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ORIGINAL ARTICLE

Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4)

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Background: Nivolumab is approved as an option for third- or later-line treatment of advanced gastric/gastroesophageal junction (G/GEJ) cancer in several countries after ATTRACTION-2. To further improve the therapeutic efficacy of first-line therapy, exploration of a nivolumab-chemotherapy combination is warranted. In part 1 (phase II) of ATTRACTION-4, the safety and efficacy of nivolumab combined with S-1 plus oxaliplatin (SOX) or capecitabine plus oxaliplatin (CapeOX) as first-line therapy for unresectable advanced or recurrent human epidermal growth factor receptor 2 (HER2)-negative G/GEJ cancer were evaluated.

Patients and methods: Patients were randomized (1 : 1) to receive nivolumab (360 mg intravenously every 3 weeks) plus SOX (S-1, 40 mg/m^2 orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m^2 intravenously on day 1 every 3 weeks) or CapeOX (capecitabine, 1000 mg/m^2 orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m^2 intravenously on day 1 every 3 weeks) until disease progression, unacceptable toxicity, or consent withdrawal.

Results: Of 40 randomized patients, 39 (nivolumab plus SOX, 21; nivolumab plus CapeOX, 18) and 38 (21 and 17, respectively) comprised the safety and efficacy populations, respectively. Most frequent (>10%) grade 3/4 treatment-related adverse events were neutropenia (14.3%) in the nivolumab plus SOX group, and neutropenia (16.7%), anemia, peripheral sensory neuropathy, decreased appetite, type 1 diabetes mellitus, and nausea (11.1% each) in the nivolumab plus CapeOX group. No treatment-related death occurred. Objective response rate was 57.1% (95% confidence interval 34.0–78.2) with nivolumab plus SOX and 76.5% (50.1–93.2) with nivolumab plus CapeOX. Median overall survival was not reached (NR) in both groups. Median progression-free survival was 9.7 months (5.8–NR) and 10.6 months (5.6–12.5), respectively.

Conclusion: Nivolumab combined with SOX/CapeOX was well tolerated and demonstrated encouraging efficacy for unresectable advanced or recurrent HER2-negative G/GEJ cancer. ATTRACTION-4 has proceeded to part 2 (phase III) to compare nivolumab plus SOX/CapeOX versus placebo plus SOX/CapeOX.

Clinicaltrials.gov ID: NCT02746796.

Key words: nivolumab, gastric/gastroesophageal cancer, capecitabine, S-1, oxaliplatin, programmed death-1

Introduction

Gastric/gastroesophageal junction (G/GEJ) cancer is the fifth most common cancer and the third leading cause of cancer deaths worldwide. In 2012, almost 1 000 000 new cases and 723 000 deaths were estimated to have occurred [1]. Incidence and mortality rates of gastric cancer are highest in Eastern Asia. Half of the total cases in the world occur here; the age-standardized incidence rate per 100 000 in men (35.4) is more than twice that in women (13.8). Furthermore, a mortality rate of ∼24 per 100 000 in men and 9.8 per 100 000 in women is reported here [1].

The standard of care for first-line treatment of unresectable advanced or metastatic G/GEJ cancer is fluoropyrimidine- and platinum-based therapy [trastuzumab is added for human epidermal growth factor receptor 2 (HER2)-positive patients] [2, 3]. Oral fluoropyrimidines (e.g. capecitabine or S-1) and oxaliplatin are replacing infusions of 5-fluorouracil and cisplatin, respectively, because of noninferior efficacy, convenience, and better tolerance [4–7]. In Asia, the standard of care for unresectable or metastatic G/GEJ cancer currently includes a doublet regimen of S-1 or capecitabine plus cisplatin or oxaliplatin [8–10]. In the West, three-drug combination regimens including docetaxel or epirubicin with the fluoropyrimidine-platinum combination have become options after the V325 and REAL-2 studies [7, 11].

Although several clinical trials have investigated the efficacy of molecular agents for G/GEJ cancer, only trastuzumab and ramucirumab achieved favorable survival times. For HER2-positive advanced G/GEJ cancer, first-line trastuzumab plus fluoropyrimidine- and platinum-based therapy can achieve an overall survival (OS) of up to 13.8 months [12]. Ramucirumab monotherapy and combined with paclitaxel showed survival benefits as second-line chemotherapy over best supportive care and paclitaxel alone, respectively [13, 14]. Despite these advances, median survival time for patients with this disease stage is poor (∼6–14 months) [5, 15]. In fact, all global phase III studies with molecular agents (including the RAINFALL study [16] that investigated ramucirumab in first-line therapy), except those mentioned earlier, provided negative results. There is clearly an unmet need for any potential novel agent that will improve survival in these patients, especially in first-line treatment.

