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Corresponding Author:	Roberto A. Pazo-Cid Hospital Universitario Miguel Servet Servicio de Oncologia Medica Zaragoza, Zaragoza SPAIN
First Author:	Roberto A. Pazo-Cid
Order of Authors:	Roberto A. Pazo-Cid
	Paula Gomila Pons
Abstract:	Long et al. (1) evaluated neoadjuvant cadonilimab plus FLOT chemotherapy (ChT) in locally advanced gastric (G) and gastroesophageal junction (GEJ) adenocarcinoma, showing a pathological complete response (pCR) rate of 21.1% and an R0 resection rate of 100%. These findings align with other perioperative immunotherapy trials, although challenges remain in optimizing event-free survival (EFS).
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Integrating immunotherapy in the treatment of resectable gastric cancer: are we in the right track?

Roberto Pazo-Cid 1,2, 3 and Paula Gomila Pons 1

1 Miguel Servet University Hospital, Medical Oncology Department, 50009, Zaragoza, Spain
2 University of Zaragoza, School of Medicine, 50009, Zaragoza, Spain
3 Aragon Institute of Health Sciences, 50009, Zaragoza, Spain

Correspondence: rpazo@salud.aragon.es

Summary
Long et al. (1) evaluated neoadjuvant cadonilimab plus FLOT chemotherapy (ChT) in locally advanced gastric (G) and gastroesophageal junction (GEJ) adenocarcinoma, showing a pathological complete response (pCR) rate of 21.1% and an R0 resection rate of 100%. These findings align with other perioperative immunotherapy trials, although challenges remain in optimizing event-free survival (EFS).

The treatment of locally advanced G/GEJ adenocarcinoma remains a significant challenge, despite advances in ChT and surgical techniques. The integration of immune checkpoint inhibitors (ICIs) into the neoadjuvant (NAT) and perioperative treatment regimens is a promising step toward improving outcomes for this patient population.

The phase II study reported by Long et al. (1) explores the combination of the novel bispecific anti-PD-1/CTLA-4 antibody cadonilimab with preoperative FLOT ChT in the NAT setting. Subsequently patients underwent surgery, followed by postoperative FLOT ChT. The study showed a pathological complete response (pCR) rate of 21.1% and a major pathological response (MPR) rate of 44.7%. All patients who underwent surgery achieved R0 resection. The combination therapy was well tolerated, with 31.6% of patients experiencing grade 3 treatment-related adverse events (TRAEs), but no grade 4 or 5 adverse events were reported.

The phase 3 trials DANTE (2), MATTERHORN (3), KEYNOTE-585 (4), and DRAGON IV/CAP05 (5) showed notable improvements in pCR rates with the addition ICIs to ChT in the perioperative setting, aligning with the pCR rate reported by Long et al. (1). In DANTE, the pCR was 24% with atezolizumab plus FLOT, versus 15% for FLOT alone (2). The MATTERHORN trial reported a pCR of 19% with durvalumab plus FLOT, compared to 7% in the control arm, with MPR rates of 27% and 14%, respectively (3). In KEYNOTE-585, pembrolizumab plus ChT achieved a pCR of 13%, versus 2.4% in the control arm (5). In the DRAGON IV/CAP05 study, the SOXRC group (camrelizumab combined with rivoceranib, S-1, and oxaliplatin) had a significantly higher pCR (18.3%) compared to the SOX group (5.0%), and the MPR was also higher in the SOXRC group (51.1%) versus the SOX group (37.8%) (5).

Unfortunately, the improvement in pCR rates with ICI plus ChT may be insufficient to translate into a survival benefit. In KEYNOTE-585, the primary endpoint of event-free survival (EFS) was not met: the median EFS was 44.4 months in the pembrolizumab group compared to 25.3 months in the placebo group (HR 0.81, 95% CI 0.67 to 0.99; p = 0.0198) (4). However, this difference did not reach the prespecified p-value threshold of 0.0178 required for statistical significance.

