Highlights in Upper Gastrointestinal Cancer

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Addition of Durvalumab to Chemotherapy Improves Event-Free Survival in Resectable Gastric/GEJ Cancer

Adding durvalumab (Imfinzi, AstraZeneca) to perioperative 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy significantly improved event-free survival (EFS) in patients with resectable gastric or gastroesophageal junction (GEJ) cancer, according to results from the phase 3 MATTERHORN trial. Although FLOT is a perioperative standard of care for resectable gastric/GEJ cancer, recurrence rates remain high, and immune checkpoint inhibitors have not been established in the perioperative setting.

The double-blind study randomized 948 patients with resectable locally advanced gastric/GEJ adenocarcinoma (stages II-IVa) 1:1 to receive 1500 mg of durvalumab or placebo every 4 weeks plus FLOT chemotherapy for 4 perioperative cycles (2 neoadjuvant, 2 adjuvant), followed by durvalumab or placebo maintenance for 10 cycles. Patients were stratified by geographic region (Asia vs non-Asia), lymph node status, and programmed death ligand 1 (PD-L1) expression.

After a median follow-up of 31.5 months, EFS was statistically significantly longer with durvalumab plus FLOT than with placebo plus FLOT (hazard ratio [HR], 0.71; 95% CI, 0.58-0.86; *P*<.001). Median EFS was not reached in the durvalumab arm and was 32.8 months in the placebo arm. The 24-month EFS rates were 67.4% with durvalumab and 58.5% with placebo.

In addition, a trend toward longer overall survival (OS) was noted with durvalumab (median not reached vs 47.2 months; HR, 0.78; 95% CI, 0.62-0.97; *P*=.025), although formal statistical testing awaits final analysis. Rates of grade 3/4 adverse events were similar in the 2 arms, with no delays in surgery or the initiation of adjuvant therapy.

"These results support durvalumab plus FLOT as a potential new global standard of care for resectable gastric/GEJ cancer," concluded presenter Yelena Y. Janjigian, MD, of Memorial Sloan Kettering Cancer Center in New York City. The study results were published simultaneously in the *New England Journal of Medicine*.

Janjigian Y, Al-Batran S-E, Wainberg Z, et al. Event-free survival in MATTERHORN: a randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel chemotherapy in resectable gastric/gastroesophageal junction cancer [ASCO abstract LBA5]. *J Clin Oncol.* 2025;43(17)(suppl).

Trastuzumab Deruxtecan Demonstrates Superior Survival Over Standard Therapy in Second-Line HER2+ Gastric Cancer

Trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca) significantly improved OS vs ramucirumab (Cyramza, Lilly) plus paclitaxel in patients with human epidermal growth factor 2–positive (HER2+) unresectable or metastatic gastric or GEJ cancer, according to primary results from the phase 3 DESTINY-Gastric04 trial. The results were presented by Kohei Shitara, MD, of National Cancer Center Hospital East in Kashiwa, Japan, and were published simultaneously in the *New England Journal of Medicine*.

The global, open-label study randomized 494 patients with biopsy-confirmed HER2+ status 1:1 to receive 6.4 mg of T-DXd per kilogram or ramucirumab plus paclitaxel as second-line treatment. The primary endpoint was OS.

After a median follow-up of 16.8 months for T-DXd and 14.4 months for ramucirumab plus paclitaxel, median OS was significantly longer with T-DXd than with the control regimen, at 14.7 vs 11.4 months, respectively (HR, 0.70; *P*=.0044). The study also demonstrated superior progression-free survival (PFS; 6.7 vs 5.6 months; HR, 0.74; *P*=.0074) and confirmed objective response rate (ORR; 44.3% vs 29.1%; *P*=.0006) with T-DXd.

Treatment-emergent adverse events occurred in 100% of the patients who received T-DXd vs 97.9% of the control patients, with grade 3 or higher events in 68.0% vs 73.8%, respectively. Notably, drug-related interstitial lung disease/pneumonitis occurred in 13.9% of the patients who received T-DXd vs 1.3% of those in the control arm.

The results support T-DXd as a second-line standard of care for HER2+ gastric cancer, with a safety profile consistent with that of previous studies.

