First-line treatment with nivolumab and chemotherapy for metastatic gastric cancer in East Asia is not supported by results of the ATTRACTION-4 trial

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Survival times reported in clinical trials for metastatic gastric cancer in Japan are generally longer than those from North or South American and European countries (1-4). Longer overall survival (OS) in the patients treated in Japan correlates with a higher proportion of patients with good prognostic factors, such as zero of performance status or prior gastrectomy if the primary lesion was operable for resectable disease, compared to American and European patients (5,6). In addition, a smaller tumor burden is also a good prognostic factor, as well as subsequent chemotherapy after the failure of first-line treatment (6), with a lead-time bias in the regional difference of OS.

The potent impact of geographic difference on clinical outcomes was clarified by the AVAGST trial, a global, placebo-controlled phase III study which compared chemotherapy plus bevacizumab with chemotherapy alone as first-line therapy against metastatic gastric cancer (*Table 1*). The median survival time (MST) of patients treated with cisplatin or 5-fluorouracil plus capecitabine was 14.1 months in Japan, 11.6 months in South Korea and other Asian countries, 9.1 months in US/western Europe, and 7.3 months in eastern Europe/South America. Median progression-free survival (PFS) by region was 5.7 months in Japan, 5.6 months in South Korea and other Asian countries, 4.4 months in US/western Europe, and 4.4 months in eastern Europe/South America (7,8). After disease progression in Asia, 77% of Japanese patients and 61% of patients in South Korea and other Asian countries received chemotherapy; the figure was 37% in US/western Europe, and 14% in eastern Europe/South America. However, the survival benefits obtained by second-line or later therapy in these areas were quite limited (1–2 months) (9-11). The hazard ratios (HRs) for OS for each region when compared against US/western Europe were 0.87 for Japan, 0.91 for South Korea and other Asian countries, and 1.47 for eastern Europe/South America (5). Similar geographic differences were observed in the AVATAR and ToGA trials of fluoropyrimidine plus cisplatin with or without trastuzumab for patients with HER2 positive gastric cancer, and in the RAINBOW, RAINBOW-Asia, RAINFALL, and RAINSTORM trials of chemotherapy with or without ramucirumab (12-17). Therefore, the establishment of treatment standards with efficacious novel drugs for Japanese patients requires that trials should be undertaken mainly in East Asia (i.e., Japan and Korea) rather than globally, where American and European patients are included. The final results of clinical trials are expected to differ because the OS of patients with gastric cancer in American and European patients is relatively shorter than that of patients in East Asian countries. In recent global trials, the proportion of enrolled Japanese patients was nominally capped at 10% to 20% and therefore

Table 1 Difference in overall survival by geographic region

Test drug	Trial, number of patients, target population	OS (months), chemotherapy *vs.* chemotherapy plus test drug	HR	P value	Geographic region	Subgroup analysis	
						OS (months) by region	HR
First-line							
Trastuzumab (13)	ToGA, 594, HER2 positive	11.1 *vs.* 13.8	0.74	0.0046	Asia including Japan, South Korea, China (55%)	–	0.82
					Central & South America (9%)	–	0.44
					Europe (33%)	–	0.63
Bevacizumab (8)	AVAGAST, 774, all	10.1 *vs.* 12.1	0.87	0.1002	Asia (66%) [Japan, South Korea (60%)]	12.1 *vs.* 13.9	0.97
					Europe (31%)	8.6 *vs.* 11.1	0.85
					Pan-America (21%)	6.8 *vs.* 11.5	0.63
Bevacizumab (12)	AVATAR, 202, all	11.4 *vs.* 10.5	1.11	0.5567	China (100%)	–	–
Ramucirumab (16)	RAINFALL, 645, all	10.7 *vs.* 11.2	0.962	0.6757	Rest of the world (91%)	–	0.997
					Japan (9%)	–	0.850
Ramucirumab (17)	RAINSTORM, 189, all	14.26 *vs.* 14.65	1.11	0.55	Japan (100%)	–	–
Nivolumab (19)	ATTRACTION-4, 724, all	17.15 *vs.* 17.45	0.90	0.26	Japan (55%)	19.12 *vs.* 16.53	1.04
					South Korea (40%)	14.88 *vs.* 19.71	0.77
Nivolumab (20)	CheckMate649, 1,581, all	11.6 *vs.* 13.8	0.80	0.0002	Asia (22%), USA and Canada (17%), rest of the world (61%)	–	–
Pembrolizumab (21)	KEYNOTE-062, 507, all	11.2 *vs.* 12.5	0.85	0.05	Europe, North America, and Australia (58%), Asia (25%), rest of the world (17%)	–	–
Sintilimab (23)	ORIENT-16, 650, all	12.3 *vs.* 15.2	0.766	0.0090	China (100%)	–	–
Tislelizumab (24,25)	RATIONALE 305, 997, all	–	–	–	China (50%), rest of the world (50%)	–	–

