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ORIGINAL ARTICLE

Nivolumab combination therapies in patients with advanced gastric and gastroesophageal junction cancer: the phase II FRACTION gastric cancer study

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Background: Nivolumab-based therapies are efficacious with acceptable safety in patients with gastric cancer (GC) and gastroesophageal junction cancer (GEJC). Novel nivolumab-based combination immunotherapies may offer enhanced efficacy in these indications. FRACTION-GC was a signal-seeking, randomized, open-label, phase II adaptive-design trial assessing efficacy and safety of nivolumab in combination with ipilimumab [cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody], relatlimab (lymphocyte-activation gene 3 antibody), or IDO1i (BMS986205, an indoleamine-2,3-dioxygenase-1 inhibitor) in patients with unresectable, advanced/metastatic GC/GEJC.

Patients and methods: Previously treated patients with GC/GEJC were randomized to receive nivolumab + ipilimumab, nivolumab + relatlimab, or nivolumab + IDO1i across two tracks: anti-programmed death-(ligand) 1/anti-CTLA-4-naïve (track 1) and -experienced (track 2). Primary endpoints were objective response rate (ORR) by investigator per RECIST v1.1, duration of response, and progression-free survival (PFS) rate at 24 weeks. Secondary endpoint was safety.

Results: Eighty-one patients in track 1 and 81 in track 2 received one combination therapy. With a median follow-up of 50.2 months, ORR [95% confidence interval (CI)] by investigator for nivolumab + ipilimumab, nivolumab + relatlimab, and nivolumab + IDO1i in track 1 was 4% (0.1% to 21.9%), 5% (0.1% to 24.9%), and 13% (4.4% to 28.1%), and for track 2 was 9% (1.1% to 28.0%), 6% (0.7% to 18.7%), and 0% (0% to 15.4%), respectively. PFS rate at 24 weeks (95% CI) was 24% (11% to 39%) for nivolumab + IDO1i track 1, 17% (16% to 32%) for nivolumab + relatlimab track 2, and not estimable for other treatment arms. Grade 3/4 treatment-related adverse events were reported in 22%, 5%, and 18% of patients receiving nivolumab + ipilimumab, nivolumab + relatlimab, and nivolumab + IDO1i in track 1 and in 35%, 11%, and 18% of patients in track 2, respectively. No treatment-related deaths were reported.

Conclusions: While ORR did not meet prespecified expansion criteria in any treatment arm, the safety profile of the combinations was manageable. FRACTION-GC represents a novel adaptive protocol for testing multiple combination immunotherapies.

Key words: nivolumab, relatlimab, gastric cancer, gastroesophageal junction cancer, immunomodulatory combination therapy

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INTRODUCTION

Gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal cancer are collectively responsible for over 1.1 million new cancer cases annually.[1] With a 71%

mortality to incidence ratio, GC/GEJC is currently the fifth leading cause of cancer-related death annually,[1] with adenocarcinoma being the most common histological type of GC/GEJC.[2] The relative 5-year survival rate is <7% for patients with metastatic GC/GEJC.[3,4]

Despite offering poor survival outcomes [median overall survival (OS) <1 year], fluoropyrimidine-plus-platinum-based chemotherapy regimens have been the first-line standard of care for GC/GEJC until recently.[5-9] Patients who have disease refractory to first-line standard-of-care chemotherapy have second-line treatment options such as docetaxel, paclitaxel, irinotecan, or ramucirumab[10-15]; however, the vast majority of patients receiving these second-line therapies continue to experience disease progression.[10,12,14,15] Administration of the programmed cell death protein 1 (PD-1) immune checkpoint inhibitor nivolumab has resulted in superior survival benefit versus placebo in heavily pretreated patients with advanced or recurrent GC/GEJC.[16] Furthermore, in combination with standard-of-care chemotherapy, nivolumab demonstrated superior OS versus chemotherapy alone in the first-line treatment of non-human epidermal growth receptor 2 (HER2)-positive advanced GC/GEJC/esophageal adenocarcinoma.[17] The combination of pembrolizumab plus chemotherapy has also demonstrated clinical benefit in patients with untreated advanced gastroesophageal cancers in the first-line setting.[18,19]

