Editorial Commentary

Pembrolizumab in advanced gastric cancer: pioneering or prosaic?

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Gastric and gastroesophageal junction (GEJ) cancers are a significant health problem worldwide with an estimated annual incidence of more than 950,000 (1). Despite newer chemotherapy regimens, the median overall survival (OS) of advanced gastric or GEJ cancer in patients treated with first-line systemic chemotherapy is typically 9–11 months (2), with a slightly better OS in the Her-2 positive subgroup when treated with Her-2 directed therapy (3). Second-line treatment usually consists of taxane or irinotecan-based cytotoxic chemotherapy and vascular endothelial growth factor receptor-2 (VEGFR-2) antibody, ramucirumab, either alone or in combination with a taxane. Once patients progress after two lines of systemic treatment, it is unknown whether there is any clinically meaningful benefit from subsequent systemic chemotherapy. Therefore, this is an area of unmet need.

Fuchs *et al.* performed an open-label, multi-center phase II study (KEYNOTE-059) to evaluate the safety and efficacy of pembrolizumab, an antibody directed against programmed cell death 1 (PD-1), in 259 patients with advanced gastric or GEJ adenocarcinoma who had disease progression after 2 or more prior chemotherapy regimens (4). In this study, treatment with pembrolizumab was associated with an objective response rate (ORR) of 11.6% (95% CI, 8.0–16.1%), with a 2.3% (95% CI, 0.9–5.0%) complete response. Median (range) response duration was 8.4 (1.6+ to 17.3+) months. In a biologically defined subgroup of patients [with programmed cell death 1 ligand 1 (PD-L1)-positive tumors], ORR was 15.6% (95% CI, 10.1–22.4%). Median OS for the entire cohort was 5.6 (95% CI, 4.3–6.9) months; however, it was slightly better in the PD-L1 positive subgroup: 5.8 (95% CI, 4.5–7.9) months. Forty-six patients (17.8%) experienced at least one grade 3 or higher treatment-related adverse events. Two patients (0.8%) discontinued treatment due to side-effects, and two deaths were attributed to treatment. Based on the results of this study, the Food and Drug Administration (FDA) approved pembrolizumab in patients with PD-L1 expressing gastric and GE junction adenocarcinomas that progressed after two or more lines of chemotherapy, and/or HER2-targeted therapy.

The results of this phase II study are in concordance with a randomized, double-blind, placebo-controlled, phase III trial (ONO-4538-12, ATTRACTION-2) which showed that another anti-PD-1 agent, Nivolumab, improves survival in patients with gastric or gastroesophageal cancer who progressed after at least two previous chemotherapy regimens (5). The median OS was 5.26 months in the Nivolumab group compared to 4.14 (3.42–4.86) months in the placebo group [hazard ratio (HR) 0.63, 95% CI, 0.51–0.78; P<0.0001]. Importantly, patients benefited from nivolumab regardless of their PD-L1 expression. This study, however, did not include a sample of patients from the Western population. This poses a challenge for the generalization of the results of this trial since outcomes in advanced gastric cancer have been shown to differ in Asian *vs.* non-Asian populations. In contrast, in the KEYNOTE-059 study population, the majority were

White (77%) followed by Asians (16%). Of note, a global, phase III, double-blind study compared the efficacy of avelumab, an anti-PD-L1 agent, against physician's choice of chemotherapy as third-line treatment in patients with advanced gastric or GEJ cancer. Avelumab did not improve survival in the overall population or the PD-L1 positive sub-group (6). Therefore, the question remains, whether anti-PD-1/PD-L1 directed immunotherapy should be considered the gold standard in the third-line setting or later.

Biomarker analysis is an active area of research in the field of cancer immunotherapy. The utility of using PD-L1 as a biomarker is limited because of heterogeneity of PD-L1 expression, change in PD-L1 status as a result of prior treatments and heterogeneity of assays to assess PD-L1 expression (2). The KEYNOTE-059 study used a novel 18-gene T-cell—inflamed gene expression profiling score as a biomarker. Patients who responded had a higher score in aggregate. Similarly, higher gene expression profiling score was associated with improved progression-free survival (PFS). As expected, patients with a microsatellite instability-high (MSI-H) status, had a significantly improved ORR of 57%, but the incidence of MSI-H was only 4%.

Clinical biomarkers are important in this regard since they can be integrated as stratification factors in clinical trials. Recently, Conforti *et al.* published a meta-analysis that included patients with melanoma and lung cancer treated with immune checkpoint inhibitors (7). It showed that men have a lower hazard ratio of death compared to women. In the subgroup analysis of KEYNOTE-059, males were found to have a superior ORR compared to females (12.6% *vs.* 8.2%), consistent with the reported data. We recently showed that obesity enhances PD-1 mediated T-cell dysfunction at least partly by leptin signaling (8), but paradoxically, obese patients respond better to treatment with anti-PD1/PD-L1 immune checkpoint inhibitors. This study suggests that body mass index (BMI) should possibly be considered as a stratification factor in future design of clinical trials with immune checkpoint inhibitors.

The side effect profile of pembrolizumab in the KEYNOTE-059 study was favorable. Overall, immune-related grade 3 and 4 adverse events did not exceed expectations; however, two deaths were considered to have resulted from treatment. Interestingly, the KEYNOTE-059 study used a fixed dose of pembrolizumab (200 mg), which has been approved by the FDA. However, recent studies, including our own study, have revealed that using a body weight based dosing regimen of Pembrolizumab could be financially beneficial without compromising the clinical outcomes (9,10). In this era of cost-effective medicine, the financial burden of immune checkpoint inhibitors should be carefully considered while deciding on a treatment regimen. This is even more important from a global standpoint since many patients in developing countries do not have access to costly treatments like pembrolizumab.

Non-randomized design of KEYNOTE-059 makes it difficult for us to understand whether immunotherapy with pembrolizumab is a better option than cytotoxic chemotherapy in advanced gastric or GEJ cancer in third or higher line setting. It was observed in the study that patients, who have a robust performance status or receive Pembrolizumab earlier during treatment, tend to do better; however, those groups of patients also tend to do well with conventional treatment. Besides, the absence of quality of life data in the KEYNOTE-059 study somewhat impairs its clinical value. A randomized phase III study, KEYNOTE-062, will help us determine whether the efficacy and tolerability of pembrolizumab is comparable to chemotherapy in advanced gastric or GEJ adenocarcinoma patients (NCT02494583).

In conclusion, the KEYNOTE-059 study provides evidence that pembrolizumab is a safe and effective option in patients with PD-L1 expressing gastric and GEJ adenocarcinoma once they progress after two or more lines of systemic treatment. Future biomarker-based studies are necessary to identify patients who are likely to benefit most from this type of treatment.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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