




Phase IIb study of pembrolizumab combined with S-1 + oxaliplatin or S-1 + cisplatin as first-line chemotherapy for gastric cancer

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Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; ASaT, all subjects as treated; BSA, body surface area; CI, confidence interval; CPS, combined positive score; CR, complete response; DCR, disease control rate; DOR, duration of response; G/GEJ, gastric/gastroesophageal junction; HER2, human epidermal growth factor receptor 2; KM, Kaplan–Meier; NE, not estimable; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L, programmed death-ligand; PFS, progression-free survival; PR, partial response; S-1, tegafur-gimeracil-oteracil potassium; SOX, S-1 and oxaliplatin; SP, S-1 and cisplatin; SP3, SP every 3 weeks; TRAE, treatment-related adverse event; TTR, time to response.

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Abstract

The KEYNOTE-659 study evaluated the efficacy and safety of first-line pembrolizumab plus S-1 and oxaliplatin (SOX) (cohort 1) or S-1 and cisplatin (SP) (cohort 2) for advanced gastric/gastroesophageal junction (G/GEJ) cancer in Japan. Herein, we update the results of cohort 1 and describe the results of cohort 2. This open-label phase IIb study enrolled patients with advanced programmed death-ligand 1 (PD-L1)-positive (combined positive score ≥ 1) human epidermal growth factor receptor 2 (HER2)-negative G/GEJ adenocarcinoma. The primary end-point was the objective response rate (ORR). Other end-points were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. One hundred patients were enrolled. In cohorts 1 and 2, median follow-up time was 16.9 and 17.1 months; ORR (central review), 72.2% and 80.4%; DOR, 10.6 and 9.5 months; DCR (central review), 96.3% and 97.8%; median PFS (central review), 9.4 and 8.3 months; and median OS, 16.9 and 17.1 months, respectively. Treatment-related adverse events (TRAEs) occurred in all patients, including peripheral sensory neuropathy (94.4%, cohort 1), decreased neutrophil count (82.6%, cohort 2), nausea (59.3% and 60.9% in cohorts 1 and 2), and decreased appetite (61.1% and 60.9% in cohorts 1 and 2). Grade 3 or higher TRAEs were reported by 59.3% (cohort 1) and 78.3% (cohort 2), including decreased platelet count (14.8%, cohort 1) and decreased neutrophil count (52.2%, cohort 2). Pembrolizumab in combination with SOX or SP showed favorable efficacy and safety in patients with PD-L1-positive, HER2-negative G/GEJ adenocarcinoma.

KEYWORDS

cisplatin, gastric cancer, oxaliplatin, pembrolizumab, S-1

1 | INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer worldwide and the second most common cancer in Japan.^{1,2} In Japan, the standard first-line chemotherapy regimen for HER2-negative advanced G/GEJ cancer is combination therapy with platinum and fluoropyrimidine agents.³⁻⁷ Of note, immune checkpoint blockade with Abs targeting the PD-1 pathway has therapeutic benefits in several cancers, including gastric cancer.⁸

Pembrolizumab (MK-3475) is a potent, highly specific, humanized IgG4/kappa-isotype mAb that directly inhibits the binding of PD-1 and its ligands PD-L1 and PD-L2. Programmed cell death-L1 expression or PD-L1 CPS ≥ 1 , calculated as the number of PD-L1-positive cells (tumor cells, macrophages, and lymphocytes) divided by the total number of cells multiplied by 100, is detected in 67%–82% of gastric cancer patients.^{9,10} The relationship between CPS and efficacy has been shown with pembrolizumab monotherapy.¹¹

The KEYNOTE-059 study evaluated the safety and efficacy of pembrolizumab plus fluoropyrimidine (5-FU) or capecitabine and cisplatin in chemotherapy-naïve patients with advanced gastric cancer.¹² The ORR, median PFS, and median OS were 60% (95% CI,

39%–79%), 6.6 months (95% CI, 5.9–10.6 months), and 13.8 months (95% CI, 8.6 months–not estimable), respectively.¹²

In the subsequent KEYNOTE-062 phase III study in patients with HER2-negative advanced gastric or GEJ adenocarcinoma with PD-L1 CPS ≥ 1 , OS with pembrolizumab alone as first-line therapy was noninferior to chemotherapy with 5-FU and cisplatin or capecitabine and cisplatin. However, OS with pembrolizumab plus 5-FU and cisplatin or capecitabine and cisplatin was not superior to 5-FU and cisplatin or capecitabine and cisplatin in patients with PD-L1 CPS ≥ 1 or PD-L1 CPS ≥ 10 .¹¹

The current study (KEYNOTE-659) investigated the efficacy and safety of pembrolizumab in combination with S-1 (tegafur-gimeracil-oteracil potassium) and oxaliplatin or S-1 and cisplatin as first-line therapy in Japanese patients with advanced G/GEJ adenocarcinoma. The results from cohort 1 (patients treated with pembrolizumab plus SOX) of this study have been reported previously and showed an ORR of 72.2% (95% CI, 58.4%–83.5%), DCR of 96.3% (95% CI, 87.3%–99.5%), PFS of 9.4 months (95% CI, 6.6 months–not evaluable), and the median OS was not reached (cut-off June 21).¹³ In this article, we report the updated results for cohort 1 (patients treated with pembrolizumab plus SOX), as

well as the efficacy and safety results for cohort 2 (patients treated with pembrolizumab plus SP).

2 | MATERIALS AND METHODS

2.1 | Study design and patients

Details of the study design have been previously published.¹³ Briefly, this nonrandomized, multicenter, open-label, phase IIb trial (KEYNOTE-659, NCT03382600/JapicCTI-183829) targeted patients with advanced G/GEJ adenocarcinoma that was PD-L1 CPS-positive and HER2-negative and evaluated the efficacy and safety of SOX (cohort 1) or SP (cohort 2) with pembrolizumab as first-line treatment. Enrollment of cohort 2 commenced following completion of enrollment of cohort 1.

For cohorts 1 and 2, the key eligibility criteria were as follows: age 18 to ≤ 75 years; no previous chemotherapy for a histologically or cytologically confirmed advanced G/GEJ adenocarcinoma; no neoadjuvant or adjuvant therapy within 6 months of enrollment (patients who completed therapy at least 6 months prior to enrollment were eligible); CPS of ≥ 1 by immunohistochemistry using 22C3 PharmDx assay by central laboratory; ECOG performance status of 0 or 1; at least one measurable lesion assessed per RECIST version 1.1 by the investigator; and adequate organ function.

Main exclusion criteria included: squamous cell or undifferentiated gastric cancer; HER2-positive status; radiotherapy within 14 days of enrollment; active central nervous system metastases and/or carcinomatous meningitis; an active autoimmune disease requiring systemic treatment in the past 2 years, excluding replacement therapy such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency; history of (noninfectious) pneumonitis that required steroids or current pneumonitis; active infection requiring systemic therapy; and grade 2 or higher peripheral sensory neuropathy.

