taking advantage of the high immunogenic nature of TNBC, immune-checkpoint inhibitors (ICIs) have managed to elicit the treatment-response in otherwise difficult to treat patients with TNBC. Especially, combining anti-programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) with a neoadjuvant chemotherapy improves anticancer responses and pathological complete response (pCR), when compared with a (neo)adjuvant chemotherapy alone (5). The Chinese Society of Clinical Oncology Breast Cancer guidelines suggest taxanes and platinum (TP) for TNBC and the combination of paclitaxel with carboplatin (TP) has been shown to prolong the survival benefit (6,7).

Currently, approved ICIs/anti-PD-1 and anti-PD-L1 for TNBC such as pembrolizumab and atezolizumab have shown differential benefits in clinical studies. However, the safety profiles, dosing strength and duration, accessibility to the wider population, and an optimal therapeutic option leave a void in the clinical practice. Given the changing cancer landscape in China and the differential treatment responses of the Chinese/Asian population, domestically developed, effective, optimal treatment strategies are required.

Tislelizumab is a humanized PD-1 monoclonal immunoglobulin G4 antibody that specifically binds the front β-sheet of PD-1, identical to the binding of PD-L1 to PD-1 increasing the affinity to PD-1 expressed on activated immune cells such as T-cells. Tislelizumab blocks and prevents PD-1 binding to its ligand PD-L1. The structure of tislelizumab has low affinity for Fcγ receptors (FcγR). In the tumor microenvironment, FcγRI is expressed on macrophages induce phagocytosis for T-cell clearance and potentially cause resistance to PD-1 blockade in other anti-PD-1 antibodies as it was shown that the FcγR binding in vivo negatively impacts the antitumor activity of anti-PD-1 antibodies (8). Tislelizumab has an extremely slow dissociation rate about 30- to 80-fold slower than other anti-PD-L1 drugs. Tislelizumab, specifically engineered to minimize Fcγ receptor binding to limit antibody-dependent phagocytosis and with a high affinity and specificity for

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PD-1. Furthermore, the antitumor activity and safety of tislelizumab have been demonstrated in Chinese and other populations with solid tumors (9,10). Tislelizumab has shown an anticancer effect in solid tumors and had been approved in China for other cancer types. It also received orphan designations for hepatocellular, esophageal, and gastric cancer from the U.S. Food and Drug Administration.

Recently in 2023 American Society of Clinical Oncology (ASCO) annual meeting, Jiang et al. reported the interim results of the cTRIO trial wherein a neoadjuvant combination; tislelizumab, with nanoparticle albumin-bound (nab)-paclitaxel and carboplatin followed by adjuvant tislelizumab, showed promising efficacy with a pCR rate of 56.5% [95% confidence interval (CI): 43.3% to 69.0%] in patients with TNBC.

This investigator-initiated trial cTRIO is ethically responsible and designed as a multicenter, open-label, phase II study in Chinese patients with early TNBC conducted nationwide to investigate the combination of tislelizumab with nab-paclitaxel and carboplatin in neoadjuvant/adjuvant therapy (11). In China, the combination of nab-paclitaxel and carboplatin are the common choice of chemotherapy and the investigators have selected it based on the advantageous outcome compared with epirubicin plus paclitaxel (7). The specified inclusion criteria were based on the target organ, tumor microenvironment, and cancer dynamics involving tumor-node-metastasis (TNM) II–III stage, T1 N1–3 or T2–4 N0–3, with a tissue sampling for the assessment of PD-L1. These criteria could potentially funnel and narrow down the characteristics of patients that would be predictive of response to tislelizumab to gain maximum clinical benefit. The intervention comprised six cycles of intravenous infusion of tislelizumab at 200 mg once every 3 weeks in combination with nab-paclitaxel (125 mg/m^2 on days 1 and 8) and carboplatin (the dose was based on the area under concentration 2, administered on days 1 and 8 every 3 weeks) before definitive surgery. Following the surgery, the patients continued to receive adjuvant tislelizumab every 3 weeks for up to eleven cycles.

The Simon Phase 2 (Simon, 1989) design was used to test the primary efficacy (pCR, ypT0/Tis ypN0) of the study drug. In the interim analysis of the first phase, 18 of 32 patients achieved pCR; hence, the study progressed to the next phase and enrolled 62 patients in total. The study met the primary endpoint conferring pCR (ypT0/Tis ypN0) in 35 of 62 patients with a pCR rate of 56.5% (95% CI: 43.3% to 69.0%). Another critical information about the efficacy of the study drug was obtained from the secondary endpoint; 27 patients achieved a pCR rate of 43.5% (95% CI: 31.0% to 56.7%) as per ypT0ypN0 staging.

The pCR was comparatively lower than that reported in the landmark KEYNOTE-522 study. Neoadjuvant pembrolizumab plus chemotherapy had a significantly higher percentage (64.8%, 95% CI: 59.9% to 69.5%) of patients achieving pCR, a 13.6% increase over placebo plus chemotherapy (51.2%, 95% CI: 44.1% to 58.3%). With pembrolizumab–chemotherapy treatment, a significant improvement in event-free survival (EFS) rate was observed at 84.5% (95% CI: 81.7% to 86.9%) with a 37% reduction in the risk of distant recurrence or death (hazard ratio for event or death: 0.63; 95% CI: 0.48 to 0.82; P<0.001). While pembrolizumab and atezolizumab have FDA approval for the treatment of TNBC, the superior treatment response reported in KEYNOTE-522 study is encouraging to evaluate PD-1 inhibitors but could also derive lessons for improvement in the development of PD-1 inhibitors. As stated earlier, tislelizumab has a unique structure to maximally inhibit the binding of PD-1 to PD-L1 with high specificity but at the same instance, it has a low affinity and minimizes the binding to FcγR thereby reducing potential resistance, an advantage over other PD-1/PD-L1 inhibitors (8).

