Safety and preliminary signs of efficacy with the combination of pembrolizumab plus oxaliplatin and S-1 in Japanese gastric cancer patients

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Gastric and gastroesophageal junction cancer (GC) represents a world-wide problem due to its high prevalence and aggressive nature. Advanced GC patients have an extremely poor prognosis with median overall survival (OS) of approximately 10 months (1). Many molecular targeted agents have been evaluated in conjunction with first-line chemotherapy treatment, however none except trastuzumab has demonstrated significant efficacy (2). Immune checkpoint inhibitors (ICI) targeting programmed death-1 (PD-1) and PD-L1 have shown preliminary good results in chemorefractory GC, although have sometimes been disappointing in earlier disease stages (*Table 1*) (3).

The KEYNOTE-659 phase IIb study was a non-randomized, multicenter, open-label phase IIb study which evaluated the safety and efficacy of pembrolizumab added to first-line chemotherapy in Japanese GC patients. Eligible patients were programmed death-1 ligand (PD-L1) positive and human epidermal growth factor receptor 2 (HER2)-negative. Kawazoe *et al.* (4) have recently reported the results KEYNOTE-659 cohort 1, which evaluated the combination of pembrolizumab with S-1 plus oxaliplatin (SOX). The results presented by Kawazoe *et al.* (4) demonstrate the safety and preliminary effectiveness required to further explore the combination of pembrolizumab in combination with first-line SOX chemotherapy.

The history of GC includes multiple randomized clinical trials evaluating targeted agents and ICIs that have been negative, mainly due to a lack of a biomarker selection and the intrinsic heterogeneity of this tumor (5). Except for the demonstrated superiority of nivolumab against placebo in chemorefractory Asian GC patients (6), there is an inconsistency of the benefit offered by the ICIs in an unselected GC population. Fortunately, comprehensive analysis of these data relating to efficacy of ICI in GC highlights some biomarkers of response, linked to the tumor cell (MSI status, tumor mutational burden) and to the stroma (Epstein-Barr virus subtype and PD-L1 expression) (7). Moreover, some clinical characteristics of the patient are probably associated with the response (8).

MSI status is today the most solid biomarker, with a consistent positive correlation demonstrated in all the treatment lines, with both anti-PD1 and anti-PD-L1 agents (3,8-10). A second moderately robust biomarker in GC is PD-L1 status assessed by the combined positive score (CPS). With regard to CPS score, a higher cutoff level better correlates with a significant immune response (3). In terms of clinical biomarkers, and taking into consideration the fragility of GC patients and the relatively long time that is required for the activation of the immune response, patients with a better ECOG status and smaller volume disease are

Table 1 Immune checkpoint inhibitors in combination with a first chemotherapy line in gastric cancer

Study	KEYNOTE-659 Cohort 1	KEYNOTE-062	KEYNOTE-059 Cohort 2	ATTRACTION-4 Part 1
Type	Phase 2	Phase 3	Phase 2	Phase 2
Treatment	Pembrolizumab + SOX	Pembrolizumab + Cis/ fluoropyrimidine	Pembrolizumab + Cis/ fluoropyrimidine	Nivolumab + SOX/CapeOx
N	54	757	25	40
PD-L1 CPS ≥1	54 (100%)	757 (100%)	16 (64.0%)	6 (16.2%)*
PD-L1 CPS ≥10	31 (57.4%)	99 (39%)	Not reported	Not reported
MSI	Not reported	17 (7%)	0 (0%)	Not reported
Patient ethnicity	Japan	Europe, America, Australia, Asia	South Korea, Japan, Israel, North America, France	Japan and South Korea
GC	46 (85.2%)	170 (66%)	Not reported	Not reported
GEJC	8 (14.8%)	85 (33%)		
Prior gastrectomy	5 (9.3%)	Not reported	5 (20.0%)	17 (42.5%)
ECOG 0	46 (85.2%)	119 (46%)	15 (60.0%)	20 (50%)
ECOG 1	8 (14.8%)	138 (54%)	10 (40.0%)	20 (50%)
ORR, n (BICR)	39 (72.2%)	125 (49%)	60.0%	25 (65.8%)
DCR, n (BICR)	52 (96.3%)	199 (77%)	20 (80%)	32 (84.2%)
Median PFS (95% CI)	9.4 m (6.6–NE)	6.9 m (5.7–7.3)	6.6 m (5.9–10.6)	9.5 m (6.9–11.1)
Treatment-related AES any grade	Not reported	235 (94%)	25 (100.0%)	39 (100.0%)
Treatment-related AES Grade ≥3	57.45%	183 (73%)	15 (60.0%)	24 (61.5%)