2.2 | Treatment

Pembrolizumab 200 mg (a 30 min i.v. infusion) and oxaliplatin (130 mg/m² i.v.) or cisplatin (60 mg/m² i.v.) were given on day 1 of each 3-week cycle and S-1 was given orally twice daily for the first 2 weeks of each 3-week cycle at a dose of 40 mg for a BSA < 1.25 m², 50 mg for a BSA from 1.25 to < 1.5 m², and 60 mg for a BSA ≥ 1.5 m². As prophylactic treatment for nausea and vomiting, patients were managed with palonosetron plus aprepitant or fosaprepitant. Additionally, the use of steroids was allowed for oxaliplatin or cisplatin-associated antiemetic purposes.

Treatment with pembrolizumab plus chemotherapy was continued until disease progression, unacceptable AEs, withdrawal of consent, or until the patient had received 35 treatments with pembrolizumab.

Patients who discontinued SOX (cohort 1), SP (cohort 2), or pembrolizumab could continue receiving pembrolizumab monotherapy, S-1 monotherapy, oxaliplatin (cohort 1), or cisplatin (cohort 2), respectively, if they had not met the discontinuation criteria.

2.3 | Assessments

Computed tomography was carried out at baseline within 21 days prior to enrollment. Subsequent tumor imaging was carried out every 6 weeks (42 days \pm 7 days) or more frequently if clinically indicated.

Tumor response was assessed according to RECIST version 1.1 by central review as well as by the investigator. Tumor imaging to confirm PR or CR was carried out at least 4 weeks after the first indication of response was observed. In clinically stable patients, disease progression was confirmed based on iRECIST between 4 and 8 weeks after the first progression.¹⁴

2.4 | End-points

The primary end-point was the ORR assessed by central review according to RECIST version 1.1. The secondary end-points were DOR, DCR, TTR, PFS, OS, and safety. The DOR was defined as the time from the date of first response (CR or PR) to the date of disease progression or death, TTR as the time from the date of enrollment to the first date of CR or PR, PFS as the time from the date of enrollment to the first documented disease progression or death due to any cause, whichever occurred first, and OS as the time from the date of enrollment to death due to any cause. For safety, AEs were monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI's Common Terminology Criteria for Adverse Events version 4.0. Subgroup analyses of OS and event rate according to PD-L1 CPS status (<10 and ≥ 10) were included as exploratory end-points.

2.5 | Statistical analysis

The target sample size was 90 patients, comprising 45 patients in cohort 1 and 45 patients in cohort 2, to account for a drop-off rate before treatment of 10%. No specific hypotheses were tested in this study. However, the planned sample sizes were considered appropriate to allow the estimation of the effect of pembrolizumab with SOX or SP according to the point estimate and 95% CI by the exact binomial method: if 28 of 40 patients achieved an objective response, the ORR was estimated to be 70.0% with a CI of 53.5%–83.4%.

The ASaT population, which consisted of all patients who received at least one dose of study treatment, was used to analyze ORR, DCR, TTR, PFS, OS, and safety. A total of 80 patients (pembrolizumab plus SOX group [cohort 1], 40 patients; pembrolizumab plus SP group [cohort 2], 40 patients) were planned to be included in the ASaT population. The analysis population for DOR

consisted of responders with a best response of CR or PR in the ASaT population. For the primary end-point (ORR), 95% CIs were calculated using the exact binomial method proposed by Clopper and Pearson.¹⁵ For DOR, PFS, TTR, and OS, KM curves and median estimates from the KM curves were provided as appropriate. All statistical analyses were undertaken using SAS version 9.4 or later (SAS Institute Inc.). Follow-up time was defined as the number of days from enrollment to the last survival follow-up date for censored subjects or the number of days from the date of enrollment to the date of death.

3 | RESULTS

3.1 | Patient characteristics

First, 54 patients were enrolled in cohort 1 from April 2018 to September 2018. Subsequently, 46 patients were enrolled in cohort 2 from September 2018 to June 2019. All patients received study treatment and were included in the ASaT population. The data cut-off date for safety and efficacy analyses was May 30, 2021, with a median follow-up time of 16.9 months in cohort 1 and 17.1 months in cohort 2.

In cohort 1, 42 patients were discontinued due to disease progression (40 had radiological disease progression, and two had clinical disease progression). Three patients discontinued due to TRAEs (enteritis, pancreatitis/pancreatic pseudocyst, and cardiac arrest). Additionally, nine patients discontinued for other reasons, including six patients who completed 35 pembrolizumab treatments and two patients who underwent surgery for curative intent. Only one patient was lost to follow-up. In cohort 2, 35 patients discontinued due to disease progression: 31 had radiological disease progression, and four had clinical disease progression. Three patients discontinued due to an AE: two had treatment-related rash, and one had pancreatitis. One patient withdrew from treatment. Seven patients discontinued for other reasons, including three patients who completed 35 pembrolizumab treatments and three patients who underwent surgery for curative intent.

The baseline demographic and clinical characteristics of patients are shown in Table 1. More than half of the population were men (79.6% in cohort 1, 60.9% in cohort 2), the median age was 66.0 and 65.0 years in cohorts 1 and 2, respectively, and CPS was ≥ 10 in 31 (57.4%) and 27 (58.7%) patients in cohorts 1 and 2, respectively.

3.2 | Treatment delivery

In cohorts 1 and 2, the median treatment duration of pembrolizumab was 6.0 and 5.1 months, respectively. The median treatment duration of SOX (cohort 1) was 4.9 months and the median treatment duration of SP (cohort 2) was 4.4 months. The actual and relative dose intensities for each drug, along with the cumulative doses, are shown in Table 2. In cohort 1, 35 (64.8%) patients

TABLE 1 Baseline demographic and clinical characteristics of Japanese patients with gastric cancer treated with first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or S-1 + cisplatin (cohort 2) (all subjects as treated population)

Characteristic	Cohort 1 (N = 54)	Cohort 2 (N = 46)
Age, years, median (range)	66.0 (32–75)	65.0 (30–75)
Sex		
Male	43 (79.6)	28 (60.9)
Female	11 (20.4)	18 (39.1)
ECOG PS (screening phase)		
0	46 (85.2)	35 (76.1)
1	8 (14.8)	11 (23.9)
Metastatic disease (at initial diagnosis)		
No	5 (9.3)	7 ^a (15.2)
Yes	49 (90.7)	39 (84.8)
Primary location		
Gastric	46 (85.2)	40 (87.0)
Gastroesophageal junction	8 (14.8)	6 (13.0)
Histological type		
Intestinal	21 (38.9)	20 (43.5)
Diffuse	32 (59.3)	24 (52.2)
Unknown	1 (1.9)	2 (4.3)
Number of metastatic sites (central review)		
<3	37 (68.5)	33 (71.7)
≥ 3	17 (31.5)	13 (28.3)
History of surgery		
No	49 (90.7)	35 (76.1)
Yes	5 (9.3)	11 (23.9)
CPS		
1–9	23 (42.6)	19 (41.3)
≥ 10	31 (57.4)	27 (58.7)

Note: Unless otherwise stated, all data are n (%). Data cut-off: May 30, 2021.