It must be noted that compared with 8 cycles of neoadjuvant and a stronger regimen used in the KEYNOTE-522 study, the cTRIO trial had a lesser number of neoadjuvant cycles and included a marginally higher percentage of patients with TNM stage III at baseline. Nevertheless, EFS and overall survival (OS) analysis from the cTRIO trial will define the antitumor effect of tislelizumab considering the long-term goal of adjuvant therapy. Of interest, in the IMpassion031 study, atezolizumab plus chemotherapy showed an increased pCR of 16.5% more than placebo–chemotherapy. However, in the NeoTRIP study, atezolizumab did not significantly improve the pCR compared with the placebo and the authors concluded that perhaps pCR may not be the most appropriate surrogate endpoint to measure the efficacy of ICIs and may not completely reflect the long-term benefits (12). Conversely, a higher improvement in EFS was independent of pCR in the KEYNOTE-522 study. The accruing cost of imported pembrolizumab is still higher (13) potentially limiting its accessibility and affordability for the average Chinese population. On the other hand, efficacious, domestically developed ICI/PD-1 inhibitor such as tislelizumab, could reduce cost and be accessible to wider population.

On keen observation of the cTRIO trial, among patients with TNM stage II, an impressive 64.3% (27/42) of patients

achieved pCR, whereas 40% (8/20) of patients with stage III had pCR. Interestingly, pCR was achieved in 50% of N+ including N3, whereas when N3 alone was considered, the efficacy was almost half (33.3%, 3/9) of the pCR achieved in the patients with N0–2 (60.4%, 32/53). Overall, 53.2% of the cohort experienced grade ≥3 treatment-emergent adverse events (AEs) and the incidence of grade ≥3 immune-related adverse events (irAEs) were 3.2%. Hypothyroidism, hyperthyroidism, severe skin reaction, and interstitial pneumonia were the most observed AEs of interest. Taken together, these data suggest that tislelizumab—TP is effective against aggressive early TNBC.

In the real-world clinical setting, safety/AEs play a critical role in the patient compliance, and ICIs are associated with irAEs in the treatment of solid tumors (14). The authors in the KEYNOTE-522 study state that the incidence rate of AE was similar between the study drug and placebo groups. However, the number of study drug-related discontinuations and immune-mediated AEs including death were numerically more in the pembrolizumab–chemotherapy group (15,16). Though comparison between different study design, study cohort size, and without head-to-head clinical trial would not provide accurate analysis but in the overall picture, the grade ≥3 treatment-related adverse events (TRAE) were 76.8% and AEs of interest were 12.9% with pembrolizumab–chemotherapy while in cTRIO, grade ≥3 TRAE were 55.2% and irAEs occurred in 3.2%. Undeniably these observation in cTRIO study are interim and requires further monitoring.

Atezolizumab was also associated with significantly higher serious AEs and abnormalities in liver transaminase compared with the placebo group (12).

The promising clinical benefit observed in the KEYNOTE-522 study is encouraging. Nevertheless, TNBC is challenging to treat; the heterogeneity and aggressive nature of TNBC ultimately result in frequent or early relapse (17). Several strategies are under various stages of development for early TNBC in China, and tislelizumab is among the new agent in this therapy area with few questions to be answered by further randomized clinical trials. Whether the observed efficacy in pCR will translate to long-term clinical benefits, such as EFS and OS is still in progress and will find the answers in the final analysis of this study. Will increasing the number of treatment cycles at the neoadjuvant phase improve the prognosis? This can be probed in a randomized study with a comparator arm and rigorous statistical plan to assess the observed efficacy in this cTRIO trial. Will other biomarkers such as TMB, lower clonal heterogeneity of tumor-infiltrating lymphocytes to provide a clearer picture in selecting patients who would respond and reach higher clinical benefit from immune-neoadjuvant therapy (18,19)? Smart clinical trials assessing the tumor microenvironment might provide clue to prognosis with a potential to tailor-made therapies. A practical approach to counter the high cost of imported drugs would be to encourage the development of domestic drugs with increased response to treatment. Reduced cost and domestic development would meet the growing demand of estimated TNBC at the local level. In China, tislelizumab is being studied in various stages of TNBC and in combinations with other ICI agents. In patients with TNBC and positive circulating tumor DNA (ctDNA) status, tislelizumab in combination with capecitabine (antimetabolites) is under prospective clinical study. ctDNA is a tumor-specific biomarker and is associated with worse prognosis especially in TNBC. Identifying this noninvasive biomarker may improve the risk stratification and treatment outcome. Another phase II trial to probe anlotinib (multi-target tyrosine kinase inhibitor) combined with tislelizumab and chemotherapy is in progress. The anticipated outcomes from these studies will also provide solution to the broader puzzle—TNBC and enhance the optimal therapeutic choices with cost-minimization and accessibility.

Despite the small number and no comparator, this study offers useful information on the safety and tolerability of tislelizumab and its efficacy in achieving pCR, which is promising considering a differential observation among the same class of drugs. However, these results are to be interpreted with caution until further validation in a large target population.

In the expanding evidence-based treatment options in neoadjuvant setting, leading the therapeutic research in Chinese patients with TNBC, tislelizumab in combination with chemotherapy holds a promising stance and economic advantage to be considered for the treatment of early TNBC.

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