Editorial Commentary

Toripalimab: a new torchlight illuminating the path for metastatic triple negative breast cancer?

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Immunotherapy has transformed the paradigm of treatment in various types of malignancies. Among the subtypes of breast cancer, triple-negative breast cancer (TNBC) has become a focal point for immune checkpoint inhibitors (ICIs) due to its lack of therapeutic targets such as estrogen, progesterone receptors and human epidermal growth factor receptor 2 (HER2), as well as its heightened immunogenicity with higher tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB) and programmed death ligand 1 (PD-L1) expression.

In TNBC, therapeutic agents based on therapeutic targets are being explored, resulting in a diversification of treatment options. Antibody-drug conjugates (ADCs) are being tried as 1st line or 2nd line treatments for metastatic TNBC. Examples include sacituzumab govitecan targeting TROP-2 (1), ladiratuzumab vedotin targeting LIV-2 (2), and trastuzumab deruxtecan targeting HER2 (3). The poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, olaparib and talazoparib, selectively kill tumor cells with deficiencies in homologous recombination repair, making them a consideration for patients with germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants (4). Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend an ICI plus chemotherapy regimen for patients with a PD-L1 combined positive score (CPS) ≥10, regardless of BRCA status.

Through the IMpassion 130 study, atezolizumab plus nab-paclitaxel regimen appeared to establish itself as a first-line treatment for PD-L1 positive metastatic or unresectable locally advanced TNBC patients showing a reduced risk of deaths by 33% (5). Due to concerns regarding the availability of nab-paclitaxel, the IMpassion 131 study proceeded with weekly paclitaxel as a substitute. However, in either the PD-L1 positive or the intention-to-treat (ITT) population, the study yielded negative findings for both progression-free survival (PFS) and overall survival (OS) (6), leading to the withdrawal of the atezolizumab-combined regimen after consultation with the Food and Drug Administration (FDA) in the United States.

On the other hand, KEYNOTE-355 trial added pembrolizumab with chemotherapy selected by the physician (including paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin), which led to significant enhancements in PFS [with a median of 9.7 versus 5.6 months, hazard ratio (HR) =0.66, 95% confidence interval (CI): 0.50–0.88] and OS (with a median of 23.0 versus 16.1 months, HR =0.73, 95% CI: 0.55–0.95) compared to chemotherapy alone in patients with high PD-L1 expression who had CPS ≥10 (7). In light of these findings, pembrolizumab-containing regimens have become the most preferred first-line treatment for PD-L1 positive metastatic TNBC patients.

Toripalimab is a selective, recombinant, humanized monoclonal PD-1 antibody developed in China. Toripalimab

Table 1 Phase III clinical trials of immunotherapy in metastatic triple-negative breast cancer

Characteristic	IMPASSION-130 (5)	TORCHLIGHT	KN-355 (7)
PD-L1+ definition	SP142 PD-L1 ≥1%	JS311 PD-L1 CPS ≥1	22C3 PD-L1 CPS ≥10
PD-L1+, %	41%	57%	39%
Immunotherapy	Atezolizumab 840 mg IV every 2 weeks	Toripalimab 240 mg IV every 3 weeks	Pembrolizumab 200 mg every 3 weeks
Chemotherapy	nab-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of 28-day	nab-paclitaxel 125 mg/m^2 IV on days 1, 8 of 21-day	nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of 28-day or paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 of 28-day or gemcitabine 1,000 mg/m^2 IV + carboplatin AUC 2 IV on days 1 and 8 of 21-day
Control	Placebo + nab-paclitaxel	Placebo + nab-paclitaxel	Placebo + chemotherapy
No. of PD-L1+ patients (immunotherapy *vs.* control)	185 *vs.* 184	191 *vs.* 101	220 *vs.* 103
Median PFS in PD-L1+ (months)	7.5 *vs.* 5.3; HR 0.63 (95% CI: 0.49–0.81); P<0.001	8.4 *vs.* 5.6; HR 0.65 (95% CI: 0.470–0.906); P=0.0102	9.7 *vs.* 5.6; HR 0.65 (95% CI: 0.49–0.86); P=0.0012
Median OS in PD-L1+ (months)	25.4 *vs.* 17.9; HR 0.67 (95% CI: 0.53–0.86); P=0.0016	32.8 *vs.* 19.5; HR 0.62 (95% CI: 0.414–0.914); P=0.0148	23.0 *vs.* 16.1; HR 0.73 (95% CI: 0.55–0.95); P=0.0093

