



Defining the role of upfront immune checkpoint inhibition in advanced HER-2 negative gastric or gastroesophageal junction adenocarcinoma

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The establishment of immune checkpoint inhibitors including for cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) has revolutionized cancer management in recent years. Targeting these immune checkpoint regulators has allowed the immune system to overcome the immune-evasion pathways expressed by cancer cells. Thirteen agents currently target the PD-1/PD-L1 pathway including anti-PD-1 nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab, and dostarlimab additionally, anti-PDL-1 atezolizumab, durvalumab, and avelumab (1). Nivolumab, pembrolizumab, sintilimab, and avelumab studies have recently been reported particularly phase 3 front-line trials in gastric adenocarcinoma (GAC) and gastroesophageal junction (GEJ) adenocarcinoma (2-6). The results of these trials show differing results thus leading to more questions.

Kang *et al.* (2) published the results of ATTRACTION-4 conducted in Japan, South Korea, and Taiwan in *Lancet Oncology*. ATTRACTION-4 evaluated front-line nivolumab in combination with fluoropyrimidine (S-1 or capecitabine) plus oxaliplatin (n=362) *vs.* placebo in combination with fluoropyrimidine + oxaliplatin (n=362). Only patients were enrolled (Japan, South Korea, and Taiwan) if GAC/GEJ was human epidermal growth factor receptor-2 (HER-2) negative. Patients were enrolled regardless of PD-L1 expression. The

primary endpoints were progression-free survival (PFS) and overall survival (OS). Median PFS was improved in the nivolumab plus chemotherapy arm showing a median PFS of 10.45 months (95% CI: 8.44–14.75) compared to placebo plus chemotherapy which showed a median PFS of 8.34 months (95% CI: 6.97–9.40), P=0.0007. Objective response rate (ORR) was also improved (57% ORR with nivolumab plus chemotherapy *vs.* 48% in the placebo plus chemotherapy group). However, the median OS did not differ between groups (median OS of 17.45 months in the nivolumab plus chemotherapy group *vs.* median OS of 17.15 months in the placebo plus chemotherapy group, P=0.26). Most patients (~85%) in both groups had PD-L1 expression of <1% with ~15% of patients in each group having a PD-L1 of ≥1%. PD-L1 status was obtained via the number of tumor cells positive for PD-L1. PD-L1 expression was not defined based on PD-L1 combined positive score (CPS) which is commonly represented in studies and utilized in clinical practice. PD-L1 CPS is defined as the percentage of PD-L1 stained cells (tumor cells, lymphocytes, and macrophages) among all the viable tumor cells. It is unfortunate that OS was not improved in this trial, therefore, the experimental arm of ATTRACTION-4 has not been approved in Japan. The OS of the control arm was remarkable and has contributed to the lack of OS advantage. The lack of OS benefit in the ATTRACTION-4 may have been attributed to the use of subsequent therapy of patients in both arms.

Most patients (66%) received subsequent therapy after progression with many receiving immune checkpoint therapy in the later line setting (27%). ATTRACTION-4 brings the question of whether combination strategy (anti-PD-1/anti-PD-L1 plus chemotherapy) or sequential treatment (chemotherapy → anti-PD-1/anti PD-L1) would be more beneficial. Additionally, from ATTRACTION-4's small percentage of PD-L1 $\geq 1\%$, it must be discussed as whether relying on PD-L1 as the marker the determines effectiveness be the best strategy in these areas of Eastern Asia. ATTRACTION-2, phase 3 exploration of nivolumab *vs.* placebo in advanced refractory (third line or greater) GAC and GEJ adenocarcinoma, showed that PD-L1 expression was likely not the most reliant maker in this population (7). ATTRACTION-2 had $\sim 15\%$ with PD-L1 tumors with $\geq 1\%$. Nivolumab in ATTRACTION-2 showed OS effectiveness regardless of PD-L1 status [median OS PD-L1 $\geq 1\%$ was 5.22 months with nivolumab *vs.* 3.83 months with placebo, hazard ratio (HR) =0.51, 95% CI: 0.21–1.25; median OS PD-L1 $< 1\%$ was 6.05 months with nivolumab *vs.* 4.19 months with placebo, HR =0.72, 95% CI: 0.49–1.05].

