Editorial Commentary

Efficacy of immunotherapy with chemotherapy as standard first-line treatment against advanced gastric cancer

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Comment on: Kang YK, Chen LT, Ryu MH, *et al*. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:234-47.

Received: 02 September 2022; Accepted: 28 September 2022; Published online: 18 October 2022.

doi: 10.21037/dmr-22-64

View this article at: https://dx.doi.org/10.21037/dmr-22-64

Gastric cancer is the most common type of cancer and the fourth leading cause of cancer death worldwide (1). The standard of care for first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative patients with advanced unresectable or recurrent gastric cancer (AGC) is a doublet regimen of a fluoropyrimidine (5-fluorouracil, capecitabine, and S-1) and a platinum compound (cisplatin and oxaliplatin) (2,3). However, the median overall survival (OS) in AGC patients is approximately 12–15 months (4-6). Various phase 3 trials have been conducted on trastuzumab since its approval as first-line treatment by the Food and Drug Administration (FDA) in 2010; however, none have yielded satisfactory results (7-11). We lacked adequate standard first-line treatments for AGC for a long time. As with other cancer types, immune checkpoint inhibitors (ICIs) were expected to be effective. Recently, four pivotal phase 3 trials (ATTRACTION-4, KEYNOTE-062, CheckMate-649, and ORIENT-16) have been conducted (12-15). Notably, ATTRACTION-4, CheckMate-649, and ORIENT-16 exhibited the efficacy of ICIs in combination with chemotherapy (*Table 1*).

ATTRACTION-4 was a multicenter double-blind phase 2 and 3 trial of nivolumab plus oxaliplatin-based chemotherapy [S-1 plus oxaliplatin (SOX) or capecitabine plus oxaliplatin (CAPOX)] versus placebo plus oxaliplatin-based chemotherapy as first-line chemotherapy in HER2-negative AGC patients (14). Patients from Asian countries/region (Japan, South Korea, and Taiwan) were randomly assigned to the treatment groups in a 1:1 ratio. The primary endpoints were progression-free survival (PFS) and OS. PFS was 10.45 months [95% confidence interval (CI): 8.44–14.75] in the nivolumab plus chemotherapy group and 8.34 months (95% CI: 6.97–9.40) in the placebo plus chemotherapy group [hazard ratio (HR) =0.68; 98.51% CI: 0.51–0.90; P=0.0007]. OS was 17.45 months (95% CI: 15.67–20.83) in the nivolumab plus chemotherapy group and 17.15 months (95% CI: 15.18–19.65) in the placebo plus chemotherapy group (HR =0.90; 95% CI: 0.75–1.08; P=0.26). An objective response was observed in 57% of the cases (95% CI: 52–63%) in the nivolumab plus chemotherapy group and 48% (95% CI: 43–53%) of those in the placebo plus chemotherapy group. The incidence of grade 3 or 4 adverse events was 57% and 49% in the nivolumab plus chemotherapy and placebo plus chemotherapy groups, respectively. The most common treatment-related grade 3 or 4 adverse events in the nivolumab plus chemotherapy and placebo plus chemotherapy groups were decreased neutrophil count (20% *vs.* 16%), platelet count (9% *vs.* 9%), and appetite (8% *vs.* 6%). The limitation of this trial was the absence of a combined positive score (CPS) categorization of programmed death-ligand 1 (PD-L1) expression.

In contrast, CheckMate-649 was a multicenter, phase 3 trial of nivolumab plus oxaliplatin-based chemotherapy (leucovorin, fluorouracil, and oxaliplatin or CAPOX), nivolumab-plus-ipilimumab, or chemotherapy as first-line regimens in AGC patients (24% Asian, 76% non-Asian) (13). Primary endpoints for nivolumab plus chemotherapy versus

Table 1 Randomized studies on first-line ICIs for gastric cancer

Study	Phase	n	Region	CPS	Regimen	Primary endpoint	OS			PFS			Subsequent therapies (placebo group) (%)	Subsequent ICIs (placebo group) (%)
							Survival (months)	HR	P value	Survival (months)	HR	P value		
ATTRACTION-4	3	724	Asia	All	XELOX/SOX+nivolumab/placebo	OS, PFS	17.5	0.9	0.257	10.5	0.68	0.0007	68	27
CheckMate-649	3	1,581	Global	CPS ≥5	XELOX/FOLFOX + nivolumab/placebo	OS, PFS (CPS ≥5, all)	14.4	0.71	<0.0001	7.7	0.68	<0.0001	41	8
				CPS ≥1			14	0.77	<0.0001	7.5	0.74	–		
				All			13.8	0.8	0.0002	7.7	0.77	–		
ORIENT-16	3	650	China	CPS ≥5	XELOX + sintilimab/placebo	OS (CPS ≥5, all)	18.4	0.66	0.0023	7.7	0.628	0.0002	–	–
				All			15.2	0.766	0.009	7.1	0.636	<0.0001		
KEYNOTE-062	3	763	Global	CPS ≥1	XP/FP + pembrolizumab/placebo	OS (CPS ≥1, ≥10), PFS (CPS ≥1)	12.5	0.85	0.05	6.9	0.84	0.04	54	16
				CPS ≥10			12.3	0.85	0.16	5.7	0.73	–		