*Tumor expression. AES, adverse events; BICR, blinded independent central review; CapeOX, capecitabine plus oxaliplatin; Cis, cisplatin; CPS, combined positive score; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastro-esophageal junction cancer; GC, gastric cancer; m, months; MSI, microsatellite-instability; N, number of patients; ORR, overall response rate; PD-L1, programmed death ligand 1; SOX, S-1 (tegafur-gimeracil-oteracil potassium) plus oxaliplatin.

more likely to derive a greater benefit from the ICI therapy (3,8). Furthermore, the activity of the ICIs is improved if given early in the tumor life (in early lines), in order to avoid lymphocyte exhaustion (11,12). And finally, the ethnicity of patient also seems to matter, as Asian patients appear to benefit more than patients from other regions of the world (3). Whether Asian patients have predominantly gastric cancers, Western patients have more junctional tumors. Although the underlying biology is shared (13), Asian and non-GC present different immune-related components which may influence in the clinical outcome (14).

In the Cohort 1 of the KEYNOTE-659 study, fifty-four Japanese GC patients were treated with pembrolizumab plus SOX as a first line of treatment. Notably, the patients included in this trial had characteristics associated with a good immune response. All of them (100%) were Japanese, 46 (85.2%) had ECOG 0, 49 (90.7%) had a previous gastrectomy, and 31 (57.4%) had PD-L1 CPS ≥10. Unfortunately, MSI status was not tested. The schema of the treatment was almost equal to the one of the KEYNOTE-062 study except for the chemotherapy backbone, which was SOX in this trial (versus cisplatin and fluoropyrimidine in KEYNOTE-062). The combination of SOX and pembrolizumab is safe; toxicity is in line with the toxicity reported in other similar clinical trials (*Table 1*). The primary endpoint was ORR assessed by blinded independent central review (BICR), which was 72.7%. Median progression-free survival (PFS) was 9.4 months (95% CI: 6.6–NE) and OS was not-reached.

Until now, three phase 2 studies [Cohort 1 of the

KEYNOTE-659 (4), Cohort 2 of the KEYNOTE-059 (12), and Part 1 of the ATTRACTION-4 (15)] and one phase 3 study [KEYNOTE-062 (3)] have reported the efficacy of the addition of an anti-PD1 treatment to the first chemotherapy line in GC patients (*Table 1*). The ORR reported by Kawazoe *et al.* (4) is the best of the four trials, as well as the other surrogate end-points. These results are encouraging, but one may consider some factors that should contributed to these findings: first, it is a phase II study with good selection of patients (ECOG 0, high PD-L1 expression, Asian ethnicity); and second, the chemotherapy backbone oxaliplatin is a better partner for pembrolizumab due to its putative effect on induced immunogenic-cell death (16).

In summary, with only 54 patients included, cohort 1 of the KEYNOTE-659 study validates the safety of the combination of pembrolizumab with a first-line SOX chemotherapy treatment in GC patients. A definitive answer on efficacy of this combination would need to wait for further validation in a phase 3 randomized control trial. That said, a recent regulatory filing for nivolumab, another PD-1 inhibitor, in conjunction with SOX chemotherapy in Japan suggests that the part 2 of the ATTRACTION-4 study, which randomize Japanese naïve GC patients to SOX chemotherapy ± nivolumab, is likely to have a positive outcome. If so, Japanese GC patients may not need to wait much longer to integrate ICI into earlier lines of treatment.

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Footnote

Conflict of Interest: Both authors have completed the ICMJE uniform disclosure from (available at http://dx.doi.org/10.21037/atm-20-4725). MA reports personal fees from MSD, personal fees from BMS, personal fees from Servier, personal fees from Lilly, outside the submitted work. ECS reports personal fees from Astellas, personal fees from Astrazeneca, personal fees from BMS, personal fees from Celgene, personal fees from Five Prime Therapeutics, personal fees from Gritstone Oncology, personal fees from Merck, personal fees from Servier, personal fees from Zymeworks, outside the submitted work.

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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