Abbreviations: CPS, combined positive score; PS, performance status.

^aIncludes one patient for whom the presence of metastasis was unknown at initial diagnosis.

underwent a dose reduction of S-1, 47 (87.0%) patients underwent a dose reduction of oxaliplatin, 44 (81.5%) patients had a dose interruption of S-1, and 31 (57.4%) patients had a dose interruption of oxaliplatin. In cohort 2, 33 (71.7%) patients underwent a dose reduction of S-1, 43 (93.5%) patients underwent a dose reduction of cisplatin, 29 (63.0%) patients had a dose interruption of S-1, and 22 (47.8%) patients had a dose interruption of cisplatin. In cohorts 1 and 2, 72.2% and 84.8% of patients, respectively, received subsequent chemotherapy. The common regimens were paclitaxel-based regimen (63.0% in cohort 1, 69.6% in cohort 2), irinotecan-based regimen (27.8% in cohort 1, 19.6% in cohort 2), trifluridine and tipiracil (22.2% in cohort 1, 19.6% in cohort 2), and nivolumab (22.2% in cohort 1, 10.9% in cohort 2).

TABLE 2 Cumulative dose and dose intensity for each drug (cohort 1: pembrolizumab with S-1 + oxaliplatin; cohort 2: pembrolizumab with S-1 + cisplatin) among Japanese patients with gastric cancer (all subjects as treated population)

	Cohort 1 (N = 54)	Cohort 2 (N = 46)
Pembrolizumab		
Cumulative dose (mg)		
Median (range)	1700.0 (400–7000)	1600.0 (400–7000)
Actual dose intensity (mg/week) ^a		
Mean (SD)	57.8 (9.1)	55.7 (10.8)
Median	59.8	57.4
Relative dose intensity (%) ^b		
Mean (SD)	86.8 (13.6)	83.5 (16.2)
Median	89.7	86.1
S-1		
Cumulative dose (mg)		
Median (range)	11130.0 (2180–55,380)	9940.0 (1500–40,460)
Actual dose intensity (mg/m ² /week) ^a		
Mean (SD)	234.5 (51.6)	223.7 (72.4)
Median	240.8	229.4
Relative dose intensity (%) ^b		
Mean (SD)	71.6 (17.1)	67.6 (22.3)
Median	72.2	68.4
Oxaliplatin		
Cumulative dose (mg/m ²)		
Median (range)	688.6 (230–1633)	NA
Actual dose intensity (mg/m ² /week) ^a		
Mean (SD)	24.2 (10.5)	NA
Median	25.8	NA
Relative dose intensity (%) ^b		
Mean (SD)	56.0 (24.2)	NA
Median	59.6	NA
Cisplatin		
Cumulative dose (mg/m ²)		
Median (range)	NA	289.5 (109–719)
Actual dose intensity (mg/m ² /week) ^a		
Mean (SD)	NA	11.2 (5.4)
Median	NA	11.4
Relative dose intensity (%) ^b		
Mean (SD)	NA	56.1 (27.2)
Median	NA	57.0

Abbreviations: BSA, body surface area; NA, not applicable.

^aActual dose intensity calculated as:

Pembrolizumab (mg/week): cumulative dose (mg)/(total treatment duration [weeks]).

S-1 (mg/m²/week): (cumulative dose during the study (mg)/BSA (at baseline) (m²))/(total treatment duration [weeks]).

Oxaliplatin/cisplatin (mg/m²/week): (cumulative dose during the study (mg)/BSA (at baseline) (m²))/(total treatment duration [weeks]).

^bRelative dose intensity (%) calculated as:

Pembrolizumab: dose intensity (mg/week)/(first amount of actual dose (mg)/3) × 100.

S-1: dose intensity (mg/m²/week)/((first amount of actual dose (mg) × 2 × 14/BSA at baseline (m²)/3) × 100.

Oxaliplatin/cisplatin: dose intensity (mg/m²/week)/((first amount of actual dose (mg)/BSA at baseline (m²)/3) × 100.

TABLE 3 Best overall response and survival results among Japanese patients with gastric cancer treated with first-line pembrolizumab with S-1+oxaliplatin (cohort 1) or S-1+ cisplatin (cohort 2) (all subjects as treated population), assessed by central review per RECIST version 1.1

Category	Cohort 1 (N = 54)		Cohort 2 (N = 46)	
	n	(95% CI)	n	(95% CI)
Objective response rate (CR+PR)	39	72.2% (58.4%–83.5%)	37	80.4% (66.1%–90.6%)
Disease control rate (CR+PR+SD)	52	96.3% (87.3%–99.5%)	45	97.8% (88.5%–99.9%)
Best overall response, n (%)				
Complete response	2 (3.7)		4 (8.7)	
Partial response	37 (68.5)		33 (71.7)	
Stable disease	13 (24.1)		8 (17.4)	
Progressive disease	2 (3.7)		1 (2.2)	
Progression-free survival, months, median		9.4 (6.6–12.6)		8.3 (5.8–15.3)
Overall survival, months, median		16.9 (13.4–20.0)		17.1 (12.6–23.1)
Time to response, months, median	1.5		1.5	
Duration of response, months, median	10.6	(5.6–NE)	9.5	(4.7–15.3)

Note: Data cut-off: May 30, 2021.

Abbreviations: CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response; SD, stable disease.

3.3 | Efficacy

The ORR assessed by central review was 72.2% (95% CI, 58.4%–83.5%; 39/54 patients) in cohort 1, and 80.4% (95% CI, 66.1%–90.6%; 37/46 patients) in cohort 2 (Table 3). Overall, 52 (96.3%) of 54 patients in cohort 1 and 44 (95.7%) of 46 patients in cohort 2 showed any tumor shrinkage from baseline (Figure 1). DCR, as assessed by central review, was 96.3% (95% CI, 87.3%–99.5%; 52 of 54 patients) in cohort 1 and 97.8% (95% CI, 88.5%–99.9%; 45 of 46 patients) in cohort 2 (Table 3).

In cohorts 1 and 2, respectively, the median PFS assessed by central review was 9.4 (95% CI, 6.6–12.6) months and 8.3 (95% CI, 5.8–15.3) months (Figure 2). Median OS was 16.9 (95% CI, 13.4–20.0) months in cohort 1 and 17.1 (95% CI, 12.6–23.1) months in cohort 2 (Figure 3). Median DOR was 10.6 (95% CI, 5.6–NE) months in cohort 1 and 9.5 (95% CI, 4.7–15.3) months in cohort 2, and median TTR was 1.5 months in both cohorts (Table 3). The updated results in cohort 1 for ORR, DCR, median TTR, and PFS (by central review) did not differ from the previously reported results.¹³ At the previous data cut-off (June 21, 2019), the median DOR and OS were not reached.