PD-L1, programmed death ligand 1; CPS, combined positive score; IV, intravenous; AUC, area under the curve; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

plus chemotherapy has recently shown significant survival benefit in metastatic cancer patients, including esophageal squamous cell carcinoma [JUPITER-06 (8)], non-small-cell lung cancer [CHOICE-01 (9)], melanoma [POLARIS-01 (10)], nasopharyngeal carcinoma [POLARIS-02 (11)], and urothelial carcinoma [POLARIS-03 (12)]. Recently released interim analysis of TORCHLIGHT study introduced new promising agent 'toripalimab' for the first line treatment for metastatic TNBC (13).

TORCHLIGHT, a randomized, double-blinded phase 3 trial, randomly assigned 531 participants to receive either toripalimab plus nab-paclitaxel (n=353; experimental arm) or placebo plus nab-paclitaxel (n=178; control arm) as first-line or second-line treatment for metastatic or recurrent TNBC. The study primarily aimed to evaluate PFS in both PD-L1-positive and ITT populations. The rate of PD-L1-positive (JS311 PD-L1 CPS ≥1) was 56.4% (300/531) in the ITT population. Among the PD-L1-positive group, 200 were assigned to the toripalimab arm, while 100 were assigned to the placebo arm. An interim analysis, meeting 75% of the PFS events, revealed a significant improvement in PFS in the toripalimab arm compared to the placebo arm among the PD-L1-positive population. The median PFS was 8.4 versus 5.6 months, with a HR of 0.65 (95% CI: 0.470–0.906, P=0.0102). A similar improvement in PFS was observed in ITT population, although it did not cross the prespecified efficacy boundary. Median overall survival was also higher in the toripalimab arm (32.8 versus 19.5 months, HR =0.62, 95% CI: 0.414–0.914, P=0.0148). Similarly, an improvement of OS improvement was observed in the ITT population favoring toripalimab. Notably, the incidence of treatment-emergent fatal adverse events were not significantly increased in toripalimab arm.

In *Table 1*, we summarized major findings from three phase 3 trials evaluating ICI-containing regimen as 1st line treatment in metastatic or recurrent TNBC. Notably, there were differences in PD-L1 positive rates across the trials. The IMpassion-130 and KEYNOTE-355 trials reported similar rates, approximately 40%, while the TORCHLIGHT trial observed a higher rate of 57%.

In the TORCHLIGHT study, PD-L1 expression was evaluated by JS311, a novel PD-L1 IHC antibody primarily staining the membrane and cytoplasm, tailored for the precise application of toripalimab. PD-L1 expression assessed by JS311 showed acceptable consistency with previously verified PD-L1 stating assays in previous studies (14). Concordance analysis between JS311 and 22C3 conducted on archival formalin-fixed paraffin-embedded biopsy samples from 103 patients, showed an overall

concordance rate of over 85%. The higher PD-L1-positive rate observed in the TORCHLIGHT study compared to KEYNOTE-355 could be attributed to the difference in the PD-L1 expression cutoffs: CPS 1 in TORCHLIGHT versus CPS 10 in KEYNOTE-355. A slightly lower PD-L1 expression threshold may offer more patients the opportunity for ICI treatment if toripalimab is available after undergoing an approval process.