Immuno-oncology agents targeting programmed death-1 (PD-1) and PD-ligand 1 (PD-L1) have shown promising activity in several malignant diseases. Tumors expressing PD-L1 bind to PD-1, an immunoinhibitory receptor expressed on T cells, and inhibit T-cell-mediated immune responses [17]. PD-L1 was detected in ∼12%–65% of gastric cancer tissues; importantly, the prognosis was poorer in patients with PD-L1 expression in tumors than in those without [15, 18]. Nivolumab, a fully human IgG4 monoclonal antibody targeting PD-1, has shown activity and improved survival as monotherapy for several advanced tumor types [19–22] or when combined with other immunotherapy for melanoma [23]. In ATTRACTION-2, a double-blind, placebo-controlled, randomized phase III study in patients with unresectable advanced or recurrent G/GEJ cancer refractory to or intolerant of ≥2 prior chemotherapy regimens, nivolumab monotherapy resulted in a significantly longer OS versus placebo [5.3 versus 4.1 months; hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.51–0.78; $P < 0.0001$]. Furthermore, nivolumab increased the 12-month OS rate (26.2% versus 10.9%), progression-free survival (PFS) rate (7.6% versus 1.5%), and objective response rate (ORR) (11.2% versus 0.0%) versus placebo [15]. In the phase I/II CheckMate 032 study in patients with chemotherapy-refractory G/GEJ/esophageal cancer, nivolumab monotherapy resulted in an ORR of 12%, median OS of 6.2 months, and 12-month OS rate of 39%. Clinical activity was observed irrespective of tumor PD-L1 expression [24].

In addition to the well-known effects of chemotherapy against tumor replication, it has been suggested that antitumor effects of chemotherapy may occur through modulation of the immune system [25, 26]. It is reported that oxaliplatin can induce immunologic death of cancer cells and thereby enhance the efficacy of immuno-oncology agents. This phenomenon, coupled with encouraging clinical activity and safety with nivolumab-chemotherapy combination as first-line therapy for advanced non-small-cell lung cancer [27], provides a strong rationale for ATTRACTION-4, a two-part study designed to evaluate nivolumab-chemotherapy combination. Part 1 aimed to explore the safety and efficacy of nivolumab with chemotherapy, whereas part 2, a double-blind study, will compare nivolumab plus chemotherapy versus placebo plus chemotherapy in terms of OS and PFS. Here, we report the results for the safety and efficacy of nivolumab plus chemotherapy as first-line therapy in unresectable advanced or recurrent G/GEJ cancer in part 1 of ATTRACTION-4.

Patients and methods

Study design

ATTRACTION-4 is a randomized, phase II/III, two-part study. Part 1 was conducted at 13 centers in Japan and South Korea from March 2016 (data cut-off date 31 July 2017). Part 2 is currently ongoing at 138 sites in Japan, South Korea, and Taiwan. In part 1 (NCT02746796), an open-label study, patients were randomized 1 : 1 using an interactive web response system to receive nivolumab with S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin (SOX) or nivolumab with capecitabine plus oxaliplatin (CapeOX) (supplementary Figure S1, available at *Annals of*

Table 1. Demographics and baseline characteristics (ITT population)

	Total $N = 40$	Nivolumab plus SOX $n = 21$	Nivolumab plus CapeOX $n = 19$
Median age (min–max), years	62.5 (37–80)	61.0 (37–77)	65.0 (39–80)
Males, *n* (%)	27 (67.5)	12 (57.1)	15 (78.9)
BMI, mean (SD), kg/m^2	21.9 (4.11)	21.5 (4.21)	22.3 (4.07)
Country, *n* (%)			
Japan	20 (50.0)	10 (47.6)	10 (52.6)
South Korea	20 (50.0)	11 (52.4)	9 (47.4)
ECOG PS, *n* (%)			
0	20 (50.0)	10 (47.6)	10 (52.6)
1	20 (50.0)	11 (52.4)	9 (47.4)
G/GEJ cancer, *n* (%)			
Advanced	24 (60.0)	15 (71.4)	9 (47.4)
Recurrent	16 (40.0)	6 (28.6)	10 (52.6)
Prior surgery, *n* (%)	17 (42.5)	7 (33.3)	10 (52.6)
Organs with metastases (≥2), *n* (%)	29 (72.5)	15 (71.4)	14 (73.7)
Tumor PD-L1 quantifiable, *n* (%)	37 (92.5)	19 (90.5)	18 (94.7)
<1% expression status	31 (83.8)	15 (78.9)	16 (88.9)
≥1% expression status	6 (16.2)	4 (21.1)	2 (11.1)

BMI, body mass index; CapeOX, capecitabine plus oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJ, gastric/gastroesophageal junction; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; SD, standard deviation; SOX, S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin.