Tumor response assessed by the investigator is shown in Table 4. In cohort 1, ORR was 72.2% (95% CI, 58.4%–83.5%), DCR was 94.4% (95% CI, 84.6%–98.8%), median PFS was 6.9 (5.6–8.3) months, and there was no difference from previously reported results. In cohort 2, ORR was 63.0% (95% CI, 47.5%–76.8%), DCR was 97.8% (95% CI, 88.5%–99.9%), and median PFS was 6.7 (5.3–8.4) months.

In an exploratory analysis of OS according to CPS status, OS in cohort 1 was 14.9 (95% CI, 9.5–19.1) months in patients with a CPS \geq 10 and 17.7 (95% CI, 13.4–23.7) months in those with a

CPS <10. In cohort 2, OS was 15.5 (95% CI, 11.5–22.9) months in patients with a CPS \geq 10 and 21.7 (95% CI, 8.3–NE) months in those with a CPS <10. Similarly, the median PFS in cohort 1 was 8.1 (95% CI, 5.5–12.6) months in patients with a CPS \geq 10 and 12.6 (95% CI, 6.6–NE) months in those with a CPS <10. The median PFS in cohort 2 was 7.0 (95% CI, 5.1–NE) months in patients with a CPS \geq 10 and 14.8 (95% CI, 5.8–16.4) months in those with a CPS <10. Kaplan–Meier event rates according to CPS are shown in Figures 4 and 5.

3.4 | Safety

Overall, TRAEs of any grade occurred in all patients in this study. The incidence of TRAEs that occurred in at least 10% of patients in this study are presented in Table 5; the most common were peripheral sensory neuropathy (51 [94.4%] in cohort 1), decreased neutrophil count (38 [82.6%] in cohort 2), nausea (32 [59.3%] in cohort 1 and 28 [60.9%] in cohort 2), and decreased appetite (33 [61.1%] in cohort 1 and 28 [60.9%] in cohort 2). Grade 3 or higher TRAEs were reported in 32 (59.3%) patients in cohort 1, and 36 (78.3%) patients in cohort 2 (Table 5). Decreased neutrophil count was the most frequently reported TRAE of grade 3 or higher, with 8 (14.8%) patients in cohort 1 and 24 (52.2%) in cohort 2. The most common reason for SP dose reduction was decreased neutrophil count. Serious TRAEs were reported in 18 (33.3%) patients in cohort 1 and 17 (37.0%) patients in cohort 2. The most common serious TRAE was adrenal insufficiency (3 [5.6%] in cohort 1 and 3 [6.5%] in cohort 2). One patient had a cardiac arrest in cohort 1, and this event was considered a treatment-related death.

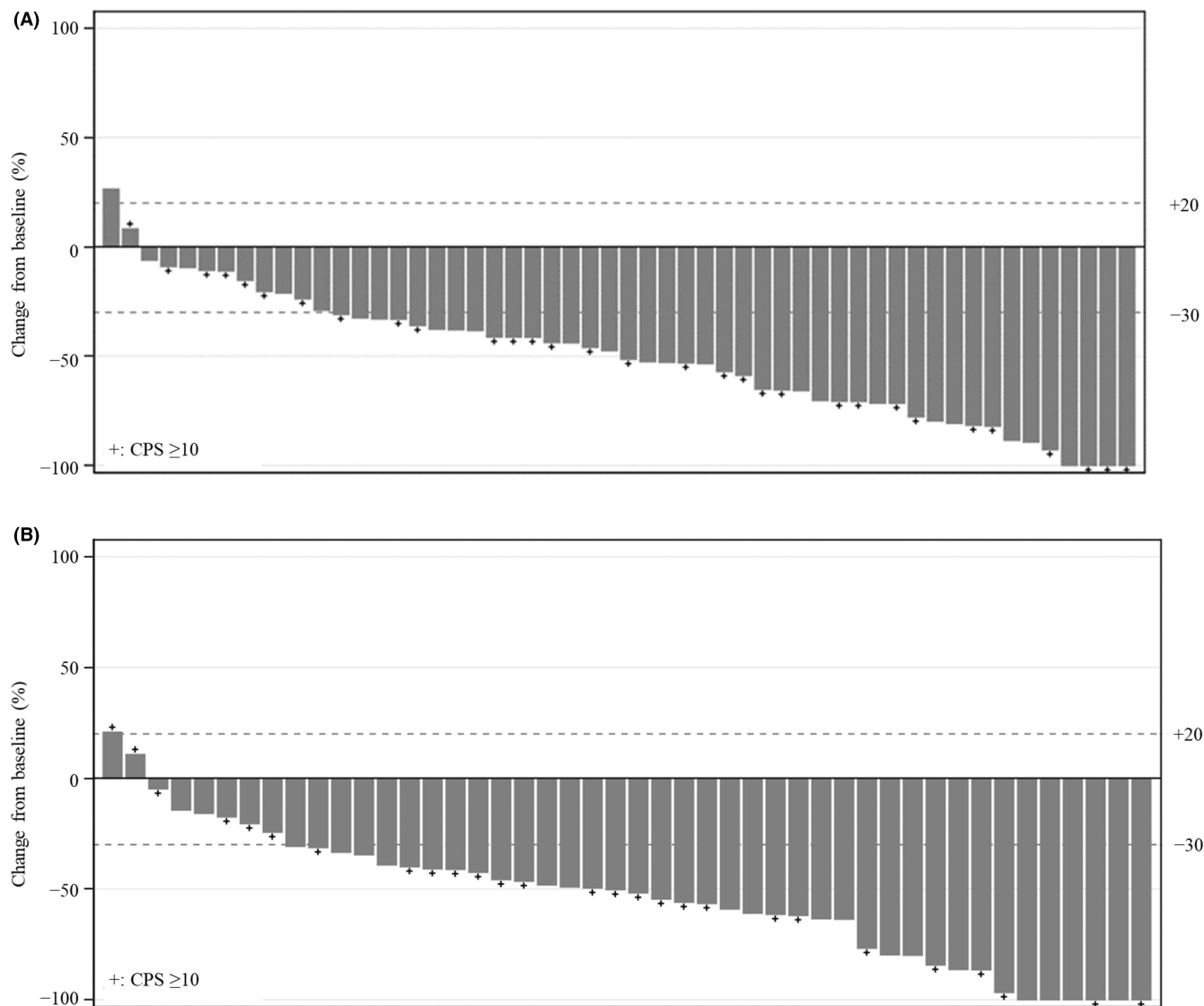


FIGURE 1 Overall tumor response in Japanese patients with gastric cancer treated with (A) first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or (B) first-line pembrolizumab with S-1 + cisplatin (cohort 2), assessed by central review according to RECIST version 1.1. Best change from baseline in the sum of the longest target lesion diameter per patient by programmed cell death-ligand 1 expression. CPS, combined positive score

4 | DISCUSSION

In this study, the efficacy and safety of combination therapy with first-line pembrolizumab plus SOX or SP was similar in both cohorts of patients with advanced G/GEJ adenocarcinoma. KEYNOTE-659 is the first study to evaluate the anti-PD-1 Ab and SP combination. In patients who received SP3 in the S-1 Optimal Schedule (SOS) study, the ORR was 59.7% (114 of 191 patients), median PFS was 5.5 (95% CI, 4.7–6.6) months, and median OS was 14.1 (95% CI, 11.4–15.8) months.¹⁶ In this study, the ORR (80.4% [95% CI, 66.1%–90.6%]), median PFS (8.3 [range, 5.8–15.3] months), and median OS (17.1 [range, 12.6–23.1] months) with pembrolizumab plus SP3. Although cross-study comparisons should be interpreted with caution, pembrolizumab in combination with SP is expected

to show promising antitumor effects compared with SP due to possible add-on antitumor effects of pembrolizumab for patients with PD-L1 expression.