Checkmate 649 evaluated nivolumab with fluoropyrimidine plus oxaliplatin (n=789), nivolumab plus ipilimumab, or fluoropyrimidine plus oxaliplatin alone (n=792) in front-line HER-2 negative GAC, GEJ adenocarcinoma, or esophageal adenocarcinoma (EAC) (3). This was a global trial and patients were enrolled from 29 countries. Twenty-two percent were from Asia, 17% from the United States and Canada, and the remainder from the rest of the world. The nivolumab plus ipilimumab arm closed early. Primary endpoints were OS and PFS. Approximately 15% of the population in each group had PD-L1 CPS ≥ 1 . Median OS in the total population was improved with median OS 13.1 months nivolumab plus chemotherapy *vs.* 11.1 months chemotherapy alone, P=0.0002. When reviewed at different PD-L1 CPS levels, the improvement held for those with CPS ≥ 5 patients (n=955) showing a median OS of 14.4 months with nivolumab plus chemotherapy *vs.* 11.1 months chemotherapy alone, P<0.0001 in this group. Median PFS was improved in the CPS ≥ 5 cohort showing a median PFS 7.7 months nivolumab plus chemotherapy *vs.* 6.1 months chemotherapy alone, P=0.0073. Those with CPS < 5 did not show improvement in OS showing a median OS 12.4 months nivolumab + chemotherapy *vs.* 12.3 months chemotherapy alone, P=0.2041. Checkmate 649, therefore, creates questions of whether the true benefit to anti-PD-1/anti-PD-L1 checkpoint inhibition is in only those with higher PD-L1 CPS score. Additionally translational

examination and further combination strategies are needed as Checkmate 649 points out there is still a large population in which combination anti-PD-1 plus chemotherapy regardless of PD-L1 CPS score produces a response. Checkmate 649 showed an ORR was 60% (complete responses of 12%) with nivolumab plus chemotherapy *vs.* 45% (complete response of 7%) in the chemotherapy alone arm. Patients with PD-L1 CPS < 1 and PD-L1 CPS ≥ 5 had ORR of 51% and 55% with nivolumab plus chemotherapy, respectively. Patients with PD-L1 CPS < 1 and PD-L1 CPS ≥ 5 had ORR of 41% and 46% with chemotherapy alone, respectively. Forty-one percent received subsequent therapy with 8% receiving immune checkpoint inhibitor therapy in subsequent therapy.

KEYNOTE-062 was a global phase 3 trial of 29 countries evaluating front line pembrolizumab (n=256) or pembrolizumab plus chemotherapy (fluoropyrimidine + cisplatin) (n=257), or placebo plus chemotherapy (n=250) in HER-2 negative advanced GAC and GEJ adenocarcinoma (4). Patients enrolled were required to have a PD-L1 CPS score ≥ 1 . Approximately 25% were from Asia with approximately 58% of cohorts being from Europe, North America, or Australia. Primary endpoints were OS in CPS ≥ 1 and CPS ≥ 10 along with PFS in CPS ≥ 1 population. Pembrolizumab monotherapy was not superior to chemotherapy in patients with CPS of 1 or greater but did prolong OS compared to chemotherapy in patients with CPS of 10 or greater with a median OS of 17.4 (95% CI: 9.1–23.1) *vs.* 10.8 (95% CI: 8.5–13.8) months but this difference was not statistically tested. Pembrolizumab plus chemotherapy was not superior to chemotherapy alone for OS in patients with CPS of 1 or greater (12.5 *vs.* 11.1 months; P=0.05) or CPS of 10 or greater (12.3 *vs.* 10.8 months; P=0.16) or for PFS in patients with CPS of 1 or greater (6.9 *vs.* 6.4 months; P=0.04). Pembrolizumab monotherapy showed shorter median PFS than chemotherapy in both those with PD-L1 CPS ≥ 1 and PD-L1 ≥ 10 (median PFS 2 *vs.* 6.4 months in those with PD-L1 CPS ≥ 1 ; median PFS 2.9 *vs.* 6.1 months in those with PD-L1 CPS ≥ 10). Subsequent therapy with immunotherapy was in 4–13%. KEYNOTE-062 contradicts the results seen in the Checkmate 649 leading to more questions surrounding the role of anti-PD-1 to chemotherapy front-line but does seem to show more potential for anti-PD-1 for those with higher PD-L1 CPS. Patients with PD-L1 CPS ≥ 10 showed a more durable response with 2-year OS rates of 40% with pembrolizumab compared to 22% with chemotherapy. Although lower ORR the duration for those that did respond was clinically longer in patients with PD-

L1 CPS ≥ 10 [ORR was 25% (complete response 7.6%) for those that received pembrolizumab *vs.* 37.8% (complete response 4.4%) with chemotherapy alone]; median duration of response was longer with pembrolizumab in this group (19.3 *vs.* 6.8 months). Chemotherapy backbones were different amongst the two studies as Checkmate 649 utilized fluoropyrimidine plus oxaliplatin whereas KEYNOTE-062 utilized fluoropyrimidine plus cisplatin. Thus, another conclusion could be that fluoropyrimidine plus oxaliplatin might be the ideal combination strategy to pursue for future study.