Oncology online). Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. All patients were examined at discontinuation of the protocol treatment and 28 days post-treatment, and were followed up. Criteria for starting part 2 are provided as supplementary material, available at *Annals of Oncology* online. The study was approved by the institutional review boards at all sites and conformed to the Declaration of Helsinki guidelines. All patients provided written informed consent.

Patients

Briefly, patients with unresectable advanced or recurrent HER2-negative G/GEJ cancer, Eastern Cooperative Oncology Group performance status of 0 or 1, and no prior chemotherapy except neoadjuvant or adjuvant chemotherapy completed ≥180 days before randomization were included. Additional details are provided as supplementary material, available at *Annals of Oncology* online.

Treatment

Patients received nivolumab (360 mg intravenously once in 3 weeks) plus SOX (S-1, 40 mg/m^2 orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m^2 intravenously on day 1 every 3 weeks) or CapeOX (capecitabine, 1000 mg/m^2 orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m^2 intravenously on day 1 every 3 weeks) (supplementary Figure S1, available at *Annals of Oncology* online). Additional details are provided as supplementary material, available at *Annals of Oncology* online.

End points and assessments

Primary end point of part 1. Safety was assessed by recording adverse events (AEs), which were coded using the Medical Dictionary for Regulatory Activities version 20.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [28].

Secondary end points of part 1. These included ORR, OS, PFS, duration of response (DOR), best overall response (BOR), disease control rate (DCR), time to response (TTR), and change in tumor burden (percent change in the sum of diameters of target lesions) over time assessed by the site investigator and centrally by the Independent Review Committee according to Response Evaluation Criteria In Solid Tumors, version 1.1 [29]. For patients with available tumor samples, PD-L1 tumor expression was determined by immunohistochemistry carried out at a central laboratory (28-8 pharmDx assay; Dako, Carpinteria, CA). PD-L1 positivity was defined as staining in ≥1% of tumor cells. Additional details are provided as supplementary material, available at *Annals of Oncology* online.

Statistical analysis

In part 1, for the safety evaluation alone, based on the previously reported incidences of grade ≥3 AEs with SOX/CapeOX, the incidence of each grade ≥3 AE was assumed to be 10%. A sample size of 15 patients per cohort was required to detect a grade ≥3 AE in ≥1 patient with approximately 80% power. The intent-to-treat (ITT) population consisted of all randomized patients, the safety analysis set (SAS) consisted of patients given ≥1 dose of nivolumab/chemotherapy, and the full analysis set (FAS) consisted of patients from the SAS who had multiple cancers measurable lesions using computed tomography/magnetic resonance imaging within 14 days before randomization.

Results

Demographics and baseline characteristics

Of 49 screened patients, 40 were randomized to receive nivolumab plus SOX ($n = 21$) and nivolumab plus CapeOX ($n = 19$) [median age (range) 62.5 (37–80) years; male 67.5%]. One

Table 2. Adverse events (SAS population)