The updated results (data cut-off date: May 30, 2021) for cohort 1 (pembrolizumab plus SOX: ORR of 72.2%, DCR of 96.3%, median PFS of 9.4 months by central review, median OS of 16.9 months, with a median follow-up of 16.9 months) showed no major differences from the results of cohort 2. For OS, no major differences were observed in the two cohorts even after considerable follow-up results were collected.

Regarding the safety profile of pembrolizumab in combination with SP, decreased neutrophil count (grade ≥ 3) was more frequently reported in cohort 2 (52.2%) than in cohort 1 (14.8%) (Table 5). Overall, the most frequently reported TRAEs in cohort 2 were anemia

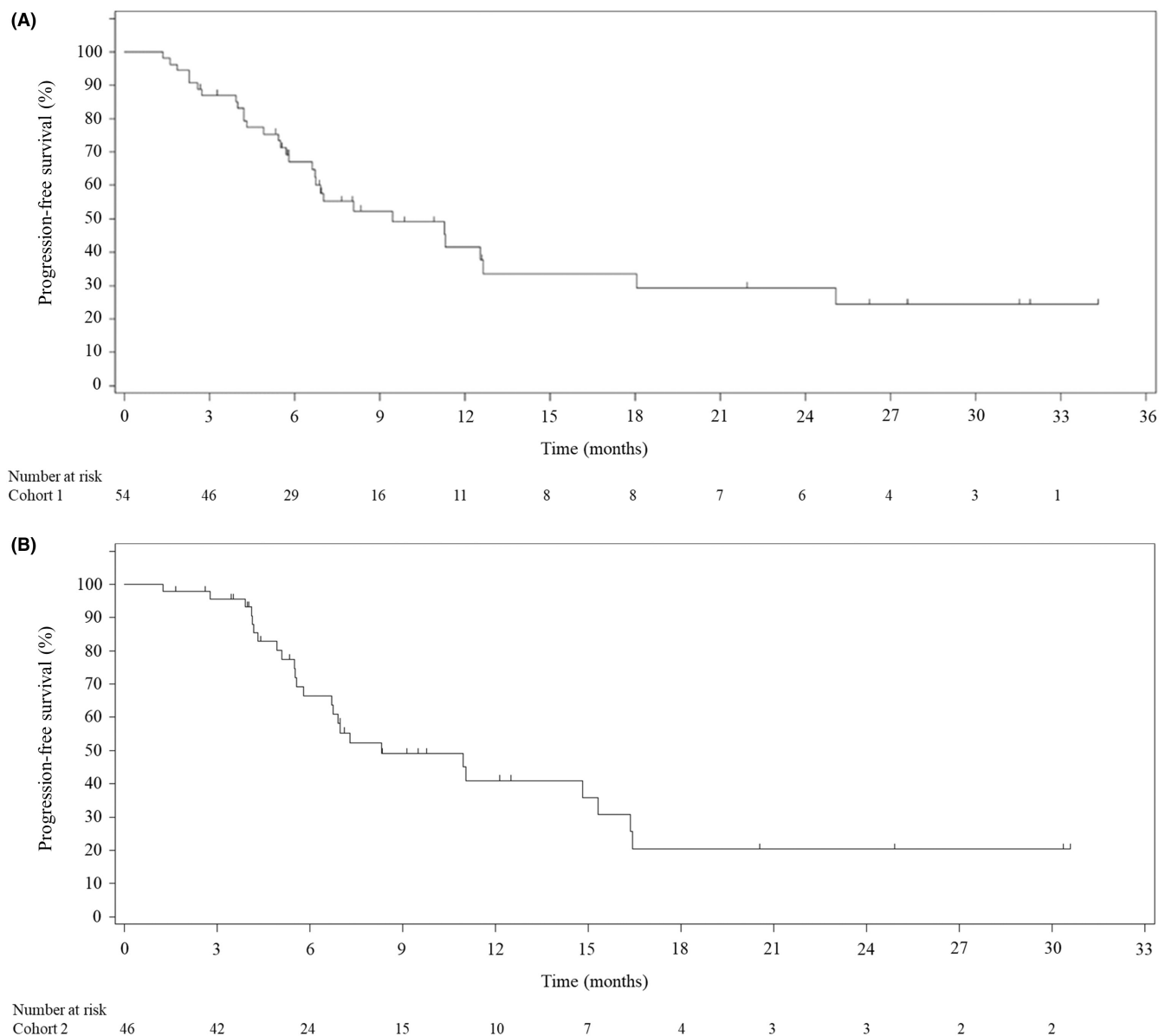


FIGURE 2 Kaplan–Meier estimates of progression-free survival in Japanese patients with gastric cancer treated with (A) first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or (B) first-line pembrolizumab with S-1 + cisplatin (cohort 2), assessed by central review

(32.6%), diarrhea (43.5%), nausea (60.9%), and fatigue (23.9%), and the respective incidences in cohort 1 were 16.7%, 38.9%, 59.3%, and 20.4%. By contrast, grade ≥ 3 platelet count decreased (including thrombocytopenia, 14.8%) and peripheral sensory neuropathy (3.7%) were more frequently reported in cohort 1 than in cohort 2 (2.2% and 0.0%, respectively). Study discontinuation because of rash was reported in two patients in this study, but treatment discontinuation due to rash was not reported in cohort 1.¹³ Grade 3 colitis was observed in three patients (5.6%) in cohort 1,¹³ but no grade ≥ 3 colitis was observed in cohort 2. The other TRAEs of interest were not notably different from those reported with pembrolizumab monotherapy.^{10,11}

Although SP is usually given every 5 weeks in Japan, in this study, SP3 treatment matched the timing of pembrolizumab treatment (every 3 weeks). In addition, the efficacy and safety of SP3

have previously been confirmed in the SOS study, a phase III study in Japan and Korea that investigated SP3 as first-line therapy in patients with advanced gastric cancer.¹⁶ The incidence and profile of AEs in this study are consistent with the SP3 safety profile reported in the SOS study, showing no novel safety concern with the combination of SP3 with pembrolizumab.^{10,11}

