Editorial Commentary

Liposomal eribulin (E7389-LF) plus nivolumab: a potential treatment option for patients with advanced gastric cancer?

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Gastric cancer remains the fifth most commonly diagnosed malignancy and a leading cause of cancer-related death worldwide, with an anticipated rise in disease burden to approximately 1.8 million new cases and 1.3 million deaths by the year 2040 (1). In the United States, there were estimated 26,500 new cases and 11,130 cancer-associated deaths in 2023 (2). Approximately one-third of new gastric cancer cases are unfortunately metastatic at diagnosis (2). The average five-year overall survival (OS) of all patients diagnosed with gastric cancer is less than 40%; however, the survival rate decreases to 7% if presenting with distant metastatic disease (2). Moreover, among patients with localized disease who are able to undergo curative-intent gastrectomy, more than one-third will still recur, with most recurrences occurring during the first two years after surgical resection, and the most common site of recurrence being distant (3). Therefore, improvements in therapies are strongly needed to improve survival outcomes.

Over the past several years, the therapeutic landscape for advanced unresectable or metastatic gastric cancer has been significantly advanced by the incorporation of immune checkpoint inhibitor (ICI) therapy and molecular targeted agents into systemic treatment approaches. First-line strategies are presently informed by upfront molecular characterization of tumor tissue, including testing for microsatellite instability (MSI), programmed death ligand 1 (PD-L1), and human epidermal growth factor receptor 2 (HER2). For patients whose tumors are MSI-high or PD-L1 combined positive score (CPS) positive (≥5) and HER2-negative, the treatment paradigm consists of a doublet of cytotoxic chemotherapy, including a fluoropyrimidine [5-fluorouracil (5-FU) or capecitabine] plus platinum (oxaliplatin typically preferred over cisplatin due to more favorable toxicity profile) combined with an anti-programmed death 1 (PD-1) monoclonal antibody (mAb). The CheckMate 649 study demonstrated that in previously untreated patients with advanced unresectable or metastatic esophageal, gastroesophageal junction (GEJ) and gastric adenocarcinoma, the addition of nivolumab to FOLFOX (5-FU plus oxaliplatin) or CAPOX (capecitabine plus oxaliplatin) chemotherapy compared with FOLFOX or CAPOX alone improved OS [13.8 *vs.* 11.6 months, hazard ratio (HR) =0.80, 95% confidence interval (CI): 0.68–0.94], progression-free survival (PFS) (HR =0.77, 95% CI: 0.68–0.87), and overall response rate (ORR) (60% *vs.* 45%) in all randomized patients, with a larger magnitude of OS benefit (14.4 *vs.* 11.1 months, HR =0.71, 95% CI: 0.59–0.86) observed in patients with higher PD-L1, CPS

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≥5 (4). Although the combination of fluoropyrimidine and platinum chemotherapy plus nivolumab received Food and Drug Administration (FDA) approval for all patients with advanced HER2-negative gastroesophageal adenocarcinoma in the frontline setting regardless of PD-L1 CPS score, additional analyses have called into question its benefit in patients with low PD-L1 expression (CPS <5) (5). Consequently, given the clearer benefit observed in patients with higher PD-L1 CPS score, current expert society guidelines recommend the addition of nivolumab to chemotherapy for patients with PD-L1 CPS ≥5 (6). The pivotal Trastuzumab for Gastric Cancer (ToGA) trial initially established HER2-directed therapy with trastuzumab in combination with fluoropyrimidine and platinum chemotherapy in the frontline setting for patients with HER2 overexpression, which comprise about 30% of the patient population (7). Given the potential for targeted antibody therapy combined with immunotherapy to improve immune cell filtration and T cell response, the phase III KEYNOTE 811 study, which investigated the addition of pembrolizumab to first-line trastuzumab plus fluoropyrimidine and platinum chemotherapy in patients with gastric and GEJ adenocarcinoma, demonstrated marked improvement in ORR (72.6% *vs.* 59.8%) with the addition of pembrolizumab, and PFS benefit primarily observed in patients with PD-L1 CPS ≥1 [10.0 *vs.* 8.1 months, HR =0.72, 95% CI: 0.60–0.87], with pending results on OS (8).