	Total N = 39		Nivolumab plus SOX n = 21		Nivolumab plus CapeOX n = 18	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE	39 (100.0)	24 (61.5)	21 (100.0)	12 (57.1)	18 (100.0)	12 (66.7)
Treatment-related SAEs	10 (25.6)	6 (15.4)	4 (19.0)	3 (14.3)	6 (33.3)	3 (16.7)
TRAEs leading to discontinuation[a]	5 (12.8)	2 (5.1)	3 (14.3)	1 (4.8)	2 (11.1)	1 (5.6)
TRAEs leading to dose delay or reduction	37 (94.9)	18 (46.2)	20 (95.2)	10 (47.6)	17 (94.4)	8 (44.4)
TRAEs (≥20%)						
Neutropenia[b]	25 (64.1)	6 (15.4)	13 (61.9)	3 (14.3)	12 (66.7)	3 (16.7)
Peripheral sensory neuropathy	24 (61.5)	3 (7.7)	12 (57.1)	1 (4.8)	12 (66.7)	2 (11.1)
Decreased appetite	23 (59.0)	2 (5.1)	12 (57.1)	0	11 (61.1)	2 (11.1)
Diarrhea	22 (56.4)	3 (7.7)	14 (66.7)	2 (9.5)	8 (44.4)	1 (5.6)
Nausea	20 (51.3)	2 (5.1)	11 (52.4)	0	9 (50.0)	2 (11.1)
Thrombocytopenia[c]	18 (46.2)	1 (2.6)	14 (66.7)	0	4 (22.2)	1 (5.6)
Fatigue	13 (33.3)	1 (2.6)	7 (33.3)	0	6 (33.3)	1 (5.6)
Vomiting	11 (28.2)	0	5 (23.8)	0	6 (33.3)	0
Constipation	10 (25.6)	0	5 (23.8)	0	5 (27.8)	0
Abdominal pain	8 (20.5)	3 (7.7)	4 (19.0)	2 (9.5)	4 (22.2)	1 (5.6)
Dysgeusia	8 (20.5)	0	3 (14.3)	0	5 (27.8)	0
Palmar-plantar erythrodysesthesia syndrome	8 (20.5)	0	0	0	8 (44.4)	0
Peripheral neuropathy	8 (20.5)	1 (2.6)	6 (28.6)	1 (4.8)	2 (11.1)	0
Pyrexia	8 (20.5)	0	4 (19.0)	0	4 (22.2)	0
Peripheral edema	7 (17.9)	0	6 (28.6)	0	1 (5.6)	0
Stomatitis	7 (17.9)	0	3 (14.3)	0	4 (22.2)	0
Anemia	6 (15.4)	2 (5.1)	2 (9.5)	0	4 (22.2)	2 (11.1)
Decreased white blood cell count	6 (15.4)	0	2 (9.5)	0	4 (22.2)	0

All values presented as *n* (%).

[a]Discontinuation may be caused due to one or more product (nivolumab/oxaliplatin/S-1/capecitabine).

[b]Includes the MedDRA preferred term 'decreased neutrophil count'.

[c]Includes the MedDRA preferred term 'decreased platelet count'.

AE, adverse event; CapeOX, capecitabine plus oxaliplatin; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAS, safety analysis set; SOX, S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin; TRAE, treatment-related adverse event.

patient did not receive the protocol treatment (SAS, $n = 39$) and one patient in the nivolumab plus CapeOX group received nivolumab for another study (FAS, $n = 38$) (supplementary Figure S2, available at *Annals of Oncology* online). Demographics and baseline characteristics were comparable between the groups (Table 1). From the SAS, 14/21 patients (66.7%) in the nivolumab plus SOX group and 15/18 patients (83.3%) in the nivolumab plus CapeOX group discontinued nivolumab treatment. Median (range) duration of treatment was 6.8 (0–15) months with median (range) follow-up time of 13.2 (12.2–15.2) months.

Safety

Mean (standard deviation [SD]) relative dose intensity of nivolumab was comparable between groups [nivolumab plus SOX, 90.7% (9.8); nivolumab plus CapeOX, 91.9% (7.2)]. All patients in the SAS in both arms experienced AEs and treatment-related AEs (TRAEs) (grade ≥3 TRAEs, 24 [61.5%]) (Table 2). Grade 3/4 TRAEs occurring in >10% of patients were neutropenia (14.3%) in the nivolumab plus SOX group, and neutropenia (16.7%), anemia, peripheral sensory neuropathy, decreased appetite, type 1 diabetes mellitus, and nausea (11.1% each) in the nivolumab plus CapeOX group. Four serious TRAEs (diarrhea, lung infection, prostatitis, and intracranial hemorrhage) occurred in four (19.0%) patients in the nivolumab plus SOX group and nine serious TRAEs (decreased appetite, type 1 diabetes mellitus, diarrhea, colitis, lung abscess, infusion-related reaction, and adrenocorticotropic hormone deficiency) occurred in six (33.3%) patients in the nivolumab plus CapeOX group. Four TRAEs (increased alanine aminotransferase, increased aspartate aminotransferase, peripheral sensory neuropathy, and intracranial hemorrhage) in three (14.3%) patients in the nivolumab plus SOX group and two TRAEs (peripheral sensory neuropathy and adrenocorticotropic hormone deficiency) in two (11.1%) patients in the nivolumab plus CapeOX group led to discontinuation of the protocol treatment. Almost all patients [nivolumab plus SOX, 20 (95.2%); nivolumab plus CapeOX, 17 (94.4%)] had TRAEs leading to reduced or delayed dosing of chemotherapy; the most frequent (>10%) ones included