Although the initial dose of oxaliplatin (130 mg/m²) was higher than that in the G-SOX study (100 mg/m²), an increase of hematological toxicities was not observed in this study. The relative dose intensity for oxaliplatin in this study (59.6%) was lower than that in the G-SOX study (79.0%).¹⁷ These toxicities could be managed by appropriate dose reduction or interruption. For first-line therapy in gastric cancer, the main platinum agents used are cisplatin and oxaliplatin. It has been suggested that oxaliplatin increases the effect of immune checkpoint inhibitors by induction of immunogenic

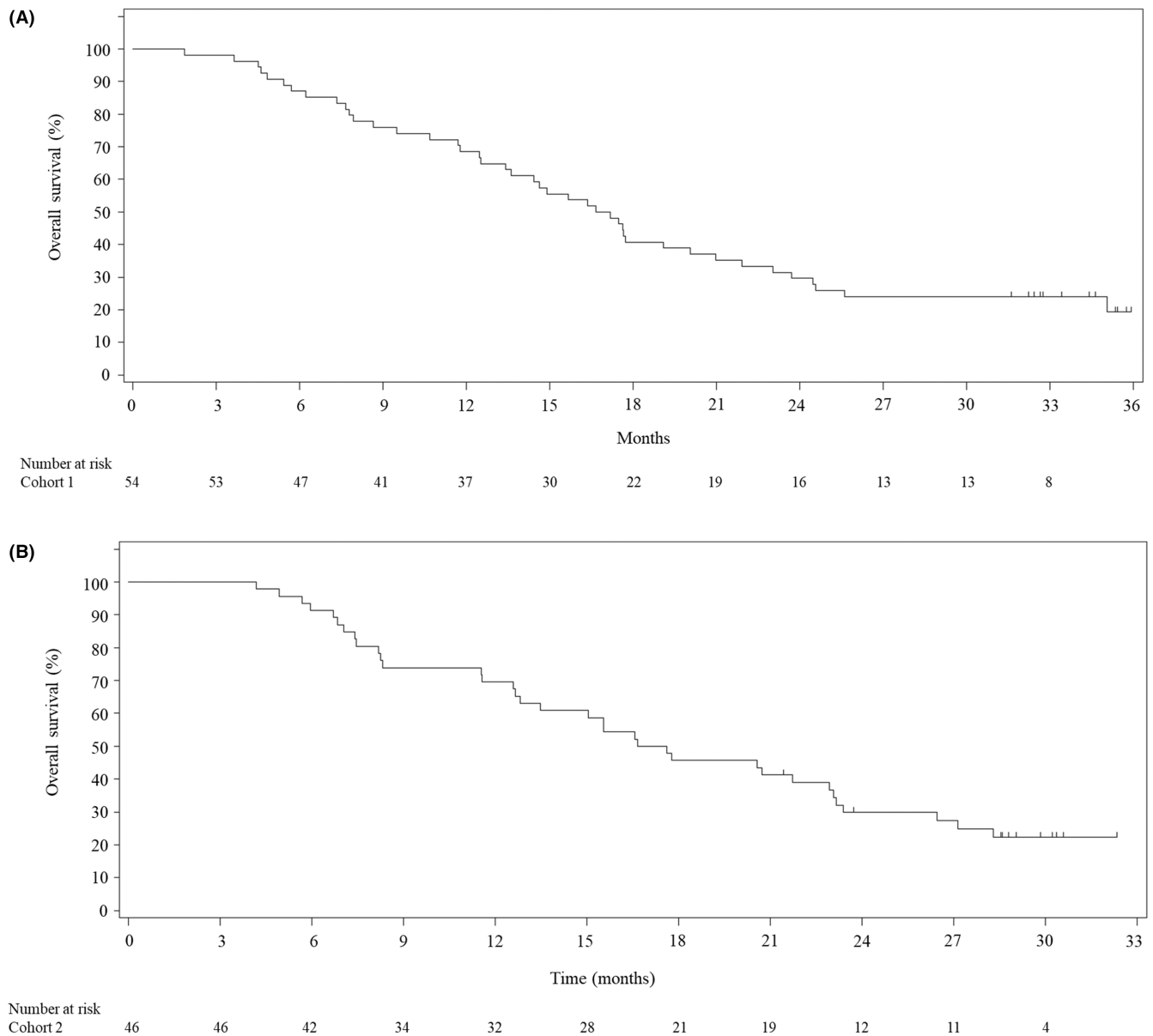


FIGURE 3 Kaplan–Meier estimates of overall survival in Japanese patients with gastric cancer treated with (A) first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or (B) first-line pembrolizumab with S-1 + cisplatin (cohort 2)

TABLE 4 Best overall response and survival results among Japanese patients with gastric cancer treated with first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or S-1 + cisplatin (cohort 2) (all subjects as treated population), assessed by investigator per RECIST version 1.1

Category	Cohort 1 (N = 54)		Cohort 2 (N = 46)	
	n	(95% CI)	n	(95% CI)
Objective response rate (CR + PR)	39	72.2% (58.4%–83.5%)	29	63.0% (47.5%–76.8%)
Disease control rate (CR + PR + SD)	51	94.4% (84.6%–98.8%)	45	97.8% (88.5%–99.9%)
Best overall response, n (%)				
Complete response	2 (3.7)	–	1 (2.2)	–
Partial response	37 (68.5)	–	28 (60.9)	–
Stable disease	12 (22.2)	–	16 (34.8)	–
Progressive disease	3 (5.6)	–	1 (2.2)	–
Progression-free survival, months, median	–	6.9 (5.6–8.3)	–	6.7 (5.3–8.4)
Overall survival, months, median	–	16.9 (13.4–20.0)	–	17.1 (12.6–23.1)

Note: Data cut-off: May 30, 2021.

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

cell death.^{18,19} In our study, regimens that included two different platinum agents were investigated, but no difference was suggested between cohorts by platinum agent. Although there are some differences in the safety profiles of the platinum agents, both SOX and SP could be candidates for use in pembrolizumab combination regimens.

In the KEYNOTE-062 study, no statistically significant benefit of the combination of pembrolizumab and 5-FU and cisplatin or capecitabine and cisplatin was shown among patients with PD-L1 CPS ≥ 1 .¹¹ However, nivolumab, another anti-PD-1 Ab, showed superiority in OS to FOLFOX (leucovorin, fluorouracil, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) in the

CheckMate 649 study.⁹ Similarly, the ORIENT-16 study, which evaluated sintilimab and chemotherapy as first-line treatment for advanced gastric cancer in China, reported statistically significant OS benefits with sintilimab in combination with chemotherapy in participants with CPS ≥ 5 , and in all randomized participants.²⁰ In contrast, in Asia, the combination of nivolumab plus SOX or capecitabine and oxaliplatin was evaluated for all-comers in the ATTRACTION-4 study,²¹ and prolonged PFS, but not OS, was observed with nivolumab.