Options for later lines of treatment for patients with gastric or GEJ adenocarcinoma without specific molecular biomarkers typically involve other chemotherapeutic agents. Paclitaxel plus ramucirumab [an anti-vascular endothelial growth factor receptor 2 (VEGFR-2) mAb] was evaluated in the RAINBOW study, which showed an improvement in median OS from 7.4 months with paclitaxel alone to 9.6 months with the addition of ramucirumab to paclitaxel (HR =0.807, 95% CI: 0.678–0.962), and an increase in response rate from 16% to 28% with the combination (9). When compared with best-supportive care alone, single-agent ramucirumab also demonstrated an improvement, though more modest, in OS for previously treated patients with gastric cancer (10). In addition, FOLFIRI (5-FU plus irinotecan) has exhibited response and survival benefit in multiple phase II trials, and may serve as a good alternative in patients who developed residual peripheral neuropathy from prior chemotherapy agents (11). Although the randomized phase II RAMIRIS study, which compared FOLFIRI/ramucirumab with paclitaxel/ramucirumab in patients previously treated with fluoropyrimidine-based therapy was formally a negative study, there was potentially a greater benefit in patients who received prior taxane therapy, warranting further investigation (12). Furthermore, for heavily pretreated patients, trifluridine-tipiracil demonstrated a modest but statistically significant improvement in OS compared with best supportive care (5.7 *vs.* 3.6 months, HR =0.69, 95% CI: 0.56–0.85), and represents another option in the third-line and beyond setting (13). On the other hand, for patients with HER2-positive tumors who progressed on initial therapy with trastuzumab, fam-trastuzumab deruxtecan, an antibody-drug conjugate consisting of an anti-HER2 antibody linked to a topoisomerase I inhibitor, may be considered in second or subsequent-line therapy. In the DESTINY-Gastric01 study, trastuzumab deruxtecan improved OS (12.5 *vs.* 8.4 months, HR =0.59, 95% CI: 0.39–0.88), PFS (5.6 *vs.* 3.5 months, HR =0.47, 95% CI: 0.31–0.71) and ORR (51% *vs.* 14%) when compared with standard cytotoxic chemotherapy such as irinotecan or paclitaxel (14). Clinical benefit in this study, which was conducted in Japan and South Korea, was later confirmed in the DESTINY-Gastric02 trial which included patients in the United States and Europe (15). Nonetheless, given limited subsequent line therapy options for most patients without targeted biomarkers and often relatively modest efficacy, there remains an unmet need for expanding our repertoire of effective treatment options beyond first-line.

Eribulin mesylate (eribulin) is a non-taxane microtubule dynamics inhibitor which has been approved for the treatment of metastatic breast cancer and sarcoma (16,17). E7389-LF is a liposome encapsulated form of eribulin which exhibits enhanced tissue bioavailability, with greater than 600-fold increase in concentration observed in pre-clinical studies (18). Activity of E7389-LF has been observed in patients with advanced solid tumors in the phase I portion of Study 120 (19). In the dose-expansion part of this study, E7389-LF, at a dose of 2.0 mg/m^2 every 3 weeks, demonstrated an ORR of 17.6%, median PFS of 3.7 months, and disease control rate (DCR) of 79.4% in a cohort of 34 patients with gastric cancer who received ≥2 prior treatment regimens, with 94% of patients having received prior ICI (20). Interestingly, all patients with observed partial responses received prior anti-PD-1 therapy. In addition to antimitotic activity, pre-clinical breast cancer models have demonstrated that E7389-LF promotes immunomodulatory activity by inducing vascular remodeling, activating IFN-γ signaling, and increasing

ICAM-1 expression on vascular endothelial cells, ultimately promoting infiltration of $CD8^+$ T cells and natural killer (NK) cells into tumors, and converting immune "cold" tumors, characterized by absence of T-cell infiltration, into immune "hot" tumors (21). Furthermore, the combination of E7389-LF plus an anti-PD-1 mAb was shown to have stronger antitumor activity compared with E7389-LF monotherapy (21).

Given possible improved ICI efficacy through the immunomodulatory activity of E7389-LF, Kawazoe and colleagues investigated the efficacy and safety profile of E7389-LF in combination with nivolumab in a cohort of patients with advanced gastric cancer in the Phase II portion of Study 120 (22). This cohort comprised 31 patients with gastric cancer in Japan who had progressed after two lines of systemic therapy, including fluoropyrimidine plus platinum as well as taxane. The primary endpoint was ORR, and secondary endpoints included PFS, safety, and pharmacokinetics. E7389-LF was administered at a dose of 2.1 mg/m^2 combined with nivolumab 360 mg intravenously every 3 weeks. Exploratory analyses examining biomarkers and tumor immune microenvironment were also performed through plasma sampling as well as tissue biopsies obtained at baseline prior to treatment initiation and prior to initiation of cycle 2 of treatment. Among the 31 patients, 20 had no prior ICI therapy, one received prior ICI, and 10 patients had unknown prior ICI exposure. Twenty patients had PD-L1 CPS <5, and 9 patients had CPS ≥5, with the PD-L1 status of 2 patients unknown. The ORR was 25.8% (95% CI: 11.9–44.6%), with DCR of 71.0% (95% CI: 52.0–85.8%). ORR did not appear to differ significantly by PD-L1 CPS, with ORR of 25.0% in patients with CPS <5 and 22.0% with CPS ≥5. Similarly, response in patients with liver metastasis (25.0%) was comparable to those without liver metastasis (26.3%).

