EDITORIAL

Where Did the Passion Go?—Rethinking Adjuvant Immune Therapy for Triple-Negative Breast Cancer

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Immunotherapy stands as one of the most transformative breakthroughs in modern cancer treatment. These innovative therapies target signaling pathways used by cancer cells to induce T-cell exhaustion at immune checkpoints, allowing the cancer to evade immune detection. In the last 10 years, immune checkpoint inhibitors have achieved long-lasting responses and, in some cases, even cures for cancers that once had poor prognoses. However, the journey to proving the efficacy of immunotherapy in breast cancer has been anything but straightforward. It took 8 years after the initial approval of an immune checkpoint inhibitor for melanoma before breast cancer saw its first approval in 2019, when atezolizumab received an indication for metastatic triple-negative breast cancer (TNBC) based on the IMpassion130 trial.[1] Shortly thereafter, the US Food and Drug Administration granted approval to pembrolizumab for metastatic TNBC, fueling optimism that patients with this aggressive form of cancer were on the cusp of reaping vast benefits from immune-based therapies. Yet excitement gave way to uncertainty following the negative results of IMpassion131,[2] leading to the voluntary withdrawal of atezolizumab's indication for TNBC. Although pembrolizumab remained in play, confidence in immune therapy for breast cancer had been shaken.

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Optimism rebounded when, less than a year after its approval for metastatic TNBC, pembrolizumab received an indication in the neoadjuvant and adjuvant settings based on the KEYNOTE-522 study. This practice-changing trial demonstrated a significantly improved pathological complete response rate, event-free survival and ultimately overall survival when pembrolizumab was combined with aggressive neoadjuvant chemotherapy for stage II and III TNBC.[3,4] As a result, in regions where available, patients with clinical stage II or III TNBC are offered the KEYNOTE-522 regimen as the standard of care.

However, if a patient undergoes surgery first and is later diagnosed with stage II or III disease, what is the best course of action? Although neoadjuvant treatment is typically recommended for patients with clinical stage II or III TNBC, one observational study found that only about half of such patients actually received it.[5] Moreover, preoperative clinical staging can sometimes underestimate pathological stage, prompting a surgery-first approach. This raises an important question: Can a patient who has already had primary surgery for TNBC still benefit from combining immunotherapy with adjuvant chemotherapy?

The ALEXANDRA/IMpassion030 trial[6] published in this issue of *JAMA* is the only study designed to address exactly this question. In this open-label study, a planned 2300 patients with pathological stage II or III TNBC who had undergone initial surgery were to be randomly assigned to an anthracycline- and taxane-based adjuvant regimen with or without the addition of atezolizumab for a full year. An interim analysis of the primary end point, invasive disease-free survival, was planned after 310 of 388 invasive disease-free survival events. An independent monitoring committee recommended temporarily stopping enrollment just 101 patients shy of the planned 2300 participants, prompting regulatory authorities to request an early interim analysis with a futility assessment. The updated statistical plan instituted an interim analysis at approximately 62% of the invasive disease-free survival events (242). The futility boundary was set at a hazard ratio of more than 1. In March 2023, after conducting the interim and futility analyses, treatment with atezolizumab was stopped and IMpassion030 was permanently closed. With only 68% (266 of 390) of the planned invasive disease-free survival events observed, a premature final analysis demonstrated a stratified hazard ratio of 1.11 (95% CI, 0.87-1.42; P = .38) and a higher rate of grade 3 or 4 adverse events with atezolizumab.

These disappointing results raise key questions: Was the failure due to the drug, the drug's target, the timing of therapy, or unidentified characteristics of the study population?

One explanation for the failure is that atezolizumab may be an inferior molecule compared with other immune checkpoint inhibitors due either to its target or to properties of the antibody such as binding affinity, IgG subclass, or clearance. With respect to the target, atezolizumab binds to programmed death ligand 1 (PD-L1) on tumor cells, blocking its interaction with the programmed death protein (PD-1) on regulatory T-cells, thus restoring immune recognition of the tumor cell. Agents such as pembrolizumab instead bind to PD-1, blocking interaction with both PD-L1 and PD-L2.[7] Because PD-L1 inhibitors only block the PD-1 and PD-L1 interaction, immune escape could theoretically occur via the PD-1 and PD-L2 axis. On the other hand, PD-1 blockade should maintain efficacy in tumors with lower expression of PD-L1 or higher expression of PD-L2, an antigen shown to be expressed in TNBC.[8] A systematic review and meta-analysis that included 19 randomized trials comparing anti–PD-1 and anti–PD-L1 agents to standard cancer treatment suggested agents that block PD-1 are associated with improved survival outcomes compared with those that block PD-L1.[9] Although interesting, no breast cancer trials were included.