Table 3. Summary of response and survival data (FAS population)

	Total *N* = 38	Nivolumab plus SOX *n* = 21	Nivolumab plus CapeOX *n* = 17
OS, median (95% CI)[a], months	NR (13.9, NR)	NR (11.9, NR)	NR (11.2, NR)
6-month rate (95% CI)[b]	94.6 (80.1, 98.6)	100.0 (100.0, 100.0)	88.2 (60.6, 96.9)
Site investigator assessment			
ORR, *n* (%) (95% CI)[c]	26 (68.4) (51.3, 82.5)	14 (66.7) (43.0, 85.4)	12 (70.6) (44.0, 89.7)
BOR, *n* (%)			
CR, *n* (%) (95% CI)[c]	1 (2.6) (0.1, 13.8)	1 (4.8) (0.1, 23.8)	0 (0.0) (0.0, 19.5)
PR, *n* (%) (95% CI)[c]	25 (65.8) (48.6, 80.4)	13 (61.9) (38.4, 81.9)	12 (70.6) (44.0, 89.7)
SD, *n* (%) (95% CI)[c]	7 (18.4) (7.7, 34.3)	4 (19.0) (5.4, 41.9)	3 (17.6) (3.8, 43.4)
PD	4 (10.5)	2 (9.5)	2 (11.8)
Not evaluable	1 (2.6)	1 (4.8)	0
PFS, median (95% CI)[a], months	9.5 (6.9, 11.1)	9.8 (6.8, NR)	7.2 (4.3, 11.2)
6-month rate (95% CI)[b]	75.0 (57.4, 86.2)	79.3 (53.7, 91.7)	69.7 (41.7, 86.1)
DCR, *n* (%) (95% CI)[c]	33 (86.8) (71.9, 95.6)	18 (85.7) (63.7, 97.0)	15 (88.2) (63.6, 98.5)
Central assessment			
ORR, *n* (%) (95% CI)[c]	25 (65.8) (48.6, 80.4)	12 (57.1) (34.0, 78.2)	13 (76.5) (50.1, 93.2)
BOR, *n* (%)			
CR, *n* (%) (95% CI)[c]	10 (26.3) (13.4, 43.1)	7 (33.3) (14.6, 57.0)	3 (17.6) (3.8, 43.4)
PR, *n* (%) (95% CI)[c]	15 (39.5) (24.0, 56.6)	5 (23.8) (8.2, 47.2)	10 (58.8) (32.9, 81.6)
SD, *n* (%) (95% CI)[c]	7 (18.4) (7.7, 34.3)	5 (23.8) (8.2, 47.2)	2 (11.8) (1.5, 36.4)
PD	2 (5.3)	1 (4.8)	1 (5.9)
Not evaluable	4 (10.5)	3 (14.3)	1 (5.9)
PFS, median (95% CI)[a], months	9.7 (6.8, 12.5)	9.7 (5.8, NR)	10.6 (5.6, 12.5)
6-month rate (95% CI)[b]	70.9 (52.5, 83.2)	72.9 (46.4, 87.8)	68.6 (40.0, 85.7)
DCR, *n* (%) (95% CI)[c]	32 (84.2) (68.7, 94.0)	17 (81.0) (58.1, 94.6)	15 (88.2) (63.6, 98.5)
TTR, median (min–max), months	1.3 (1.2–6.2)	1.3 (1.2–3.0)	1.3 (1.2–6.2)
DOR, median (95% CI)[a], months	9.9 (5.8, NR)	9.9 (3.9, NR)	9.7 (4.4, NR)

[a]Estimated using the Kaplan–Meier method and 95% CI of median was calculated using the Brookmeyer and Crowley method.
[b]Estimated using the Kaplan–Meier method and 95% CI was estimated using the Greenwood formula for variance and double logarithmic transformation.
[c]95% CI was calculated using the Clopper–Pearson method.
BOR, best overall response; CapeOX, capecitabine plus oxaliplatin; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SOX, S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin; TTR, time to response.

thrombocytopenia (57.1%), neutropenia (47.6%), nausea (19.0%), diarrhea, vomiting, abdominal pain, peripheral sensory neuropathy, and fatigue (14.3% each) in the nivolumab plus SOX group, and neutropenia (44.4%), decreased appetite (27.8%), palmar-plantar erythrodysesthesia syndrome (22.2%), nausea, diarrhea, vomiting, peripheral sensory neuropathy (16.7% each), and peripheral neuropathy and type 1 diabetes mellitus (11.1% each) in the nivolumab plus CapeOX group. No treatment-related deaths occurred.