Designing therapeutics for a broader range of immune targets in GC/GEJC may lead to durable, long-term responses in this population. Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint that can be targeted by relatlimab.[20] Indoleamine 2,3-dioxygenase 1 is an immunoinhibitory enzyme that allows tumor escape through kynurenine production and is a target of IDO1i (BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor).[21] Nivolumab plus relatlimab has demonstrated significant progression-free survival (PFS) benefit versus nivolumab monotherapy in patients with previously untreated metastatic melanoma,[22] and nivolumab plus IDO1i has demonstrated safety and tolerability in heavily pretreated patients with bladder cancer.[21]

There are practical challenges with systematically evaluating novel immunotherapeutic agents in clinical trials, with numerous potential targets in the immune system. Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) studies are adaptive high-throughput trials conducted in patients with advanced lung cancer, renal cancer, and GC. FRACTION-GC, a signal-seeking, randomized, open-label, phase II adaptive-design clinical trial, was conducted to assess the efficacy and safety of novel immunotherapies in patients with inoperable advanced or metastatic GC or GEJC. This trial design allows for efficient testing of different combinations to identify the most promising for further study. In this article, we report the first results from the nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i arms in both tracks 1 and 2 in FRACTION-GC. Results from an additional three arms in which patients were treated with rucaparib-based combination therapies are not reported here as they did not have sufficient patients randomized for any effect to lead to statistically meaningful conclusions.

PATIENTS AND METHODS

Study design and patients

The master FRACTION study design has been described previously.[23] FRACTION-GC (trial registration number: NCT02935634) was a randomized, open-label, phase II study in patients with inoperable advanced or metastatic GC or GEJC. Patients with esophageal cancer were eligible but none was enrolled. Eligible patients were ≥18 years of age with a life expectancy of at least 3 months, an Eastern Cooperative Oncology Group performance status of 0 or 1, and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Adenocarcinoma and/or squamous cell carcinoma must have been histologically confirmed. Documentation of GEJC involvement could have included biopsy, endoscopy, or imaging. Patients with HER2-overexpressing tumors whose disease progressed after treatment with trastuzumab (or were ineligible for or unwilling to be treated with trastuzumab) were also eligible.

The study design consisted of two tracks; patients in both tracks were randomized to receive nivolumab plus ipilimumab or another nivolumab combination therapy. Patients were eligible for track 1 if they were naïve to anti-PD-1, anti-PD-ligand (L) 1, and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) treatments. Track 2 consisted of patients who had previously received anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 treatments. Patients were permitted to be re-randomized into a new study treatment on track 2 after progression on a study treatment in either track 1 or 2. Prior treatment with platinum-based chemotherapy in the adjuvant, neoadjuvant, or recurrent setting was permitted.

Dosing regimens were as follows: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses, followed 6 weeks later with nivolumab 480 mg every 4 weeks; nivolumab 240 mg every 2 weeks plus relatlimab 80 mg every 2 weeks; nivolumab 480 mg every 4 weeks plus IDO1i 100 mg daily. Nivolumab and ipilimumab were administered intravenously, and IDO1i was administered orally. Randomization block sizes for track 1 were two for nivolumab plus ipilimumab and nivolumab plus relatlimab and one for nivolumab plus IDO1i. All randomization block sizes for track 2 were 12. Dosing continued until progressive disease (PD; per RECIST v1.1), death, unacceptable drug toxicity, withdrawal of consent, or study end. Dose delays were permitted for treatment-related adverse events (TRAEs). Dose modifications were not allowed for nivolumab, ipilimumab, or relatlimab. The dose of IDO1i was permitted to be changed to 50 mg in the event of adverse events (AEs) or grade 3 fatigue, nausea, vomiting, or anemia that did not meet criteria for discontinuation. Treatment beyond initial PD was permitted if the patient tolerated the study drug and benefited from study treatment, per investigator assessment.

The study was conducted according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the study protocol. The protocol was approved by the institutional review board or independent ethics committee at each site. All patients provided written informed consent per the Declaration of Helsinki principles. Consent was obtained directly from patients.