Shitara K, Gumus M, Pietrantonio F, et al. Trastuzumab deruxtecan vs ramucirumab + paclitaxel in second-line treatment of patients with human epidermal growth factor receptor 2-positive unresectable/metastatic gastric cancer or gastroesophageal junction adenocarcinoma: primary analysis of the randomized, phase 3 DESTINY-Gastric04 study [ASCO abstract LBA4002]. *J Clin Oncol.* 2025;43(17)(suppl).

Phase 2 Trial Investigating Sacituzumab Govitecan in Advanced Esophageal Cancer

A phase 2 clinical trial is investigating sacituzumab govitecan (SG; Trodelvy, Gilead) as a treatment option for patients with recurrent or metastatic esophageal squamous cell carcinoma that is no longer responding to standard platinum-based chemotherapy or immune checkpoint inhibition. SG is an antibody-drug conjugate targeting TROP2, a transmembrane protein that is overexpressed in esophageal squamous cell carcinoma.

This prospective, single-arm, multicenter trial conducted by Jhe-Cyuan Guo, MD, PhD, and colleagues from National Taiwan University Hospital in Taiwan is evaluating the intravenous administration of 10 mg of SG per kilogram on days 1 and 8 of each 21-day cycle. Eligible patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1.

The study has a planned enrollment of 35 patients over 24 months, accounting for a 10% dropout rate. The primary endpoint is ORR by RECIST 1.1, with the study powered to detect an ORR of at least 25% vs a historical control of 10% or less. In the first stage, 16 patients will be enrolled, and at least 2 responses will be required to proceed to the second stage of 15 additional patients. Secondary endpoints include OS, PFS, duration of response, and safety outcomes.

Enrollment began in August 2024, with 5 of the 35 planned patients enrolled as of December 2024. The trial will also conduct biomarker analyses exploring TROP2 expression and other molecular markers associated with treatment efficacy, treatment resistance, and toxicity.

Guo J-C, Wu T-C, Huang T-C, et al. A phase II study of sacituzumab govitecan for advanced esophageal squamous cell carcinoma patients (SG-ESCC) [ASCO abstract TPS 4208]. *J Clin Oncol*. 2025;43(16)(suppl).

CAR T-Cell Therapy Shows Significant Survival Benefit in Advanced Gastric Cancer

Claudin18.2-specific chimeric antigen receptor (CAR) T-cell therapy (satri-cel) achieved significant improvements in PFS and OS in comparison with standard treatment in patients with previously treated advanced gastric or GEJ cancer, according to a new study.

"This is the first confirmatory RCT of CAR T-cell therapy in solid tumors," noted lead investigator Changsong Qi, MD, of Peking University Cancer Hospital in Beijing, China.

The phase 2 CT041-ST-01 trial enrolled 156 patients with CLDN18.2-positive advanced gastric/GEJ cancer who had received at least 2 prior lines of treatment. Patients were randomized 2:1 to receive satri-cel (up to 3 infusions of 250×10^6 cells) or physician's choice of treatment. The median number of prior systemic therapies was 2 in both arms, with approximately 70% of the patients having peritoneal metastasis.

After a median follow-up of 8.90 months, satri-cel significantly improved median PFS in comparison with standard treatment (3.25 vs 1.77 months; HR, 0.366; 95% CI, 0.241-0.557; $P<.001$). Median OS also showed improvement (7.92 vs 5.49 months; HR, 0.693; 95% CI, 0.457-1.051; 1-sided $P=.0416$).

The safety analysis revealed that 95.5% of the patients who received satri-cel experienced cytokine release syndrome, predominantly grade 1 to 2 (90.9%); only 4.5% experienced grade 3 events. No immune cell–associated neurotoxicity syndrome (ICANS) occurred in either group.

Dr Qi concluded that satri-cel had achieved statistically significant improvements in PFS and OS with manageable safety, supporting its potential as a new standard of care for advanced gastric/GEJ cancer. The study results were published simultaneously in the *Lancet*.

Qi C, Liu C, Peng Z, et al. Claudin18.2-specific CAR T cells (satri-cel) vs treatment of physician's choice for previously treated advanced gastric or gastroesophageal junction cancer: primary results from a randomized, open-label, phase II trial (CT041-ST-01) [ASCO abstract 4003]. *J Clin Oncol*. 2025;43(16)(suppl).