The present study findings cannot be directly compared because the results were affected not only by the differences in platinum agents but also by differences in target populations,

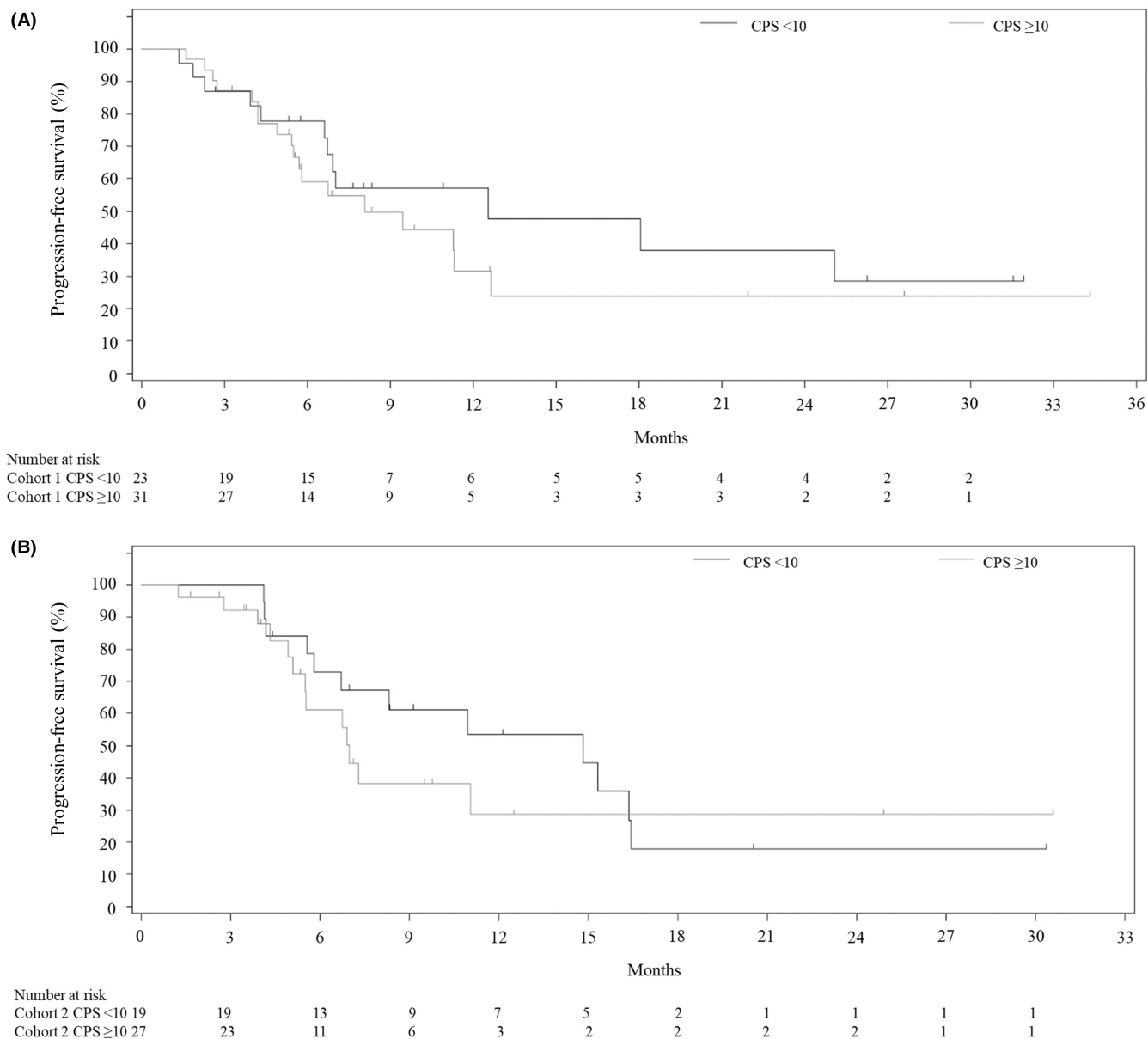


FIGURE 4 Kaplan–Meier estimates of progression-free survival in Japanese patients with gastric cancer treated with (A) first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or (B) first-line pembrolizumab with S-1 + cisplatin (cohort 2) according to combined positive score (CPS), assessed by central review