Efficacy

Objective response rate. The ORRs by site investigator assessment were comparable in both groups [nivolumab plus SOX, 14/21 (66.7%, 95% CI 43.0–85.4); nivolumab plus CapeOX, 12/17 (70.6%, 44.0–89.7)] (Table 3); ORRs were 12/21 (57.1%, 34.0–78.2) and 13/17 (76.5%, 50.1–93.2), respectively, when assessed centrally. In patients with PD-L1-positive tumors (nivolumab plus SOX, 4; nivolumab plus CapeOX, 1), ORR was 2/4 (50.0%) and 1/1 (100.0%), respectively, whereas in patients with PD-L1-negative tumors, ORR was 10/17 (58.8%) and 12/16 (75.0%), respectively (central assessment).

Disease control rate. DCR was 18/21 (85.7%, 63.7–97.0) with nivolumab plus SOX and 15/17 (88.2%, 63.6–98.5) with nivolumab plus CapeOX by site investigator assessment and 17/21 (81.0%, 58.1–94.6) and 15/17 (88.2%, 63.6–98.5), respectively, by central assessment.

Time to response. Median TTR (min–max) (central assessment) was 1.3 months (1.2–3.0) with nivolumab plus SOX and 1.3 months (1.2–6.2) with nivolumab plus CapeOX.

Duration of response. Median DOR (central assessment) was 9.86 months [3.91–not reached (NR)] with nivolumab plus SOX and 9.69 months (4.37–NR) with nivolumab plus CapeOX.