ICI, immune checkpoint inhibitor; CPS, combined positive score; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; XELOX, capecitabine plus oxaliplatin; SOX, S-1 plus oxaliplatin; FOLFOX, leucovorin, fluorouracil plus oxaliplatin; XP, capecitabine plus cisplatin; FP, fluorouracil plus cisplatin.

chemotherapy alone were OS or PFS in patients with PD-L1 CPS ≥5. The nivolumab plus chemotherapy treatment was significantly beneficial to OS and PFS for both primary endpoint groups with PD-L1 CPS ≥5 tumors [median OS, 14.4 *vs.* 11.1 months; HR =0.71 (98.4% CI: 0.59–0.86; P<0.0001)] and median PFS 7.7 *vs.* 6.0 months; HR =0.68 (98% CI: 0.56–0.81; P<0.0001). The secondary endpoints of OS were also median 14.0 *vs.* 11.3 months (HR =0.77; P<0.0001) in PD-L1 CPS ≥1 patients and median 13.8 *vs.* 11.6 months (HR =0.80; P<0.0002) in all randomized patients.

The Chinese phase 3 ORIENT-16 trial recently reported PD-1 inhibitor sintilimab plus chemotherapy being superior to chemotherapy for OS in both PD-L1 CPS ≥5 (median 18.4 *vs.* 12.9 months; HR =0.66; 95% CI: 0.51–0.86; P<0.0023) and all randomized populations (median 15.2 *vs.* 12.3 months; HR =0.766; 95% CI: 0.63–0.94; P<0.0090) (15).

Lastly, KEYNOTE-062 was a multicenter, phase 3 trial of pembrolizumab, pembrolizumab plus cisplatin-based chemotherapy (fluorouracil and cisplatin or capecitabine and cisplatin), or chemotherapy as the first-line regimen in AGC patients (12). Pembrolizumab plus chemotherapy was not superior to chemotherapy in terms of OS in patients with PD-L1 CPS ≥1 (12.5 *vs.* 11.1 months; HR =0.85; 95% CI: 0.70–1.03; P=0.05) or PD-L1 CPS ≥10 (12.3 *vs.* 10.8 months; HR =0.85; 95% CI: 0.62–1.17; P=0.16) or in terms of PFS in patients with PD-L1 CPS ≥1 (6.9 *vs.* 6.4 months; HR =0.84; 95% CI: 0.70–1.02; P=0.04).

The nivolumab plus chemotherapy significantly improved PFS but not OS in the ATTRACTION-4 trial. This may be attributed to the fact that the ATTRACTION-4 trial was conducted in Asian countries/region and included a large number of Japanese patients (55%). Additionally, a higher proportion of patients in the placebo group had received subsequent therapies and additional ICIs (68% and 27% in ATTRACTION-4 *vs.* 41% and 8% in CheckMate-649). The reason for the failure of pembrolizumab plus chemotherapy treatment in KEYNOTE-062 was assumed to be different from PD-L1 CPS staining kits, and that difference between them was used for oxaliplatin and cisplatin.

Nonetheless, ATTRACTION-4, CheckMate-649, and ORIENT-16 consistently exhibited the benefit of immunotherapy plus chemotherapy, which was then established as the standard first-line treatment for AGC.

The FDA, Japan, and China approved the addition of nivolumab plus chemotherapy as the first-line treatment for AGC patients, irrespective of their PD-L1 CPS score.

However, the National Comprehensive Cancer Network (NCCN) guidelines recommend it as a preferred regimen only for patients with PD-L1 CPS ≥5, whereas the European Medicines Agency approval is limited to patients with PD-L1 CPS ≥5. The clinical significance of the PD-L1 CPS score varies among countries. CheckMate-649 and ORIENT-16 trials suggested that low PD-L1 CPS scores tend to reduce the synergistic effect of ICIs and chemotherapy on OS and PFS (16). Recently, Zhao *et al.* reported a study using Kaplan-Meier subtraction data of PD-L1 subgroups that were previously unreported and were retrieved from phase III trials of CheckMate-649 and KEYNOTE-062. The data suggested that the addition of ICIs to chemotherapy in low-CPS score patients failed to demonstrate the survival benefit (17). However, the limitations of this report were the results of its sub-analysis, the different PD-L1 CPS staining kits, and PD-L1 CPS cut-off values. Therefore, the association between PD-L1 CPS status and the treatment efficacy of the addition of ICIs to chemotherapy as well as reliable PD-L1 CPS cut-off values (CPS ≥1 or CPS ≥5 or CPS ≥10) remain unclear. To overcome these limitations, further larger-scale clinical trials must be conducted in the future. Currently, not all patients can use ICIs in subsequent therapies. Therefore, ICIs are recommended for first-line treatment for AGC regardless of PD-L1 CPS.

In conclusion, the ATTRACTION-4 trial supports nivolumab plus oxaliplatin-based chemotherapy as a standard first-line treatment for HER2-negative AGC. However, only a limited number of patients from selected hospitals participated in randomized clinical trials. Although the adverse events were reportedly manageable, they increased by approximately 10% with the addition of ICIs. Further attention must be paid to adverse events with the addition of ICIs, especially because of the increased PFS of first-line treatment. Further accumulation of knowledge from clinical practice is desired.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.org/article/view/10.21037/dmr-22-64/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-22-64
Cite this article as: Taira K, Kimura A, Nakata A, Tanaka F, Nagami Y, Fujiwara Y. Efficacy of immunotherapy with chemotherapy as standard first-line treatment against advanced gastric cancer. Dig Med Res 2023;6:12.