Unlocking the promise of neoadjuvant immunotherapy in gastroesophageal cancers: insights from the PANDA trial

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Anti-PD-1 immune checkpoint inhibitors (ICIs) in combination with chemotherapy have become the standard of care in metastatic gastroesophageal cancers (GEC) after the landmark KEYNOTE-590, CheckMate-648, CheckMate-649, and KEYNOTE-859 trials showed improvement in overall survival (OS) (1-4). In the adjuvant setting, nivolumab improved disease-free survival (DFS) from 22.4 months compared to 11 months with placebo in resected esophageal cancer (5). These studies set up a logical platform for the neoadjuvant use of ICIs in GEC.

Neoadjuvant immunotherapy has several potential advantages. Firstly, resectable GEC patients tolerate systemic treatment better before surgery. Secondly, it can help treat micro-metastasis early. Thirdly, higher tumor burdens before surgery likely generate more neoantigens that produce more polyclonal T-cells. Finally, it is also hypothesized that neoadjuvant immunotherapy can help overcome the immunosuppressive effects of surgery (6).

This article examines the results of Verschoor *et al.*'s phase 2 PANDA trial, which focused on atezolizumab treatment for patients with resectable gastric/gastroesophageal junction (G/GEJ) cancer. In PANDA, a single-center open-label trial, patients underwent neoadjuvant treatment consisting of four cycles of atezolizumab plus docetaxel, oxaliplatin, and capecitabine, after a single cycle of atezolizumab monotherapy. To the best of our knowledge, this is the first trial describing the safety and effectiveness of atezolizumab monotherapy, followed by atezolizumab plus chemotherapy in previously untreated, resectable G/GEJ cancer. The primary endpoint focused on safety and feasibility, while the secondary endpoints included pathologic response, survival outcomes, translational analyses of the tumor microenvironment (TME), and associations with clinical response to immunotherapy and chemotherapy in patients with G/GEJ tumors.

Results from the phase 2 PANDA trial showed a major pathological response (Mandard Tumor Regression with ≤10% of viable tumor) in 14/20 [70%, 95% confidence interval (CI): 46–88%] patients along with 9/20 (45%, 95% CI: 23–68%) pathologic complete responses (pCR) (7). Among 18 patients with a proficient mismatch repair (pMMR) tumor, 7 out of 18 patients (39%) achieved a pCR. Out of the 14/20 responders, 13/14 patients were disease-free and alive after a median follow-up of 47 months (7). No patients were delayed for resection, and 19/20 (95%) of patients had tumor-free surgical resection margins. The side effect profile of atezolizumab was favorable in the PANDA trial. Atezolizumab was tolerated well; only 2/10 (10%) of patients experienced grade 3 immune-related adverse events. There was no grade 4 or higher immune-related

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adverse events.

The trial begs the question of whether the improvements in pathologic response will translate to improved survival in patients with resectable G/GEJ cancer. Pathologic response has been shown to be a strong prognostic factor and has also been shown to have some potential association with OS in randomized controlled trials (8). In this particular study, there was a strong association between the pathologic response and survival as 13 out of 14 (93%) responders did not have disease recurrence after a median follow-up of 47 months compared to 5 out of 6 nonresponders who had recurrence and died from their disease. Only one of the nonresponders remained disease-free. Furthermore, the PANDA 2 trial's 3-year recurrence rate was 27%, as opposed to the predicted 50% recurrence rate after FLOT treatment (9). Clinical outcomes were strongly correlated with pathologic response: patients who were responders had better OS (P=0.0006) and DFS (P=0.0001) than nonresponders.