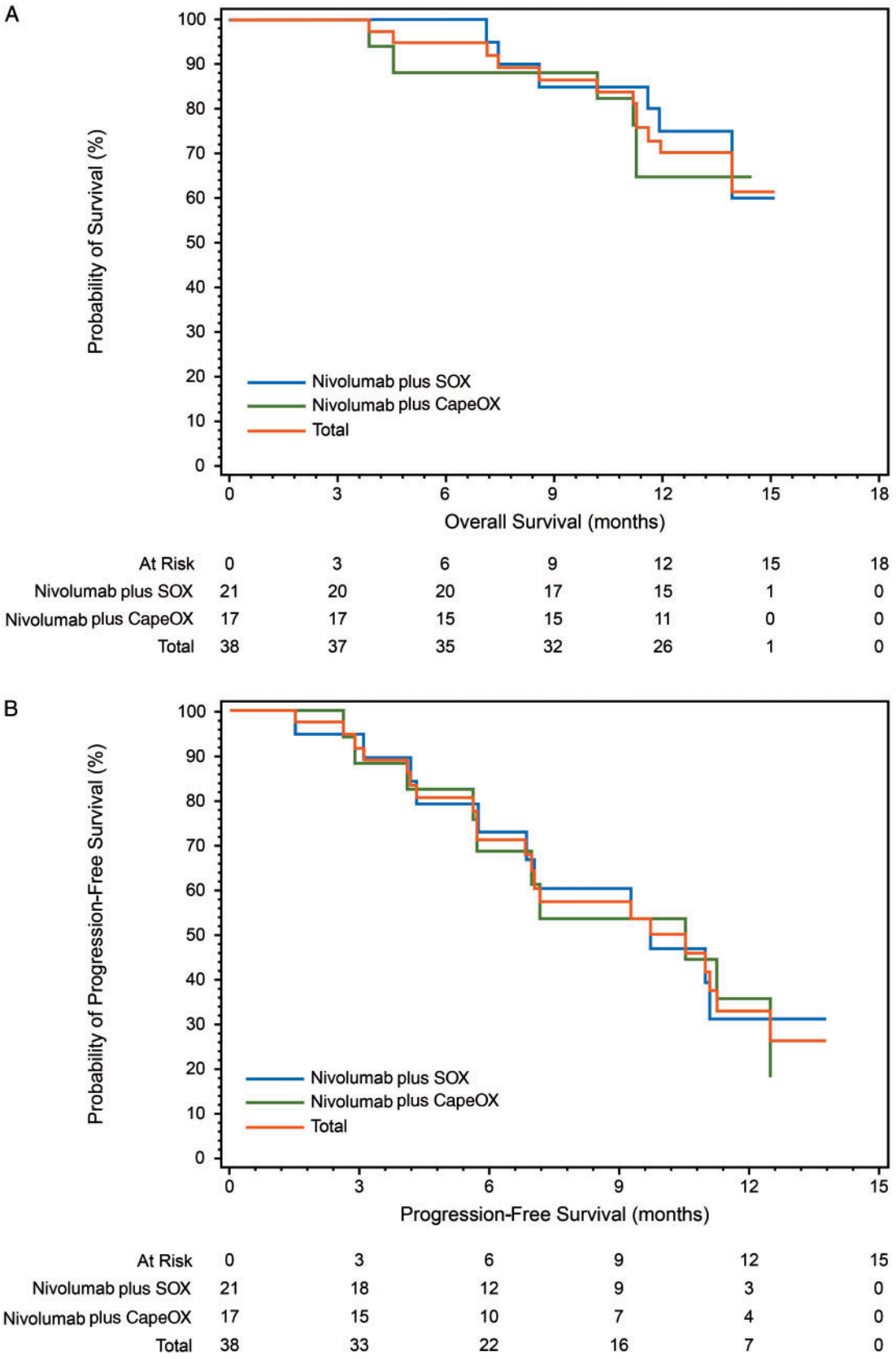

Figure 1. Kaplan–Meier curves for (A) overall survival and (B) progression-free survival (central assessment) (FAS population) CapeOX, capecitabine plus oxaliplatin; FAS, full analysis set; SOX, S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin.

