When survival curves cross: are we at a crossroads of immunotherapy in gastric cancer?

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The first U.S. Food and Drug Administration (FDA) approval of a programmed cell death protein (PD-1) inhibitor specifically for advanced gastroesophageal cancer occurred with the passing of pembrolizumab on September 22, 2017 (1). This milestone achievement in gastroesophageal cancer was predicated on the success of KEYNOTE-059, a multicenter, non-randomized, open-label, 3-cohort, phase II trial investigating the efficacy of pembrolizumab in patients across 17 countries with advanced gastric or gastroesophageal cancer (2). Approval was specifically based on the results of cohort 1 in which 259 patients with metastatic or recurrent adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II and III) whose disease had progressed after ≥2 prior chemotherapy regimens including a fluoropyrimidine, a platinum doublet, and trastuzumab [for human epidermal growth factor receptor 2 (HER2)/neu-positive tumors] were enrolled to receive fixed-dose pembrolizumab alone at 200 mg intravenous (IV) infusion over 30 minutes on day 1 of every 3-week cycles. Overall response rate (ORR) was the primary endpoint by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Among 259 patients, 148 (57.1%) were positive for programmed death-ligand 1 (PD-L1) [defined by a CPS or combined positive score (number of PD-L1-positive tumor cells, macrophages, and lymphocytes divided by the total number of tumor cells, multiplied by 100) ≥1], 30 (11.6%) experienced an ORR [95% confidence interval (CI), 8.0–16.1%], and 6 (2.3%) experienced a complete response (CR) [95% CI, 0.9–5.0%]. The median progression-free survival (PFS) was 2.0 months (95% CI, 2.0–2.1) and the median overall survival (OS) was 5.6 months (95% CI, 4.3–6.9) in the overall cohort. Notably, the ORR was 15.5% (95% CI, 10.1–22.4%, 23 of 148 patients) in PD-L1-positive tumors compared to 6.4% (95% CI, 2.6–12.8%, 7 of 109 patients) in PD-L1-negative tumors with a median (range) response duration of 16.3 months (1.6–17.3+ months) and 6.9 months (2.4–7.0+ months) in PD-L1-positive and PD-L1-negative tumors, respectively. Out of 259 patients, 46 (17.8%) experienced ≥1 grade 3-5 treatment-related adverse events (AEs), while 46 (17.8%) experienced ≥1 immune-mediated AEs of any grade (12 patients (4.6%) experienced grade 3–4 events with hypothyroidism (23 or 8.9%), hyperthyroidism (9 or 3.5%), and colitis (6 or 2.3%) being most common).

Following the success of KEYNOTE-059, which widely established pembrolizumab as a standard third-line and beyond treatment in PD-L1-positive metastatic gastroesophageal cancer, KEYNOTE-061 investigated the efficacy of pembrolizumab as a second-line therapy in advanced gastroesophageal cancer (3). In this randomized, open-label, global, phase III study, 592 patients with unresectable or metastatic gastric or gastroesophageal adenocarcinoma who had progressed on first-line therapy with a platinum and fluoropyrimidine (as well as trastuzumab if HER-2-positive) were randomized (1:1) to receive IV 200 mg pembrolizumab every 3 weeks or IV 80 mg/m²...
paclitaxel on days 1, 8, and 15 every 4-week cycles. OS and PFS in patients with PD-L1 CPS ≥1 (using the same PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay as KEYNOTE-059) were the primary endpoints with the significance threshold for OS being P=0.0135 (one-sided). Pembrolizumab did not significantly prolong OS (median 9.1 months, 95% CI, 6.2–10.7) compared to paclitaxel [median 8.3 months, 95% CI, 7.6–9.0, hazard ratio (HR) 0.82, 95% CI, 0.66–1.03, one-sided P=0.0421]. Median PFS for pembrolizumab versus paclitaxel was 1.5 months (95% CI, 1.4–2.0) vs. 4.1 months (95% CI, 3.1–4.2) with a HR of 1.27 (95% CI, 1.03–1.57). The ORR was 16% (95% CI, 11–22%) for pembrolizumab and 14% (95% CI, 9–19%) for paclitaxel. Grade 3–5 treatment-related AEs occurred in 42/294 (14%) patients receiving pembrolizumab and 96/276 (35%) patients receiving paclitaxel; deaths attributed to pembrolizumab occurred in 3/294 patients (1%) and paclitaxel occurred in 1/276 patients (<1%). The most common immune-related grade 3–5 AEs associated with pembrolizumab included hepatitis (4/294 patients or 1%), hypophysitis (2/294 patients or <1%), and pneumonitis (2/294 patients or <1%).