Table 1 *(continued)*

Table 1 *(continued)*

Test drug	Trial, number of patients, target population	OS (months), chemotherapy *vs.* chemotherapy plus test drug	HR	P value	Geographic region	Subgroup analysis	
						OS (months) by region	HR
Second-line							
Lapatinib (26)	TyTAN, 261, HER2 positive	8.9 *vs.* 11.0	0.84	0.1044	Japan (38%)	14.6 *vs.* 12.0	–
					China (37%)	7.6 *vs.* 9.7	–
					South Korea, Taiwan (25%)	–	–
Ramucirumab (14)	RAINBOW, 665, all	9.6 *vs.* 7.4	0.807		Europe, Israel, Australia, US, Mexico, South America (66%)	5.9 *vs.* 8.5	0.732
					Japan, South Korea, Hong Kong, Singapore, Taiwan (34%)	10.5 *vs.* 12.1	0.986
Ramucirumab (15)	RAINBOW-Asia, 440, all	8.71 *vs.* 7.92	0.963	0.7426	China (89%), Malaysia, Philippines, Thailand	–	–
Pembrolizumab (22)	KEYNOTE-061, 395, CPS ≥1	8.3 *vs.* 9.1, paclitaxel *vs.* test drug	0.82	0.0421, one-sided	Europe, Israel, North America, and Australia (67%)	–	0.81
					Asia (26%)	–	0.90
Second or later line							
Nivolumab (10)	ATTRACTION-2, 493, all	4.14 *vs.* 5.26, BSC *vs.* test drug	0.63	<0.0001	Japan (46%)	–	0.63
					South Korea (45%)	–	0.72
					Taiwan (9%)	–	0.46

CPS, combined positive score; OS, overall survival; BSC, best supportive care; HR, hazard ratio.

only minimal safety data related to Japanese patients were obtained. However, the ratio of patients entered into trials from European and American countries should be decreased in order to identify drugs that clearly prolong the survival of Japanese and other East Asian patients. This is because there are differences in post-progression survival time, which are mainly caused by lead-time bias after the failure of test treatment in patients with good prognosis. The survival effect is also weakened in populations with longer survival times, resulting in different outcomes between East Asia and the rest of the world (18).