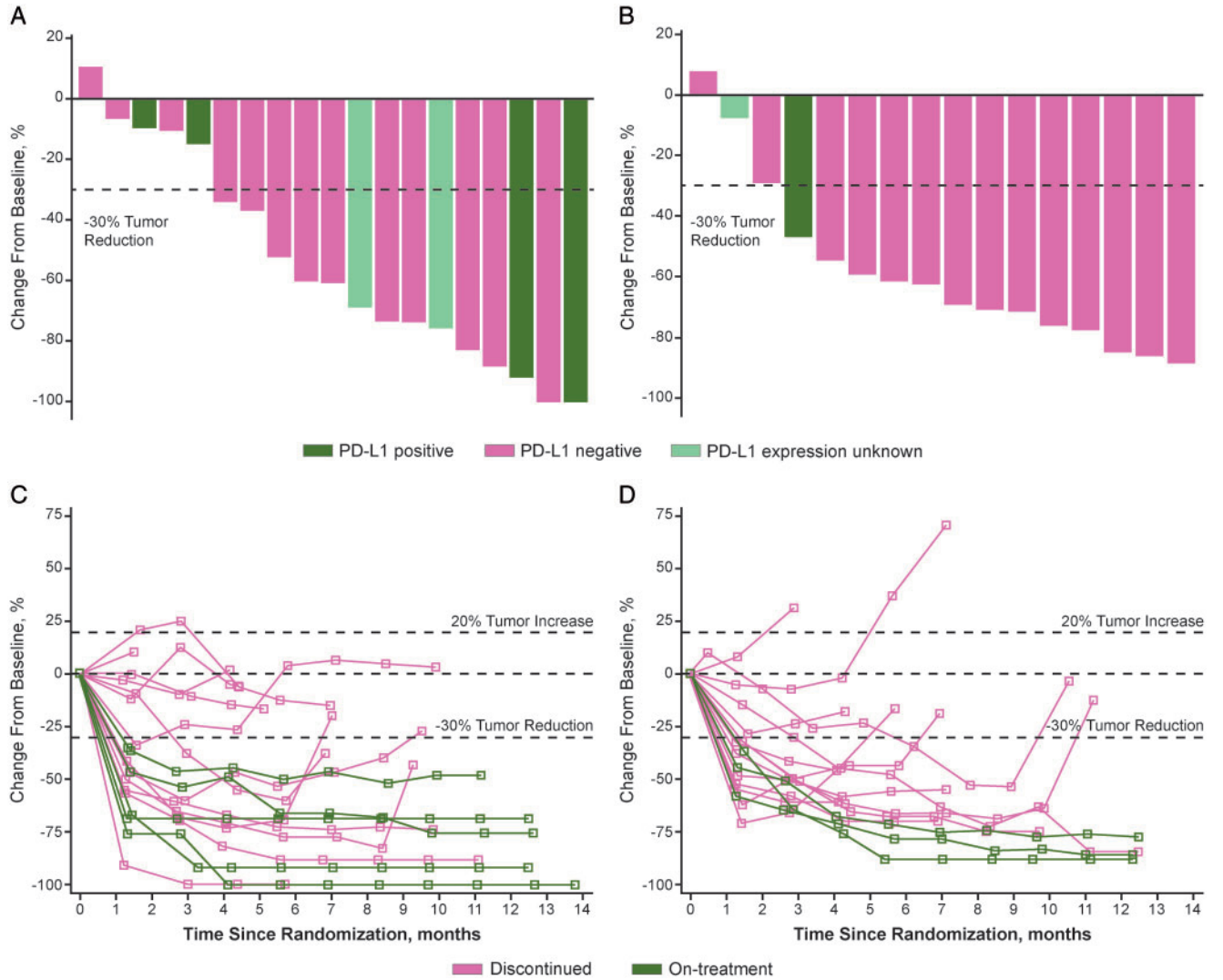

Figure 2. (A) Best change from baseline in the sum of longest target lesion diameters in each patient receiving nivolumab plus SOX. (B) Best change from baseline in the sum of longest target lesion diameters in each patient receiving nivolumab plus CapeOX. (C) Percent change in sum of longest diameters of target lesion from baseline in each patient receiving nivolumab plus SOX. (D) Percent change in sum of longest diameters of target lesion from baseline in each patient receiving nivolumab plus CapeOX (central assessment) (FAS population). CapeOX, capecitabine plus oxaliplatin; FAS, full analysis set; PD-L1, programmed death-ligand 1; SOX, S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin.

Overall survival. Median OS was NR (13.9 months–NR) for the total population, NR (11.9 months–NR) for the nivolumab plus SOX group, and NR (11.2 months–NR) for the nivolumab plus CapeOX group (Figure 1A).

Progression-free survival . Median PFS for the overall population was 9.7 months (6.8–12.5) and 9.5 months (6.9–11.1) by central and investigator assessment, respectively. Median PFS was 9.8 months (6.8–NR) for nivolumab plus SOX and 7.2 months (4.3–11.2) for nivolumab plus CapeOX by site investigator assessment and 9.7 months (5.8–NR) and 10.6 months (5.6–12.5), respectively, by central assessment (Figure 1B).

Change in tumor burden over time. All patients except one each in both groups showed a tumor burden reduction as the best response (central assessment) (Figure 2A and B). Change in size of target lesion from baseline over time is shown in Figure 2C and D.

Discussion

Part 1 of the ATTRACTION-4 study demonstrated that nivolumab plus chemotherapy has a manageable safety profile and clinically relevant antitumor activity.

In this study, the incidences and types of TRAEs were consistent with those known to be associated with chemotherapy and nivolumab [15, 19, 21–23]. While peripheral sensory neuropathy, decreased neutrophil count, and decreased platelet count were some of the most frequently reported TRAEs in both groups (Table 2), these are expected AEs associated with oxaliplatin and/or fluoropyrimidines [30–32] and were mostly grade 1/2 AEs.

Discontinuations due to TRAEs were reported in five patients. No treatment-related deaths occurred. Immune-related toxicities were also comparable to those reported with other immunotherapies in similar patient populations [33].

An objective response (complete response or partial response) was observed in approximately two-thirds of patients regardless of the chemotherapy administered with nivolumab; this is numerically higher than that reported previously for SOX or CapeOX in patients with G/GEJ cancer [5, 7, 34]. Overall, DCR in both groups was comparable with that previously reported for SOX or CapeOX [34]. Similar to previous studies with immunotherapies, early and durable responses were achieved (Table 3) [15, 33]. Notably, antitumor response with nivolumab was independent of tumor PD-L1 status; this was in line with previous studies of nivolumab in G/GEJ cancer [15]. Responses were coupled with a clinically relevant PFS that was numerically longer compared with previous studies with SOX and CapeOX [5]. While median OS was not reached within a median follow-up time of 13.2 months, it appears that it would be longer than 15 months. Long durable survival benefit beyond median OS of immune checkpoint inhibitors has been observed in other cancer types. Survival benefits of adding nivolumab to standard doublet chemotherapy for first-line treatment of advanced G/GEJ cancer should be confirmed in part 2 of ATTRACTION-4.

Because no substantial differences in the safety and efficacy were observed between the two groups, it is considered that nivolumab could be combined with either chemotherapy.

Although these results from part 1 of ATTRACTION-4 present novel and clinically relevant findings, the patient population is relatively small and this part of the study lacks a standard of care comparator arm. Part 2 of ATTRACTION-4, being conducted in a larger population, will play an important role in validating these results.

In conclusion, these results suggest that nivolumab in combination with SOX or CapeOX in patients with untreated unresectable advanced or recurrent G/GEJ cancer may be a potential therapeutic option with a manageable safety profile and encouraging efficacy that warrants evaluation in a phase III study.

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