Adjuvant Nivolumab Shows Sustained Disease-Free Survival Benefit in Resected Esophageal Cancer

Adjuvant nivolumab (Opdivo, Bristol Myers Squibb) achieved a sustained long-term disease-free survival (DFS) benefit vs placebo in patients with resected esophageal or GEJ cancer following neoadjuvant chemoradiotherapy, according to final OS results from the phase 3 CheckMate 577 study, presented by Ronan J. Kelly, MD, of Baylor University Medical Center in Dallas, Texas. Although the primary endpoint of DFS improvement was maintained, OS did not reach statistical significance.

The global, randomized trial enrolled 794 patients with resected stage II/III esophageal or GEJ cancer who had residual pathologic disease after neoadjuvant chemoradiotherapy and surgery. Patients were randomized 2:1 to receive 240 mg of nivolumab or placebo every 2 weeks for 16 weeks, followed by 480 mg of nivolumab or placebo every 4 weeks, with a maximum duration of treatment of 1 year.

At a median follow-up of 78.3 months, adjuvant nivolumab continued to show DFS benefit vs placebo (HR, 0.76; 95% CI, 0.63-0.91), with a median DFS of 21.8 vs 10.8 months. Although median OS was numerically longer with nivolumab than with placebo (51.7 vs

35.3 months), the difference was not statistically significant (HR, 0.85; 95.87% CI, 0.70-1.04; *P*=.1064). The 5-year OS rate was 46% with nivolumab vs 41% with placebo.

Median distant metastasis–free survival was also longer with nivolumab than with placebo, at 27.3 vs 14.6 months (HR, 0.75), and PFS on subsequent systemic therapy was longer with nivolumab (HR, 0.81). Nivolumab remained well tolerated with longer follow-up, with treatment-related adverse events occurring in 71% of patients who received nivolumab vs 48% of those who received placebo.

These results further support adjuvant nivolumab as standard of care for patients with resected esophageal or GEJ cancer and residual pathologic disease following neoadjuvant chemoradiotherapy.

Kelly R, Ajani J, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: first results of overall survival from CheckMate 577 [ASCO abstract 4000]. *J Clin Oncol*. 2025;43(16)(suppl).

Sacituzumab Govitecan Safe, Efficacious in Advanced or Metastatic Pancreatic Cancer

SG shows satisfactory safety and efficacy in patients with advanced or metastatic pancreatic cancer that is refractory to chemotherapy, according to a retrospective trial in a Chinese population.

For the trial, 19 patients with refractory advanced or metastatic pancreatic cancer received intravenous SG on days 1 and 8 of 21-day cycles—either alone or in combination with other treatment regimens—until disease progression or unacceptable toxicity.

After up to 2 years of follow-up, the median PFS was 3.15 months. There were 12 patients who received the full 10-mg dose of SG per kilogram and 7 patients who received less than 75% of the standard dose because of poor physical condition; 3 of these patients received a combination regimen. The median PFS was 2.25 months (95% CI, 1.0-3.0 months) in the reduced-dose group vs 3.45 months (95% CI, 0.8-7.0 months; HR, 0.14; *P*=.08) in the full-dose group, and median PFS was 3.05 months (95% CI, 0.8-7.0) in the SG monotherapy group vs 3.5 months (95% CI, 1.0-9.0) in the combined treatment group. All of the 7 patients who underwent TROP2 immunohistochemistry testing exhibited moderate to high expression of TROP2; the median PFS for this subgroup was 3.7 months (95% CI, 2.0-3.8 months). The ORR was 20% among the 15 patients in whom efficacy could be evaluated.

Hematologic adverse events occurred in 11 patients, and grade 3 or higher adverse events—all neutrophil decreases—occurred in 4 patients.

Study author Xiaofei Zhang, MD, from Shanghai Jiao Tong University in Shanghai, China, concluded that "SG-based regimens seem to represent a potential new therapeutic option for advanced pancreatic cancer patients with good performance status."

Zang X. Real world evidence for patients with advanced and metastatic pancreatic cancer treated with sacituzumab govitecan: a retrospective trial in China [ASCO abstract e16412]. *J Clin Oncol*. 2025;43(16)(suppl).