ATTRACTION-4 was a double-blind phase III study of 724 patients with HER2-negative metastatic gastric or gastroesophageal junction cancer in Japan, South Korea, and Taiwan. This trial showed no difference in OS between the nivolumab with oxaliplatin plus S-1 or capecitabine groups (17.45 *vs.* 17.15 months, respectively; HR, 0.90; P=0.26) and a marginal difference in PFS between the nivolumab plus chemotherapy and chemotherapy alone groups (10.45 *vs.* 8.34 months, respectively; HR, 0.68; P=0.0007) (19). Patient enrichment by molecular markers was not performed at enrollment, and PD-L1 protein expression in tumor cells was not a predictive factor of nivolumab combined chemotherapy in ATTRACION-4. CheckMate 649 was a global open-label phase III of 1,581 patients from 29 countries with metastatic gastric, gastro-esophageal junction, and esophageal adenocarcinoma. The malignancies in these patients are clearly distinct from those with gastric cancer. In CheckMate 649, patients were assigned to a nivolumab plus oxaliplatin plus 5-fluorouracil/leucovorin or capecitabine group or a placebo plus 5-fluorouracil/leucovorin or capecitabine group. Twenty-two percent of patients were enrolled from Asia, 17% from US and Canada, and 61% from the rest of the world. Nivolumab plus chemotherapy demonstrated superior MST compared with chemotherapy (14.4 *vs.* 11.1 months; HR, 0.71; P<0.0001) in patients with a PD-L1 combined positive score (CPS) ≥5, which was a primary endpoint (20). Nivolumab resulted in statistically significant improvement of MST, in nivolumab plus chemotherapy compared to chemotherapy alone (13.8 *vs.* 11.6 months; HR, 0.80; P=0.0002) and median PFS (7.7 *vs.* 6.9 months; HR, 0.68; P<0.0001) in all enrolled patients regardless of CPS score. It is important to note that there was a limited number of Japanese patients included in CheckMate 649. The relationship of the results of ATTRACTION-4 and CheckMate 649 were quite similar to the results of several previous multinational trials, reporting geographical differences or subgroup analyses for Japanese patients in global trials with high reproducibility.

We need to provide appropriate and effective drugs at the right time to prolong OS. Therefore, optimal chemotherapy in the metastatic setting for gastric cancer should be chosen based on the clinical and epidemiological landscapes of each country. Nivolumab, which did not show any OS benefit in ATTRACTION-4, has been approved for use and is covered by public insurance for all metastatic gastric cancer patients in Japan. Experts treat patients in clinical trials, such as ATTRACTION-4, and determine the maximal effect of new drugs for specific eligible patients without severe complications. However, approved drugs often do not show efficacy in the real world of clinical practice. After drug approval, some surgeons and general physicians administer anti-cancer agents without predicting adverse events based on liver or kidney dysfunction or other pharmacokinetic determinants. This leads to suboptimal management of adverse reactions or consideration of the negative impact of anticancer agents on the patients' quality of life, and is likely due to the scarcity of medical oncologists in Japan. Therefore, the efficacy of novel drugs should be re-evaluated using real-world big data related to OS and cost in clinical practice. Minimally, prognostic factors should be adjusted when worldwide data are combined. KEYNOTE-062 examined 763 patients with PD-L1 CPS of ≥1 consisting of 59% of patients from Europe/North America/Australia, 24% from Asia, and 17% from the rest of the world. KEYNOTE-062 was a negative global phase III trial that showed non-inferiority in terms of OS in patients treated with pembrolizumab monotherapy compared to patients treated with cisplatin plus 5-fluorouracil or capecitabine (10.6 *vs.* 11.1 months, respectively). The MST of 12.5 months with pembrolizumab plus chemotherapy was not superior to chemotherapy alone, which conferred an OS of 11.1 months in patients with CPS of ≥1 (HR, 0.85; P=0.05) (21). The population of Asian patients was limited to 22% in KEYNOTE-062. However, the trial gave negative results at P=0.05 due to the incorporation of multiple primary endpoints and alpha consumption by dispense to each endpoint. In the population with CPS of ≥10, MST with pembrolizumab plus chemotherapy was not superior to that obtained with chemotherapy (12.3 *vs.* 10.8 months; HR, 0.85; P=0.16). The CPS was not a predictive factor of the response to pembrolizumab treatment. Fifty of 763 patients (6.6%) had microsatellite instability-high (MSI-H) tumors. In an exploratory analysis of patients