Avelumab and durvalumab also target PD-L1 and have been clinically tested in breast cancer. Although each reported promising results in a randomized TNBC study,[10,11] atezolizumab has been evaluated more extensively in patients with breast cancer but with inconsistent results. The IMpassion130

trial demonstrated improved progression-free survival with atezolizumab for metastatic TNBC, but failed to meet the overall survival end point in the intent-to-treat population; the IMpassion131 and 132 studies in the same setting had negative results.[2,6,12] In the neoadjuvant setting, atezolizumab also showed mixed results. The IMpassion050 study in high-risk, *HER2*-positive early-stage breast cancer failed to demonstrate an improvement in a pathological complete response rate by adding atezolizumab to chemotherapy plus trastuzumab and pertuzumab.[13] However, in high-risk early-stage TNBC, the IMpassion031 study did meet its coprimary end points of a pathological complete response rate in both the intention-to-treat analysis and the subanalysis focused on the PD-L1-positive population, and showed a trend toward improved event-free and overall survival with atezolizumab, although it was underpowered for these end points.[14,15] The larger NeoTRIP trial, however, did not replicate these findings because atezolizumab failed to show an improved pathological complete response rate or event-free survival benefit when combined with taxane and platinum preoperatively followed by adjuvant anthracycline-based chemotherapy.[16] Although no head-to-head studies compare atezolizumab with pembrolizumab, it was hoped that results from the GeparDouze/NSABP B-59 trial, which used a similar design as the KEYNOTE-522 study, would offer insights into their relative benefits. The study employed the same chemotherapy backbone, although GeparDouze population is larger (1520 vs 1174 patients in KEYNOTE-522) assigned patients 1:1 to treatment arms (2:1 in KEYNOTE-522), allowed anthracycline to be given in dose-dense frequencies and allowed for adjuvant capecitabine per investigator discretion among those with residual disease. Results were presented at the 2024 San Antonio Breast Cancer Symposium. Although the pathological complete response rate was improved by 6.3% with the use of atezolizumab, the primary end point, event-free survival, was not significantly improved (HR, 0.8; 95% CI, 0.62-1.03; log-rank $P = .08$). These disappointing results may suggest that atezolizumab is less effective, although the differences in study design make a fair comparison impossible.[17]

The authors of the IMpassion030 trial reasonably suggest that the negative results may be attributed to the timing of immune checkpoint inhibitor therapy. Administering immune checkpoint inhibitors before tumor resection allows the immune system to recognize abundant tumor antigens, whereas postsurgery treatment, after the tumor has been removed, may limit opportunities for immune activation. If this theory holds, adjuvant immune checkpoint inhibitor treatment could be less effective than neoadjuvant therapy. Studies in non-small cell lung cancer have shown benefits from adjuvant-only immune checkpoint inhibitor, although giving an immune checkpoint inhibitor before and after surgery seems to yield better outcomes.[18-20] In breast cancer, however, the benefits of postoperative single-agent immune checkpoint inhibitor remain uncertain. Data from the A-BRAVE trial[10] suggest that avelumab improves overall survival, even though it does not prevent short-term recurrences. The ongoing phase 3 SWOG1418/NRG-BR006 trial will provide further insight into whether adjuvant pembrolizumab improves outcomes for patients with residual TNBC following neoadjuvant chemotherapy.

Another possible reason for mixed results in immune checkpoint inhibitor trials for TNBC is the inherent variability in tumor subtypes. Unlike *HER2*-amplified breast cancer, where *HER2* is a clear molecular driver that can be identified and targeted, TNBC is heterogeneous[21] and not driven by a single molecular feature. Certain TNBC subtypes may be more responsive to immune modulation, but without a validated biomarker or genomic signature to identify patients most likely to benefit, studies have inevitably enrolled patients with varying levels of immune-responsive tumors.[22] This variability can skew results, particularly if treatment arms are imbalanced in terms of immune responsiveness. Additionally, many studies, including the IMpassion030 trial, lack critical data such as *BRCA* variation status for a large proportion of patients, further complicating the interpretation of outcomes. Future trials focusing on molecularly defined TNBC subtypes will be crucial.

Another factor to consider is the difference in follow-up between the treatment arms in the IMpassion030 trial. Patients in the atezolizumab arm were monitored longer for adverse events and more frequently in clinic than were those in the chemotherapy-only arm, which could have led to overreporting of adverse events and recurrences in the atezolizumab group. The early termination of the trial, due to futility, also limits our understanding of long-term outcomes such as distant disease-free survival, overall survival, and safety. Even though halting the trial was the right decision, long-term follow-up for secondary outcomes remains essential, both in positive and negative trials. This is a critical ethical responsibility to trial participants, especially in studies that fail to demonstrate benefit.

So what does this mean for clinical practice? IMpassion030 may have been our last large-scale trial of adjuvant immune checkpoint inhibitor in TNBC. With no other major studies planned in this setting, any patient diagnosed with TNBC should be referred to a medical oncologist before surgery to consider neoadjuvant immune checkpoint inhibitor–based chemotherapy. Currently, there is no evidence to support offering adjuvant immune checkpoint inhibitor treatment to patients who have already had surgery. However, the passion for exploring immune therapy in breast cancer is far from extinguished. As trial results continue to emerge, it is critical that translational research is prioritized to identify patients most likely to respond to these therapies and to continue long-term follow-up to better understand both efficacy and safety outcomes.

ARTICLE INFORMATION

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