Editorial

CheckMate-032 Study: promising efficacy with nivolumab-based immunotherapy in pretreated esophagogastric cancer

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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 20, 2018. Accepted for publication Nov 29, 2018.
doi: 10.21037/jtd.2018.12.02
View this article at: http://dx.doi.org/10.21037/jtd.2018.12.02

Esophagogastric junction (EGJ) cancer is one of the aggressive malignant tumors, and more than 60% of EGJ cancer patients develop recurrence or metastasis in the clinical course (1). Despite active frontline systemic chemotherapy, the prognosis of patients with recurrent or metastatic EGJ cancer is poor, and poor physical condition of the patient at the time of progression may render her/him inappropriate for active systemic cytotoxic chemotherapy (2). Based on the increasing results of programmed death-1 (PD-1) inhibitors in various settings of cancer therapy, including pembrolizumab, it has been approved for treatment of patient with chemotherapy-refractory programmed death-ligand 1 (PD-L1)-positive gastric/EGJ cancer, nivolumab was also approved specifically for pretreated advanced EGJ cancer irrespective of PD-L1 status in Japan, based on superior survival data shown in the ATTRACTIONS-2 trial (3,4).

To enhance the response rates in patients with advanced cancers, dual PD-1/cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blockade with nivolumab plus ipilimumab has shown synergistic response in trials of metastatic melanoma, small-cell lung cancer, and DNA mismatch repair-deficient/MSI-high (MSI-H) metastatic colorectal cancer (5-8). Combination immunotherapy with nivolumab and ipilimumab was performed for advanced gastric, esophageal, and GEJ adenocarcinoma in the phase I/II CheckMate 032 trial (9). Patients received nivolumab alone, nivolumab 1 mg/kg with ipilimumab 3 mg/kg (N1+I3), or nivolumab 3 mg/kg with ipilimumab 1 mg/kg (N3+I1). A high objective response rate (ORR) was shown irrespective of PD-L1 status. More patients in the N alone group harbored PD-L1-positive (38%) and microsatellite instability-high (MSI-H) (28%) tumors, compared to 24% and 9% for the N1+I3 group and 30% and 8% in the N3+I1 group, respectively. ORR was better in PD-L1 ≥1% tumors (19% N alone, 40% in N1+I3, 23% in N3+I1), although responses were also found in PD-L1 <1% tumors (12% N alone, 22% in N1+I3, 0% in N3+I1). Most patients in the N3+I1 group discontinued treatment due to disease progression (73%); in addition, the number of patients that discontinued the study drug due to treatment-related adverse event (TRAE) was higher in N1+I3, about 18%, than the 3% in N alone and the 13% in N3+I1. Only 36% of patients across all groups received subsequent anticancer therapy after discontinuing treatment. For survival outcomes, the median progression-free survival (PFS) was 1.4 months in the N alone group compared to 1.4 months for the N1+I3 group and 1.6 months in the N3+I1 group. Also, 12-month PFS was reached in 8%, 17%, and 10% of the N alone, N1+I3, and N3+I1 groups, respectively. Median overall survival (OS) was 6.2 months in the N alone, with 39% of patients achieving a 12-month OS. In comparison, an OS of 6.9 months with 35% of patients reaching 12-month OS was seen in the N1+I3 group, and an OS of 4.8 months with 24% of patients achieving a 12-month OS was noted in the N3+I1 group. The results of CheckMate 032 suggest that immune checkpoint blockade offers a consistent clinical benefit in patients across Asian

and Western countries, despite the morphologic and molecular characteristics of EGJ cancer.

The safety profile showed that the study drugs were generally well tolerated with manageable toxicities. TRAEs were seen in 69% of patients in the N alone versus 84% in the N1+I3 and 75% in the N3+I1 groups. In the N alone, N1+I3, and N3+I1 groups, 17%, 47%, and 27% of the patients, respectively, experienced grade 3/4 TRAEs, leading to discontinuation in 3%, 20%, and 13% of patients. The N1+I3 regimen has been approved for treatment of melanoma. A study showed that, despite a higher ORR of 24% in the N1+I3 and 12% in the N alone groups, similar median OSs were found in the two regimens. However, the enhanced clinical benefit found with N1+I3 was accompanied by a more frequent development of grade 3/4 AEs than found with N alone, similar to the CheckMate 032 study.

Tumor PD-L1 and MSI-H status were investigated as potential biomarkers for response to these treatment regimens. In the ATTRACTION-2 trial (4), tumor PD-L1 was not predictive of GEJ cancer survival. The ORR seemed numerically higher in PD-L1-positive versus PD-L1-negative tumors, and responses were also found in patients with MSI-H or non-MSI-H tumor. While the ORR was higher in the MSI-H subgroup, further researches with large-scale subsets are required to validate these findings.

The findings in CheckMate 032 propose that nivolumab plus ipilimumab can be a treatment combination for advanced EGJ cancer. On the ground of improved ORR and encouraging OS with N1+I3, the approach could be considered to provide clinical merit relative to currently available therapeutic options for first-line metastatic EGJ cancer. The results of the CheckMate 649, phase III trial (NCT02872116), are eagerly anticipated (10).

Acknowledgements

None.

Footnote

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

Cite this article as: Sun DS, Kim JJ, Ko YH. CheckMate-032 Study: promising efficacy with nivolumab-based immunotherapy in pretreated esophagogastric cancer. J Thorac Dis 2019;11(Suppl 3):S394-S395. doi: 10.21037/jtd.2018.12.02

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