In light of the negative results from KEYNOTE-061, which would have provided further impetus for advancing and establishing pembrolizumab as a second-line option in PD-L1-positive metastatic gastroesophageal cancer, the only FDA-approved indications for immunotherapy (i.e., the PD-1 inhibitor pembrolizumab) in advanced gastroesophageal cancer remain in the third-line and beyond setting for tumors that are PD-L1-positive (CPS ≥1) and refractory to all standard therapy setting for tumors that show microsatellite instability (MSI) based on a tumor agnostic approval (1,4). KEYNOTE-061 was an international, large, randomized phase III trial that was adequately powered to detect significant differences in OS and PFS between second-line pembrolizumab and paclitaxel. A comparison of patient demographics shows that both KEYNOTE-059 and -061 enrolled a majority of patients who were male, older (median age in early 60s), and non-Asian in geographic region of study with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 (2,3). Disease characteristics that were largely comparable across both studies included a similar proportion of HER2+ tumors and majority of patients that had not undergone gastrectomy.

However, primary tumors in KEYNOTE-061 were mostly located to the stomach (68% and 63% for pembrolizumab and paclitaxel arms, respectively) compared to gastroesophageal (51.4% overall) in KEYNOTE-059. Only 1.5% of patients had peritoneal metastases in KEYNOTE-059, while 26% and 25% of patients on the pembrolizumab and paclitaxel arms, respectively, had peritoneal metastases in KEYNOTE-061. In KEYNOTE-059, 1.9% of patients were classified in a histologic category inclusive of diffuse subtype, while 26% and 20% of patients in the pembrolizumab and paclitaxel arms, respectively, had diffuse subtypes in KEYNOTE-061. Investigations are ongoing on the molecular signatures including those involved in the immune response that may differ based on anatomic location along the gastroesophageal tract (5,6). A protocol-specified subgroup analysis identified that a significant OS benefit in favor of pembrolizumab over paclitaxel was observed in PD-L1-positive tumors located to the gastroesophageal junction in KEYNOTE-061 (3). Intriguingly, the diffuse subtype histology has been implicated with the worst prognosis in advanced gastric cancer along with a largely immune suppressive tumor microenvironment (TME) whereby PD-L1 may not serve as the ideal target for immune checkpoint blockade in this subgroup (7). These variations in disease characteristics across KEYNOTE-059 and KEYNOTE-061 and across arms within KEYNOTE-061 could explain the lack of significant improvement observed with pembrolizumab in KEYNOTE-061.

The lack of improvement in PFS with pembrolizumab compared to paclitaxel in KEYNOTE-061 was observed regardless of independent central review by RECIST 1.1 or irRECIST 1.1 (3). It is noteworthy to mention that the paclitaxel arm in KEYNOTE-061 did slightly better in terms of median OS with paclitaxel (8.3 months) compared to the paclitaxel arm (7.4 months) in the phase III RAINBOW trial (8). KEYNOTE-061 was also of an open-label design, which ultimately resulted in a greater number of patients who were randomized but were not given study drug in the paclitaxel arm than in the pembrolizumab arm; these patients may have subsequently received other therapies for which the authors argue may have diluted the relative benefit of pembrolizumab over paclitaxel (3). Additionally, KEYNOTE-061 was amended to exclude patients with PD-L1 CPS <1 after 83% of patients were enrolled based on recommendations by the independent data monitoring committee due to outcomes in patients with CPS <1. Stratification factors were changed as well after 21% of patients were enrolled, and altogether these amendments may have introduced bias and affected the results of the study.

A review of the Kaplan-Meier survival curves in
KEYNOTE-061 shows that in the PD-L1 CPS ≥1 cohort, the paclitaxel arm outperformed the pembrolizumab arm within the first 8 months of randomization. Notably, the OS curves crossed at 8 months and after this divergence, there was a sustained separation of the curves in favor of pembrolizumab. The investigators proposed that this observation was likely due to the improved durability of benefit in patients who had prolonged stable disease (SD) response in the pembrolizumab arm. Furthermore, it has been argued that a weighted log-rank test, rather than the Kaplan-Meier method, may have been a better alternative for survival analysis in KEYNOTE-061 given that it places more weight on events that occur around the center of the duration of follow-up (i.e., near the time the OS curves crossed) and less emphasis on early or late events. When a post-hoc analysis was done using the weighted log-rank test, a significant treatment difference in favor of pembrolizumab was observed (one-sided P=0.0009).