The first results of the Orient-16 trial were reported by Xu *et al.* (5). Orient-16, a phase 3 trial, evaluated the role of front-line sintilimab in combination with fluoropyrimidine plus oxaliplatin (n=327) *vs.* placebo plus fluoropyrimidine plus oxaliplatin (n=323) in a Chinese population of advanced HER-2 negative GAC or GEJ adenocarcinoma patients. Patient could enroll regardless of PD-L1 status. The primary endpoint was OS. PD-L1 CPS ≥ 5 was seen in 61.1% of the population. Sintilimab plus chemotherapy showed an improvement in OS in those with CPS ≥ 5 compared to chemotherapy alone showing a median 18.4 *vs.* 12.9 months, P=0.0023. OS was improved also in all patients showing a median of 15.2 months compared to 12.3 months with chemotherapy alone, P=0.0090. OS benefits were seen in all CPS cutoffs (CPS ≥ 1 , 5, and 10). Median PFS was improved in all patients (7.1 *vs.* 5.7 months, P<0.0001) and those with CPS ≥ 5 (7.7 *vs.* 5.8 months, P=0.0002). ORR was also improved with 58.2% *vs.* 48.4%. We await final results and publication of Orient-16 to help determine the placement in this Chinese population. Additionally, we look forward to a full description of patients including the percentage of patients that received subsequent therapy.

JAVLIN Gastric 100 results were published by Moehler *et al.* (6). This was a global phase 3 trial in advanced HER-2 negative GAC and GEJ adenocarcinoma patients. JAVLIN was to evaluate the role of avelumab maintenance therapy (started after 12 weeks of first-line fluoropyrimidine plus oxaliplatin) (n=249) *vs.* continued chemotherapy (n=250). Patients were stratified by region (Asia *vs.* non-Asia). Primary end point was OS after induction chemotherapy in all randomly assigned patients or by PD-L1 positive patients in which PD-L1 protein expression in $\geq 1\%$ of tumor cells was considered positive. PD-L1 status was seen in 12% of the avelumab group and 9.6% in the chemotherapy arm with this method. In a post-hoc exploratory analysis using the PD-L1 CPS method, 29.7% were PD-L1 positive in the avelumab arm and 25.2% in the chemotherapy arm. Median OS did

not differ between groups (median OS was 10.4 months with avelumab *vs.* 10.9 months with continued chemotherapy, P=0.1779) in all patients or in those with PD-L1 $\geq 1\%$ (median OS was 16.2 months with avelumab *vs.* 17.7 months with chemotherapy, P=0.6352). For those that were PD-L1 positive using the CPS method with a CPS ≥ 1 , median OS was 14.9 months with avelumab *vs.* 11.6 months with chemotherapy. Subsequent immunotherapy was receiving in 2.4% of those in avelumab arm and 8.4% of patients in the continued chemotherapy arm. Subsequent chemotherapy was received by 51.4% and 49.2% of patients in the avelumab arm and the continued chemotherapy arm, respectively. Although the primary objective was not met, JAVLIN Gastric 100 brings the question of what method should be used to establish PD-L1 positivity in gastric studies and the importance of consistency of inclusions amongst studies.

The data surrounding these five studies have led to progress but additionally have created more uncertainties. We hope evaluating these studies will help guide future studies surrounding anti-PD-1/anti-PD-L1 therapy in advanced GAC, GEJ adenocarcinoma, and EAC and the importance of consistency amongst trial designs and continued growth in translational medicine to help expand on the role in the front-line setting. Checkmate 649's results led to the United States Food & Drug Administration approval, the European Commission approval, and Japanese approval for front-line advanced HER-2 negative GAC, GEJ adenocarcinoma, and EAC in combination with fluoropyrimidine plus oxaliplatin. Currently, nivolumab plus fluoropyrimidine with oxaliplatin is the standard of care approach for front-line advanced PD-L1 CPS ≥ 5 HER-2 negative, GAC, GEJ adenocarcinoma, EAC patients. We hope further exploration will define the predictive role of PD-L1 in relation to response with anti-PD-1/anti-PD-L1 in the frontline setting. KEYNOTE-859 and BGBA317 305 are examples that will help to shed light. We believe defining the best method to determine PD-L1 positivity is still confusing and inconsistent across studies. As all these phase 3 results show, there is still more work needed at understanding why there are patients that show no response to chemotherapy plus anti-PD-1/anti-PD-L1 showing that there are different combinations strategies to explore to overcome GAC resistance to checkpoint therapy. Current trials are underway exploring dual checkpoint inhibitor therapy, checkpoint inhibitor therapy in combination with multikinase inhibitors/other targeted agents, checkpoint inhibitor therapy in combination with radiation, and utilizing chimeric antigen receptor T-cells (8). We wait

for more answers surrounding this exciting time in GAC investigation.

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Footnote

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