In addition, a post-hoc study of IMpassion-130 revealed a co-positivity rate of approximately 36% for 22C3 and SP142 assays, with around 10–16% of patients showing single PD-L1 positivity (15). Combining this finding with the TORCHLIGHT study, it can be inferred that more than half of advanced TNBC patients could benefit from immunochemotherapy. Subgroup analysis of TORCHLIGHT showed varying survival benefits based on PD-L1 CPS score, with hazard ratios (HRs) of 0.88, 0.67, and 0.55 in CPS <1, 1≤ CPS <10, and CPS ≥10 subgroups, respectively. This underscores the rationale that immune-hot tumors may derive greater benefit from ICI addition compared to immune-moderate tumors.

Similar to IMpassion-130, the TORCHLIGHT study employed nab-paclitaxel as the backbone chemotherapy. Taxanes, such as nab-paclitaxel, can enhance the immune response by reprogramming tumor-associated macrophages and increasing TILs levels. Although nab-paclitaxel may exhibit different activity compared to paclitaxel, as suggested by the GeparSepto trial, concerns related to cost or approval issues could still hinder the use of the toripalimab plus nab-paclitaxel regimen. Moreover, the negative findings of IMpassion-131 raise doubts about the potential survival benefits of toripalimab when combined with paclitaxel or other chemotherapeutic agents. It's worth noting that subgroup analysis of KEYNOTE-355 demonstrated significant benefits of pembrolizumab when administered concurrently with paclitaxel.

The three 3 phase studies demonstrated a similar safety profile. Treatment-related adverse events did not show significant differences compared to the placebo group, while the overall frequency of immune-related adverse events (irAEs) was higher compared to the placebo group. The most frequent grade 3 or higher irAEs were increased liver enzyme levels in the toripalimab group (aspartate aminotransferase: 2.8% *vs.* 0.6%, alanine aminotransferase: 2.5% *vs.* 0.6%), immune-related hepatitis in the atezolizumab group (5.1% *vs.* 3.0%), and rash in the pembrolizumab group (2% *vs.* 0%). Thyroid-related complications and pneumonitis were notable irAEs with higher frequencies in the immunotherapy groups, but grade 3 or higher events were below 1% in all three studies.

Lastly, the TORCHLIGHT study exclusively enrolled Chinese patients, whereas the other two trials included a global population from multiple continents. Therefore, when interpreting the findings of the TORCHLIGHT study, it's essential to consider ethnicity, particularly because it focused solely on East Asian patients.

Administering ICIs as a first-line treatment in metastatic TNBC significantly improves survival outcomes. However, their use remains limited in non-immunogenic tumors, and systemic chemotherapy remains the primary treatment for patients without germline BRCA mutations. For these patients, treatments that increase tumor immunogenicity to make them candidates for ICIs would be desirable.

Ionizing Radiation can significantly enhance the antitumor immune response by impacting almost all steps of the cancer-immunity cycle (16). These effects include enhancing tumor antigen release and presentation, promoting the activation of immune cells, increasing the density of TILs, facilitating T cell recognition of tumor cells, and boosting the antitumor effect. Changes induced in the tumor microenvironment by ionizing radiation can transform "cold" tumors into "hot" tumors, enhancing responsiveness to ICIs (17).

Similarly, ADCs can induce anti-tumor immunity through direct activation and maturation of dendritic cells or through immunogenic cell death. Both mechanisms have been shown to engage the adaptive immune response by improving cross-presentation of tumor-derived antigens and priming specific CD8+ effector T cells, thereby triggering an immune response against the tumor. Although more clinical evidence is needed, the synergy between ADCs and ICIs holds promise for future treatments (18).

Conclusion

The combination of toripalimab with nab-paclitaxel led to a notable enhancement in PFS, while maintaining a favorable safety profile, among patients with metastatic or recurrent TNBC in which the tumors express PD-L1. Given the findings of the interim study, the OS outcomes in the toripalimab are noteworthy in the TORCHLIGHT study. Future statistical analyses will examine the final PFS outcomes in the ITT population and assess OS in the overall study population.

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