In short, heterogeneities in patient characteristics, tumor biology, and study design altogether comprise the nuances that may explain the difference in results produced by KEYNOTE-059 and KEYNOTE-061. Given the evidence at hand, is it safe to say that we are at a crossroads of immunotherapy in advanced gastroesophageal cancer? Perhaps more important to glean beyond these differences in study outcomes is a concept that is pervasive across both KEYNOTE-059 and -061: immune checkpoint blockade is exquisitely effective in the right patient, and translates to a clinically meaningful duration of response [median 8.4 months, 95% CI, 1.6–17.3+ months in KEYNOTE-059 and median 18.0 months with pembrolizumab (95% CI, 8.3–not estimable)] vs. 5.2 months with paclitaxel (95% CI, 3.2–15.3] in KEYNOTE-061]. In a sense, despite KEYNOTE-061 not meeting its pre-specified endpoint, it still affirms the accelerated approval of pembrolizumab as third-line therapy in a selected patient population garnered from KEYNOTE-059. A total of 7 patients (4.0%) in KEYNOTE-059 were MSI-H and experienced an ORR of 57.1% (95% CI, 18.4–90.1%) with pembrolizumab compared to an ORR of 9.0% (95% CI, 5.1–14.4%) in 167 patients who were non-MSI-H (2). Echoing this observation, in a post-hoc analysis of KEYNOTE-061, an ORR of 47% (7/15 patients) was seen with tumors that were MSI-H (irrespective of CPS) treated with pembrolizumab compared to an ORR of 17% in 2/12 patients with MSI-H tumors in the paclitaxel arm (3). Median OS was also significantly prolonged with pembrolizumab (not reached, 95% CI, 5.6–not reached) over paclitaxel (8.1 months, 95% CI, 2.0–16.7, HR 0.42, 95% CI, 0.13–1.31) in MSI-H tumors, irrespective of CPS. Furthermore, post-hoc analysis also showed that in advanced gastroesophageal cancer tumors having a PD-L1 CPS ≥10, pembrolizumab conferred a superior OS benefit over paclitaxel [median 10.4 (95% CI, 5.9–17.3) vs. 8.0 months (95% CI, 5.1–9.9), respectively] with a HR of 0.64 (95% CI, 0.41–1.02). On protocol-specified subgroup analyses in KEYNOTE-061, significant OS benefit in favor of pembrolizumab over paclitaxel was seen in patients with ECOG PS of 0 and primary tumors located to the gastroesophageal junction.

Therefore, MSI appears to be a valid predictive biomarker for immunotherapy in advanced gastroesophageal cancer patients. Recently, gastric cancers with evidence of Epstein-Barr virus (EBV) infection has also generated interest as a biomarker highly predictive of response to PD-1 inhibitors based on high response rates observed in a phase II trial in a Korean cohort of patients (9). Initial analyses of high throughput molecular data generated from The Cancer Genome Atlas for gastric adenocarcinomas paved the rationale for this approach given the high expression of immune checkpoint molecules observed in the EBV-infected subset (5,6,10). However, in the Korean phase II trial there still remained a small but discrete proportion of advanced gastric cancer patients whose tumors were non-EBV infected and microsatellite stable which still derived benefit from pembrolizumab. Beyond MSI, EBV status, and PD-L1 expression, future investigations should seek to uncover additional biomarkers for immunotherapy in gastroesophageal cancer, of which there is growing evidence to suggest that tumor mutational burden (TMB), aspects of the TME including tumor-infiltrating lymphocytes (TILs), and gene expression profiling may serve as candidates in this arena (11). Checkpoint inhibitors deserve ongoing development in advanced gastroesophageal cancer given the high unmet need for effective systemic therapies in a relatively poor prognosis population. Combinatorial approaches with chemotherapy in first-line therapy for advanced disease have been ongoing adding pembrolizumab or nivolumab in the phase III KEYNOTE-062 and Checkmate-649 studies, respectively (clinicaltrials.gov registration NCT02494583 and NCT02872116). Importantly, such future clinical studies should seek to add to the knowledge afforded by KEYNOTE-059 and 061 in characterizing patient and disease features that would assist in selecting the ideal candidates for PD-1/PD-L1 inhibition.
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Footnote

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References


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