Prior research has examined the use of atezolizumab and other ICIs in conjunction with FLOT as a perioperative therapy for resectable stomach or gastroesophageal junction (GEJ) cancer. In the DANTE trial, which transitioned from phase II to a phase III study, the addition of atezolizumab to perioperative FLOT chemotherapy for resectable esophagogastric adenocarcinoma demonstrated significant benefits. The atezolizumab/FLOT group exhibited higher rates of histopathologic complete regression (24% *vs.* 15%; one-sided P=0.032) and downstaging (10). The MATTERHORN trial is a phase 3 randomized placebo control trial that analyzed perioperative durvalumab plus FLOT in patients with resectable G/GEJ cancers. Durvalumab was shown to significantly improve the pCR (19%) as compared to FLOT alone at 7% (odds ratio =3.08; P<0.00001) (11). The KEYNOTE-585 study, evaluating pembrolizumab plus chemotherapy in locally advanced G/GEJ adenocarcinoma, demonstrated a significant improvement in the pCR rate with pembrolizumab plus chemotherapy compared to placebo plus chemotherapy, showing an absolute difference of 10.9% (95% CI: 7.5–14.8%) (12). However, while there was a potentially clinically relevant gain in median event-free survival (EFS), this did not translate into a statistically significant improvement in EFS [44.4 months with pembrolizumab *vs.* 25.3 months with placebo; hazard ratio (HR) =0.81, 95% CI: 0.67–0.99; P=0.0198]. Similarly, there was no statistically significant improvement in OS with pembrolizumab plus chemotherapy compared to placebo plus chemotherapy (60.7 *vs.* 58.0 months; HR =0.90, 95% CI: 0.73–1.12; P=0.174). We see from these randomized studies that combining immunotherapy with chemotherapy significantly improves pCR; however, this has not shown a translation to improvement in OS. In the PANDA study, we saw that there is an improvement in both DFS and OS for those who are responders *vs.* nonresponders. However, we must remember that this is a single arm, non-randomized study. Therefore, it remains to be seen whether addition of ICIs to chemotherapy is beneficial to a biomarker non-selected population of resectable G/GEJ cancers until the mature survival data from the MATTERHORN study are available.

Several studies have examined the association between circulating tumor DNA (ctDNA) clearance and recurrence in GECs. The interest in analyzing ctDNA clearance stems from the hypothesis that micrometastatic disease at the time of surgical resection underlies the majority of recurrences. The findings of these studies have been consistent, as patients with ctDNA clearance have better outcomes (13). PANDA study analyzed ctDNA and found it was cleared in 11 of 11 responders, where 3 of the 6 nonresponders remained positive (P=0.029). The levels of ctDNA were also analyzed and found to be significantly higher in nonresponders (P=0.0065). This study further shows the association between ctDNA and pCR in neoadjuvant treatment, as previously described.

Identifying biomarkers predictive of response to immunotherapy remains a critical area of ongoing research and will help in improving the efficacy of immunotherapy. Traditional biomarkers have always had limited roles in this setting. Unlike the DANTE study, the combined positive score (CPS) score and tumor mutational burden (TMB) did not predict outcomes in PANDA trial. The DANTE study showed that patients with higher CPS scores had better pCRs. In contrast, PANDA study looked at important translational outcomes, including the number of $CD8^+PD\text{-}1^+$ T cells and the percentage of $CD8^+PD\text{-}1^+$ T cells over the total number of $CD8^+$ T-cells. The study indicated that at baseline, responders had a significantly higher value of $CD8^+PD\text{-}1^+$ T-cells than nonresponders (P=0.034) and that the proportion of $CD8^+PD\text{-}1^+$ T cells among $CD8^+$ T cell numbers was significantly higher in responders than nonresponders (P=0.019). These could serve as an important biomarker in future studies. There was also some association in the study between regulatory T-cells (Tregs), eosinophils, and mast cell signatures when comparing nonresponders to responders, which needs further exploration.

In the PANDA study, after one cycle of atezolizumab, there was a change in the TME composition. However, there was minimal difference in the TME when atezolizumab was given with chemotherapy. This is an exciting discovery, as this could impact future trial designs. In summary, this is an important proof of concept study that showed priming the TME possibly leads to a higher pCR. However, based on the results of the KEYNOTE-585 study and pending the survival analysis from the MATTERHORN trial, the higher pCR rates with ICIs are yet to show improved OS, and further strategies should be examined to determine how to use checkpoint inhibitors optimally. One of the strategies used in the PANDA trial was priming the TME with one dose of atezolizumab. Whether we can fuel this TME further with a mix of other checkpoint inhibitors, such as CTLA-4, is still to be observed, considering that anti-CTLA-4 drugs are known to decrease Tregs, which were elevated among non-responders in the PANDA trial. The clinical and translational findings of the PANDA trial are encouraging and need to be further evaluated in future randomized studies.

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