with MSI-H and a CPS of ≥1, an extension of MST with pembrolizumab was "not achieved" compared with the 8.5-month MST with chemotherapy (HR, 0.29). In KEYNOTE-062, the median PFS was 11.2 months for pembrolizumab, not reached (NR) for pembrolizumab plus chemotherapy, and 6.6 months for chemotherapy (22). The ORIENT-16 trial with 650 gastric cancer patients regardless of PD-L1 expression was a double-blind phase III study to evaluate the efficacy of sintilimab, an anti-PD-1 antibody, in combination with oxaliplatin plus capecitabine *vs.* chemotherapy alone as the first-line treatment in China. Sintilimab plus chemotherapy showed a significant improvement in MST compared with chemotherapy alone (15.2 *vs.* 12.3 months; HR, 0.766; P=0.0090) in all patients. The MST was significantly prolonged in patients with a CPS ≥5 treated with sintilimab plus chemotherapy compared to chemotherapy alone (18.4 *vs.* 12.9 months; HR, 0.660; P=0.0023) (23). Thus, the CPS is not a predictive factor of sintilimab. Sintilimab plus chemotherapy is effective as a first-line treatment in China. BeiGene announced positive results of phase III trial, RATIONALE 305, of tislelizumab, an anti PD-1 antibody, *vs.* placebo in combination with platinum plus fluoropyrimidine as a first-line treatment for patients with gastric or gastroesophageal junction adenocarcinoma with PD-L1 expression at the interim analysis, however, final analysis is required to evaluate the OS benefit in the intention-to-treat population. Half of patients were enrolled from China in the RATIONALE 305 (24,25). The TyTan phase III trial evaluated paclitaxel with or without lapatinib (a HER2 tyrosine kinase inhibitor) as second line against HER2-amplified gastric cancer in patients from China, Taiwan, South Korea, and Japan. The MST was 11.0 months in patients treated with lapatinib plus paclitaxel and 8.9 months in those treated with paclitaxel alone (P=0.104). Regional differences were also observed in the East Asian trial, TyTAN. The MST was 9.7 months in patients treated with lapatinib plus paclitaxel and 7.6 months in those treated with paclitaxel alone (P=0.035) in China. In Japanese patients, the corresponding MSTs were 12.0 and 14.6 months (P=0.62), respectively (26).

Article 25 of the Japanese Constitution declares that "*all people shall have the right to maintain a certain standard of healthy and cultured life*" and that "*the state shall try to promote and improve the conditions of social welfare*, *social security*, *and public health*" for this purpose (27). Article 25 states that citizens have a right to their best health and declares that it is the state's responsibility to ensure this right can be realized. Against this background, universal healthcare coverage through the public health insurance system was established in 1961. Today, the Japanese public health insurance system includes the following benefits (28).

(I) Provides public medical insurance coverage to all Japanese citizens;
(II) Allows patients to use medical institutions of their choice;
(III) Provides high grade medical treatment at low cost;
(IV) While based on the social insurance system, the government uses public funds to maintain the mandatory nature of the health insurance system.

Differences in the survival of advanced gastric patients can be observed based on regions. Under the universal health coverage, Japanese patients can receive any drugs approved by the Ministry of Health, Labour, and Welfare and easily obtain access to clinics and hospitals by themselves with a low co-payment cost. Therefore, gastric cancer is generally identified earlier, with a smaller tumor burden by computed axial tomography scan, even in stage IV cases. These differences impact OS in global clinical studies. Patients with good performance status will be in the study longer and those patients can receive subsequent therapies with good performance status even at the beginning of third-line therapy. The longer survival of Japanese patients depends on their good performance status. These patients could have more frequent opportunities to receive subsequent therapies because of their longer post-progression survival. Given that the survival benefit of second- or later-line therapy is small, post-protocol therapy itself does not have a large impact on OS.

In conclusion, the results of ATTRACTION-4 showed that first-line chemotherapy with nivolumab for Japanese and Korean patients with metastatic gastric cancer has no significant effect on OS. PD-1 expression and CPS score were not predictive factors of the effect of this treatment on OS. However, MSI-H gastric cancer patients may be good candidates for first-line usage of pembrolizumab. Geographic differences, with differences in medical environments, have a great impact on OS beyond the need to add new agents. Therefore, optimal chemotherapy for gastric cancer should be chosen based on the medical environment in each country.

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Footnote

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