Editorial

Immune checkpoint inhibitors in esophagogastric cancer: still a long way to go

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Comment on: Janjigian YY, Bendell J, Calvo E, *et al.* CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. J Clin Oncol 2018;36:2836-44.

Submitted Nov 12, 2018. Accepted for publication Nov 20, 2018.
doi: 10.21037/jtd.2018.11.111
View this article at: http://dx.doi.org/10.21037/jtd.2018.11.111

Immune checkpoint inhibitors (ICIs) targeting the programmed death 1/programmed death-ligand 1 (PD1/PD-L1) pathway have revolutionized treatment for various cancers. Evasion of the immune system is one of the hallmarks of cancer and chronic inflammation can facilitate cancer progression. Targeting gastrointestinal malignancies, a group of cancers that are, in part, inflammation-driven, is an appealing strategy but, with the exception of microsatellite unstable cancers (MSI-H), most patients do not benefit from ICI monotherapy (1-3). For patients with esophageal, gastroesophageal junction and gastric cancer (EGC), pembrolizumab is approved for PD-L1$^+$ gastric or gastroesophageal junction adenocarcinoma after failure of at least two prior lines of therapy. The efficacy though is far from ideal. As shown in *Table 1*, data from key anti-PD1/PD-L1 monotherapy studies—with the exception of KEYNOTE-061 (conducted in the second-line setting in PD-L1$^+$ disease) and the small EGC cohorts in KEYNOTE-028 and KEYNOTE-012 studies (including PD-L1$^+$ esophageal carcinoma and gastric cancer, respectively) (4,5,7)—demonstrate that the efficacy of ICI in patients with advanced, heavily pre-treated disease is moderate at best. More importantly, ICI monotherapy does not appear better that single-agent chemotherapy in either the second- or third-line setting.

How can we improve the efficacy of ICI in EGC cancer? Janjigian and colleagues provide one possible answer in the CheckMate 032 study (10). The investigators hypothesized that dual ICIs with the anti-PD1 monoclonal antibody, nivolumab, plus the anti-cytotoxic T-cell lymphocyte antigen 4 (CTLA4) antibody, ipilimumab, can be more effective than anti-PD1 monotherapy. One hundred sixty patients with advanced, pretreated EGC were randomly assigned to nivolumab 3 mg/kg (NIVO3) every 2 weeks, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3) every 3 weeks for four cycles; or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3 + IPI1) every 3 weeks for four cycles. All combination regimens were followed by NIVO3 every 2 weeks. Fifteen percent of the patients had esophageal primary and 79% had received at least 2 prior lines of therapy. The primary endpoint was overall response rate (ORR). The ORR was 12% with NIVO3, 24% with NIVO1+IPI3, and 8% with NIVO3 + IPI1. The median progression-free survival (PFS) and overall survival (OS) were 1.4/6.2, 1.4/6.9, and 1.6/4.8 months, in the NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1 groups, respectively. As expected, grade 3 and 4 treatment-related adverse events (TRAEs) were more common in the NIVO1 + IPI3 and NIVO3 + IPI1 arms (47% and 27%, respectively compared to 17% in NIVO3 alone arm). Even though ORR appears higher with NIVO1 + IPI3, the long-term outcomes are similar to NIVO3 (12-month OS of 35% *vs.* 39%) and not much different compared to other ICI monotherapy (6,8,9). This can be related to the toxicity profile of NIVO1 + IPI3 (serious TRAEs, and TRAE leading to discontinuation in 43% and 20% of patients, respectively) that may easily decompensate a patient with advanced EGC.