In terms of secondary endpoints, median PFS was 2.69 months (95% CI: 1.91–2.99), and was similar regardless of PD-L1 CPS (2.60 months in CPS <5, and 2.79 months in CPS ≥5). Median follow-up time for OS was nearly 1 year, and median OS was 7.85 months [95% CI: 4.47–not estimable (NE)]. OS for patients with CPS <5 was 6.62 months, and 7.85 months in those with CPS ≥5. In safety assessments, 80.6% of patients experienced grade ≥3 treatment related adverse events (AEs), predominantly cytopenias, with incidence of grade ≥3 neutropenia 71.0%. Fifty-one point six percent of patients experienced at least one treatment-related AE leading to dose reduction of E7389-LF.

To evaluate changes in biomarkers with treatment, immunohistochemistry (IHC) for PECAM1 (CD31) and panCK/CD8 was performed on tumor samples for patients who had both screening and cycle 2 day 1 biopsies, to categorize immune phenotypes and to measure microvessel density and CD8-positive tumor-infiltrating lymphocytes. Immune phenotypes were determined using a density proportion score (DPS) for panCK-CD8, which is based on the density of inflammatory cells within the tumor (19). Scores were assessed in two compartments or "nests": the tumor stroma and tumor epithelial nests. Tumor immune phenotypes were characterized as "immune-inflamed" (≥20% of tumor epithelial nests with moderate to high densities of infiltrating CD8 cells), "immune-excluded" (lower DPS in tumor epithelial nests and ≥20% of tumor stroma with moderate to high density of infiltrating CD8 cells) or "immune-desert" (no or low densities of infiltrating CD8 cells in both tumor epithelial nests and tumor stroma). Consistent with observations from pre-clinical studies, treatment with E7389-LF plus nivolumab led to increases from baseline in microvessel density (suggesting vascular remodeling activity), tumor-infiltrating lymphocytes and enhanced IFN-γ signaling markers. Higher levels of specific vascular and IFN-γ related markers after treatment were associated with longer PFS, compared with those with lower levels, suggesting the potential to utilize these biomarkers to correlate with and predict efficacy. Nonetheless, clear associations of biomarker changes with clinical outcomes such as survival could not be assessed due to limited numbers of patients with tumor tissue available for analysis.

Thus, in this small cohort of heavily pre-treated patients with advanced gastric adenocarcinoma, Kawazoe *et al.* demonstrated an impressive ORR of 25.8% with the combination of E7389-LF plus nivolumab. The study is limited by its small sample size of only Japanese patients, and thus its significance cannot be generalized to a larger global, more diverse population. Another major limitation of the study was the lack of clarity regarding the status of previous immunotherapy administration. Patients who had enrolled in prior randomized studies of first-line chemotherapy with or without ICI for advanced gastric cancer were allowed to participate in Study 120; however, it was not known whether these patients had received ICI or control in those studies. This is important to note given the efficacy of immunotherapeutic agents after first-line chemotherapy has been variable. Pembrolizumab received initial accelerated FDA approval based on clinical response benefit seen in previously treated patients with

PD-L1-positive (CPS ≥1) advanced gastric and GEJ adenocarcinoma in the phase II KEYNOTE-059 study (23). Nonetheless, its approval was later withdrawn after trials such as the phase III KEYNOTE-061 was unable to confirm significant improvement in OS when pembrolizumab was compared with chemotherapy such as paclitaxel in the second-line setting (24). The randomized phase III ATTRACTION-2 trial, which compared nivolumab with placebo in patients with gastric or GEJ adenocarcinoma who received at least two prior lines of therapy, demonstrated modest improvement in OS (5.26 *vs.* 4.14 months, HR =0.63, 95% CI: 0.51–0.78) (25). However, this study was conducted in patients entirely from Asia without PD-L1 biomarker selection; furthermore, less than 50% of patients with tumor samples were retrospectively analyzed for PD-L1 status. Moreover, with many patients now receiving immunotherapy in combination with chemotherapy in the frontline setting, the role of ICI therapy in later lines of treatment is unclear. Consequently, the impact of prior ICI on its future efficacy if reintroduced and combined with agents such as E7389-LF in subsequent lines of therapy in this patient population is uncertain, and future studies are needed to answer this important question. Other ongoing clinical studies such as the SWOG S2303/PARAMUNE trial which evaluates second-line paclitaxel plus ramucirumab with or without nivolumab in patients with advanced gastroesophageal adenocarcinoma with PD-L CPS ≥1, are also investigating whether ICI after utilization in the first-line setting may improve clinical outcomes, particularly given the potential tumor immune microenvironment modulatory effects of antiangiogenic agents, when combined with ICI.

The results presented by Kawazoe *et al.* present a promising signal of efficacy of E7389-LF plus nivolumab in patients with advanced gastric cancer who have progressed on prior therapies. The immunomodulatory activity of E7389-LF provides a strong rationale for its combination with nivolumab. However, more data is needed to demonstrate whether vascular and immune biomarker signatures may correlate with clinical outcomes and predict response. Overall, these findings warrant further investigation and confirmation in future studies with a larger, diverse population of patients. Although frontline options for advanced, unresectable or metastatic gastroesophageal adenocarcinoma have improved, there remains a clear need to expand the treatment landscape, particularly in patients who have been previously treated with chemoimmunotherapy, to improve their long-term survival.

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Footnote

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