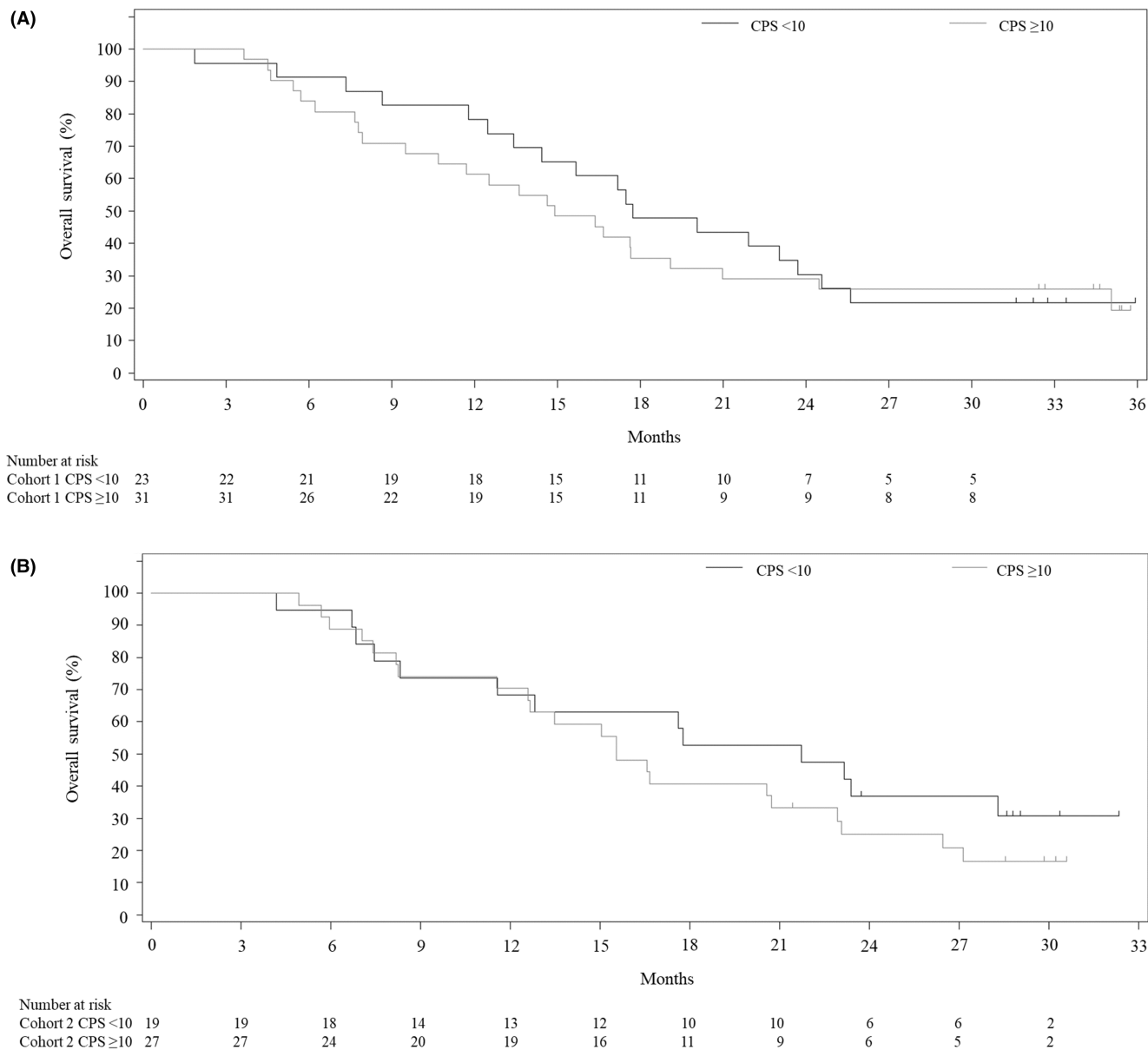


FIGURE 5 Kaplan-Meier estimates of overall survival in Japanese patients with gastric cancer treated with (A) first-line pembrolizumab with S-1+oxaliplatin (cohort 1) or (B) first-line pembrolizumab with S-1 + cisplatin (cohort 2) according to combined positive score (CPS)

including PD-L1 expression status, post-study treatment, and statistical analysis methods. The target population of this study consisted of patients with PD-L1 CPS ≥ 1 . Exploratory analyses did not show enrichment of efficacy in CPS ≥ 10 , although it is difficult to assess the survival benefit of pembrolizumab because of the single-arm study design. Similar results were observed in this study to those of KEYNOTE-062, in which no difference by CPS status was observed in the cohort that received combination therapy.¹¹ In contrast, superiority of OS was shown in patients with CPS ≥ 1 and CPS ≥ 5 , but not with CPS <1 or CPS <5 in the CheckMate 649 study, a global study with a larger sample size using 28-8 PharmDx PD-L1 assays.⁹ The survival benefit of pembrolizumab and the impact of CPS will be further evaluated in

the ongoing trial, KEYNOTE-859 (NCT03675737), a randomized, multicenter, double-blind study of first-line pembrolizumab plus chemotherapy 5-FU plus cisplatin or capecitabine plus oxaliplatin versus placebo plus chemotherapy for patients with advanced G/GEJ cancer.

The present study had several limitations. It was a single-arm phase II study, and we were unable to confirm the additional effects of pembrolizumab on SOX or SP. Therefore, further evaluation is required to confirm the results of combination therapy with pembrolizumab plus chemotherapy as a first-line treatment in patients with gastric cancer.

In conclusion, the combination of pembrolizumab plus SOX or SP showed favorable efficacy and manageable safety as first-line

TABLE 5 Incidence of treatment-related adverse events (TRAEs) occurring in at least 10% of patients and TRAEs of interest among Japanese patients with gastric cancer treated with first-line pembrolizumab with S-1 + oxaliplatin (cohort 1) or S-1 + cisplatin (cohort 2) (all subjects as treated population)

TRAE, n (%)	Cohort 1 (N = 54)		Cohort 2 (N = 46)	
	Any grade	Grade \geq 3	Any grade	Grade \geq 3
Any event	54 (100.0)	32 (59.3)	46 (100.0)	36 (78.3)
Neutrophil count decreased ^a	24 (44.4)	8 (14.8)	38 (82.6)	24 (52.2)
Decreased appetite	33 (61.1)	1 (1.9)	28 (60.9)	4 (8.7)
Nausea	32 (59.3)	0 (0.0)	28 (60.9)	1 (2.2)
Constipation	10 (18.5)	0 (0.0)	22 (47.8)	0 (0.0)
Diarrhea	21 (38.9)	2 (3.7)	20 (43.5)	0 (0.0)
Anemia	9 (16.7)	3 (5.6)	15 (32.6)	7 (15.2)
Stomatitis	14 (25.9)	0 (0.0)	15 (32.6)	0 (0.0)
Dysgeusia	19 (35.2)	0 (0.0)	14 (30.4)	0 (0.0)
Malaise	20 (37.0)	0 (0.0)	13 (28.3)	0 (0.0)
Peripheral sensory neuropathy	51 (94.4)	2 (3.7)	12 (26.1)	0 (0.0)
Platelet count decreased ^b	29 (53.7)	8 (14.8)	11 (23.9)	1 (2.2)
Fatigue	11 (20.4)	0 (0.0)	11 (23.9)	1 (2.2)
Vomiting	9 (16.7)	1 (1.9)	10 (21.7)	0 (0.0)
White blood cell count decreased	7 (13.0)	1 (1.9)	9 (19.6)	5 (10.9)
Rash ^c	16 (29.6)	0 (0.0)	11 (23.9)	2 (4.3)
Aspartate aminotransferase increased	9 (16.7)	0 (0.0)	7 (15.2)	1 (2.2)
Hiccups	2 (3.7)	0 (0.0)	7 (15.2)	0 (0.0)
Hyponatremia	0 (0.0)	0 (0.0)	6 (13.0)	4 (8.7)
Blood creatinine increased	1 (1.9)	0 (0.0)	6 (13.0)	0 (0.0)
Skin hyperpigmentation	3 (5.6)	0 (0.0)	6 (13.0)	0 (0.0)
Edema peripheral	4 (7.4)	0 (0.0)	5 (10.9)	0 (0.0)
TRAEs of interest, n (%)				
Adrenal insufficiency	3 (5.6)	3 (5.6)	3 (6.5)	2 (4.3)
Hypothyroidism	5 (9.3)	0 (0.0)	3 (6.5)	0 (0.0)
Hyperthyroidism	2 (3.7)	0 (0.0)	2 (4.3)	0 (0.0)
Colitis ^d	6 (11.1)	4 (7.4)	1 (2.2)	0 (0.0)
Pneumonitis ^e	4 (7.4)	1 (1.9)	1 (2.2)	0 (0.0)
Type 1 diabetes mellitus	1 (1.9)	1 (1.9)	1 (2.2)	1 (2.2)

Note: Data cut-off: May 30, 2021.

^aIncludes neutropenia.

^bIncludes thrombocytopenia.

^cIncludes rash maculopapular, butterfly rash, and rash papular.

^dIncludes autoimmune colitis, enterocolitis, and enteritis.

^eIncludes pneumonia, interstitial lung disease, and autoimmune lung disease.

treatment in Japanese patients with PD-L1-positive, HER2-negative G/GEJ adenocarcinoma.

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ETHICS STATEMENT

Approval of the research protocol by an institutional review board: This study was approved by the institutional review board/independent ethics committee at each of the 25 study centers. It was carried out in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonization Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice Guidelines, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

CONSENT

All patients provided written informed consent before enrollment

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