In resectable G/GEJ adenocarcinoma, the optimal sequence, timing, and treatment combination when integrating ICI with multimodality therapy must be optimized to avoid unnecessary toxicity while maximizing the potential for clinical benefit. ATTRACTION-5 was the first phase 3 trial to compare the efficacy of adjuvant ICI plus ChT with placebo plus ChT in patients with pathological stage III G/GEJ adenocarcinoma undergoing surgery (6). Adjuvant nivolumab plus ChT did not show clinical benefit in terms of relapse-free survival (RFS). The VESTIGE trial (EORTC 1707) was a randomized, phase II study designed to evaluate the efficacy of adjuvant ICIs using nivolumab and ipilimumab in patients with G/GEJ who were at high risk for recurrence (7). It included patients with tumor-positive lymph nodes (ypN+) or incomplete surgical resection (R1) following NAT. The results suggested that postoperative nivolumab and ipilimumab were not superior to ChT in improving disease free survival (DFS) in patients with resected high-risk G/GEJ adenocarcinoma and, in fact, showed worse outcomes, with a median DFS of 11.9 months for nivolumab/ipilimumab versus 23.3 months for chemotherapy ($p = 0.02$).

The CheckMate 577 trial studied the effect of adjuvant nivolumab immunotherapy compared to placebo in patients with esophageal/GEJ cancer who had residual disease, either in the primary tumor (ypT1 or higher) or in lymph nodes (ypN+), after preoperative ChT-radiotherapy (ChTRT) (8). DFS was improved with adjuvant nivolumab compared to placebo (HR 0.69; 95% CI, 0.56–0.86). Additionally, the risk of distant recurrence or death was 26% lower (HR 0.74; 95% CI, 0.60–0.92), and distant metastasis-free survival was 10.7 months longer with adjuvant nivolumab than with placebo. The role of ChTRT in treating resectable G/GEJ cancer is currently unclear, as it has been largely replaced by perioperative ChT. Given the possibility that RT could enhance the effects of ICIs, further studies are needed to understand its value in the context of NAT.

In the study by Long et al. (1), subgroup analysis found no statistical differences in pCR across different PD-L1 CPS and microsatellite instability (MSI) status. In CheckMate 577, nivolumab was similarly effective regardless of tumor-cell PD-L1 expression (8). Nonetheless, mismatch repair deficient (dMMR)/MSI-high resectable G/GEJ cancers have demonstrated a pCR rate of nearly 60% with the combination of an anti-PD1 with an anti-CTLA-4 in phase II trials, such as GERCOR NEONIPIGA (9).

In the Phase II PANDA trial, 21 patients with resectable G/GEJ received NAT with one cycle of atezolizumab monotherapy, followed by four cycles of atezolizumab plus docetaxel, oxaliplatin, and capecitabine (10). A major pathologic response (MPR) (≤10% residual viable tumor) was observed in 70% (95% CI, 46–88%) of patients, including a pCR of 45% (95% CI, 23–68%). A strong relationship was found between MPR and significantly higher DFS ($P = 0.0001$) and OS ($P = 0.0006$) in responders compared to non-responders. The use of single-agent PD-1/L1 axis blockade followed by the subsequent combination with ChT led to TME alterations, with increased immune activation. A significant increase in CD8+ T cell infiltration was observed after atezolizumab monotherapy in responders ($P = 0.009$), while CD8+ T cell infiltration remained stable in non-responders ($P = 1.0$). The addition of an anti-CTLA-4 could help by improving Treg cell depletion. In this regard, an induction dose of candonilimab in the NAT setting could be explored to enhance efficacy outcomes.

In the PANDA study, circulating tumor DNA (ctDNA) concentration 12 weeks after surgery was associated with response and DFS (10). Biomarkers, including PD-L1 expression, MSI-H/dMMR status, and ctDNA, may be valuable in guiding treatment decisions when integrating ICIs in the therapy of resectable G/GEJ cancer.

In conclusion, ICIs show great promise in the NAT setting of locally advanced G/GEJ cancer, as demonstrated by the results of Long et al (1) study. Clinical and translational evaluation of tumor biology after NAT can provide valuable insights. Although the addition of ICIs to ChT has

demonstrated superior pathological regression rates compared to standard preoperative ChT, pCR may be not a reliable surrogate endpoint for EFS. Disappointing outcomes for unselected patients in the adjuvant setting suggest that effective, predictive biomarker-guided patient selection is required to demonstrate a meaningful survival benefit from ICIs in resectable G/GEJ cancer. Finally, the timing of initiation of ICIs and ChT, the duration of ICIs treatment and its potential synergy with RT are questions that need to be addressed in the future.

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Declaration of Interests

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P.G.P. declares no competing interests.

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