Endpoints and assessments

Primary endpoints were objective response rate [ORR; defined as proportion of treated patients with a best overall response of complete response (CR) or partial response (PR)], median duration of response (DOR), and PFS rate at 24 weeks (defined as proportion of treated patients who did not experience PD or death at 24 weeks after first dose), all per investigator assessment and per RECIST v1.1 for each treatment combination. Secondary endpoints were assessments of safety and tolerability of each treatment combination. Other key endpoints included OS rates and biomarkers.

Assessments were carried out at baseline (within 28 days before the first dose), every 6 weeks for 24 weeks, and then every 12 weeks thereafter until disease progression or discontinuation. Tumor imaging assessments were completed using computed tomography or magnetic resonance imaging per RECIST v1.1. Confirmation of PR or CR was required at least 4 weeks after the initial scan reporting a response.

Baseline tumor biopsies or archival tissues were analyzed for IDO1, CD8, LAG-3, and PD-L1 by immunohistochemistry (IHC). The IHC assays for IDO1, CD8, and LAG-3 used Mouse IE7, C8/144B, and 17B4, respectively. Tumor cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx IHC assay (Agilent Technologies, Inc., Santa Clara, CA). Tumor cell PD-L1 expression was defined as complete circumferential or partial linear plasma membrane staining in a minimal of 100 viable tumor cells. Microsatellite instability-high (MSI-H)/mismatch repair (MMR)-deficient status (assessed by PCR and/or IHC) was documented by an accredited laboratory per local guidelines.

AEs were evaluated at baseline and at follow-up visits at 30, 60, and 100 days after first dose using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Causal relationships to study drug were determined by the investigator.

Statistical analysis

Sample sizes were guided by Simon's two-stage design, taking into account different patient populations and existing options in each track. For track 1, a minimum of 19 patients were required in stage 1 for an initial evaluation of efficacy. If the total number of responses observed in stage 1 was $\leq$4 (of 19 patients), the study treatment combination arm was not considered efficacious; otherwise, enrollment to stage 2 continued, and an additional 35 patients were treated. If the total number of responses at the end of stage 2 was $\leq$15 (of 54 patients), the study treatment combination arm was terminated; if there were $>$15 responses, the study treatment combination arm was considered for further development. For track 2, a minimum of 21 patients were required in stage 1. If the total number of responses observed in stage 1 was $\leq$1 (of 21 patients), enrollment was terminated. An additional 20 patients were treated after progression to stage 2. If the total number of responses at the end of stage 2 was $\leq$4 (of 41 patients), the study treatment combination arm was terminated; if there were $>$4 responses, the study treatment combination arm was considered for further development. For the sample sizes, patients who were re-randomized to a different study treatment in track 2 were counted once for each randomization; patients re-treated within the same study treatment arm were only counted once. Safety was assessed continuously and considered in the decision to continue or terminate a study treatment arm.

An ORR estimate and corresponding two-sided 95% exact confidence interval (CI) per the Clopper—Pearson method was provided. DOR was summarized for patients who achieved confirmed PR or CR using the Kaplan—Meier product-limit method, and the two-sided 95% CIs were calculated based on the log—log transformation using the Brookmeyer and Crowley methodology. PFS rate at 24 weeks and OS rate at 1 year were estimated using the Kaplan—Meier method, and the corresponding 95% CIs were derived based on the Greenwood formula. Median OS and median PFS were estimated using the Kaplan—Meier method, and the 95% CIs were computed using the Brookmeyer and Crowley methodology.

Safety analyses were carried out in all treated patients. Descriptive statistics of safety are presented using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

RESULTS

Patients

From November 2016 to August 2019, 251 patients were screened; 81 patients received one of the three combination therapies in track 1, and 81 patients received one of the three combination therapies in track 2. Eight patients from each track were re-randomized on to a new study therapy after progression on initial study treatment (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.104107).