Table 1 Studies with anti-PD1/PD-L1 monoclonal antibodies in esophageal, gastroesophageal junction and gastric cancer

Agent	Study phase	Sample size	Disease site	ORR (%)	Median PFS (months)	Median OS (months)
Pembrolizumab (4)	I	39	G/GEJ	22	1.9	11.4
Pembrolizumab (5)	I	23	E/GEJ	30	1.8	7
Pembrolizumab (6)	II	259	G/GEJ	11.6	2	5.6
Pembrolizumab (7)	III	296	G/GEJ	16	1.5	9.1
Nivolumab (8)	III	330	G/GEJ	11	1.61	5.26
Avelumab (9)	III	185	G/GEJ	2.2	1.4	4.6

E, esophageal; G, gastric; GEJ, gastroesophageal junction; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

How do we move forward? Perhaps the timing of introduction of ICI is not ideal. In KEYNOTE-059, the ORR was higher in patients receiving pembrolizumab as third *vs.* fourth line treatment (9). Further, in treatment-naïve patients with PD-L1$^+$ tumors, the ORR with single-agent pembrolizumab was 26% in KEYNOTE-059 (Cohort 3) and the median survival was not reached (11,12). In addition, pembrolizumab plus cisplatin and 5-fluorouracil in the first-line setting (KEYNOTE-059/Cohort 2) resulted in an ORR of 60% (73% for PD-L1$^+$ tumors); the median OS was 14 months for the 25 patients enrolled in this cohort (12,13). Multiple studies are now evaluating upfront chemoimmunotherapy and dual ICIs in patients with advanced EGC compared to chemotherapy alone as well as for treatment of patients with EGC in the localized setting. The second question raised is whether an anti-CTLA4 molecule together with an anti-PD1/PD-L1 drug is the best combination in this setting. There are multiple other immune checkpoint agents (immune agonists like OX40 and CD137 or antagonists such as LAG-3 and TIM-3) that can potentially add on to the activity of existing ICIs. Building into the paradigm of basket trials with mutation-specific targeted agents, the phase II Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) study is designed to rapidly evaluate new combinations of strategies (14). In this study, patients who do not respond to the assigned treatment have the option to start a new regimen.

Finally, how can we best select patients for treatment with ICIs? The only approved biomarker is PD-L1 by immunohistochemistry (22C3 clone); the combined proportional score (CPS, defined as staining of cancer and contiguous mononuclear cells) should be >1 for treatment with pembrolizumab. In KEYNOTE-059, the ORR in PD-L1$^+$ tumors (i.e., CPS >1) was 15.5% *vs.* 6.4% in PD-L1$^-$ tumors (6) while in a *post hoc* analysis of KEYNOTE-061, in patients with CPS>10, the median OS was 10.4 months with pembrolizumab (*vs.* 8 months in the paclitaxel arm; HR =0.64) (7). What is interesting though is that PD-L1 positivity can differ depending on the timing of testing (15,16). Further, the discriminatory activity of PD-L1 positivity is not consistent between studies including the study by Janjigian *et al.*, with the caveat that different antibody clones are used (8-10). In KEYNOTE-059, T-cell inflamed tumors based on gene expression profiling had a higher probability of response and longer PFS; a CPS >20 was associated with a high T-cell inflamed score (6). In KEYNOTE-012, an interferon-related gene signature was not predictive of response (4). High tumor mutation burden (TMB) has been proposed as a predictive biomarker for response to ICIs in multiple cancers (17); about half of patients with esophageal adenocarcinoma can have a mutagenic signature based on whole-genome sequencing characterized by high TMB (18) and indeed, high TMB (>10/Mb) appears to predict long-term benefit from ICIs in retrospective studies (19,20).

In summary, Janjigian *et al.* are to be congratulated for the successful completion of a very challenging trial. We need to better define the patient population that can benefit the most from ICIs in esophageal or gastric cancer, the timing of ICI introduction to their care, and the best combination strategy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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Cite this article as: Fountzilas C, Hochwald SN. Immune checkpoint inhibitors in esophagogastric cancer: still a long way to go. J Thorac Dis 2019;11(2):351-353. doi: 10.21037/jtd.2018.11.111