At data cut-off (May 2022), median duration of follow-up (time from the first dose date to data cut-off) was 50.2 months (range 32.2-64.7 months). Demographics and baseline disease characteristics were generally balanced across all arms and tracks. The study population was predominantly White and male, with a median age of 62-63 years (range 27-85 years) (Table 1). The majority of patients had at least one previous systemic therapy ($<$10% of patients in track 1 were treatment naïve). In track 1, platinum-based chemotherapy was the predominant prior treatment. In track 2, all patients had been previously treated with systemic therapy, and most had received at least two prior

Table 1. Baseline patient demographics and clinical characteristics

	Track 1			Track 2		
	NIVO + IPI (n = 23)	NIVO + RELA (n = 20)	NIVO + IDO1i (n = 38)	NIVO + IPI (n = 23)	NIVO + RELA (n = 36)	NIVO + IDO1i (n = 22)
Age, years						
Median	62.0	61.5	62.5	62.0	63.0	63.5
Range	35-85	31-77	31-81	27-82	32-78	47-79
<65, *n* (%)	13 (57)	12 (60)	20 (53)	13 (57)	20 (56)	12 (55)
Sex, *n* (%)						
Female	5 (22)	3 (15)	14 (37)	2 (9)	6 (17)	8 (36)
Male	18 (78)	17 (85)	24 (63)	21 (91)	30 (83)	14 (64)
Race, *n* (%)						
White	22 (96)	18 (90)	32 (84)	18 (78)	31 (86)	18 (82)
Black/African American	0 (0)	0 (0)	1 (3)	0 (0)	3 (8)	2 (9)
Asian	1 (4)	2 (10)	1 (3)	2 (9)	1 (3)	2 (9)
Indian/Alaska Native	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Native Hawaiian/other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (4)	1 (3)	0 (0)
Other	0 (0)	0 (0)	2 (5)	1 (4)	0 (0)	0 (0)
Not reported	0 (0)	0 (0)	1 (3)	1 (4)	0 (0)	0 (0)
Tumor type at primary diagnosis, *n* (%)						
Gastric	11 (48)	7 (35)	16 (42)	11 (48)	13 (36)	11 (50)
GEJ	12 (52)	13 (65)	22 (58)	12 (52)	23 (64)	11 (50)
Prior systemic regimens, *n* (%)						
0	2 (9)	2 (10)	3 (8)	0 (0)	0 (0)	0 (0)
1	7 (30)	10 (50)	19 (50)	8 (35)	11 (31)	6 (27)
2	6 (26)	5 (25)	6 (16)	3 (13)	3 (8)	4 (18)
3	6 (26)	2 (10)	4 (11)	5 (22)	11 (31)	8 (36)
≥4	2 (9)	1 (5)	6 (16)	7 (30)	11 (31)	4 (18)
Disease stage at study entry, *n* (%)						
Locally recurrent	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	1 (5)
Metastatic	23 (100)	18 (90)	38 (100)	22 (96)	35 (97)	21 (96)
Locally advanced	0 (0)	0 (0)	0 (0)	1 (4)	1 (3)	0 (0)
ECOG performance status, *n* (%)						
0	14 (61)	12 (60)	15 (40)	7 (30)	15 (42)	5 (23)
1	9 (39)	8 (40)	22 (58)	16 (70)	20 (56)	17 (77)
2	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
WHO classification at study entry, *n* (%)						
Adenosquamous carcinoma	4 (17)	3 (15)	1 (3)	1 (4)	3 (8)	2 (9)
Mucinous adenocarcinoma	6 (26)	5 (25)	3 (8)	7 (30)	13 (36)	3 (14)
Papillary serous adenocarcinoma	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Signet ring cell	0 (0)	2 (10)	5 (13)	3 (13)	2 (6)	1 (5)
Tubular adenocarcinoma	4 (17)	1 (5)	7 (18)	3 (13)	4 (11)	1 (5)
Other	8 (35)	9 (45)	21 (55)	7 (30)	12 (33)	15 (68)
Not reported	0 (0)	0 (0)	1 (3)	2 (9)	2 (6)	0 (0)

Some patients may be reported multiple times under different tracks and treatment group combinations due to re-randomization. Percentages based on number of patients treated. Percentages in each category may not equal 100% due to rounding.
ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; IDO1i, BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor; IPI, ipilimumab; NIVO, nivolumab; RELA, relatlimab; WHO, World Health Organization.

regimens. Most patients had stage IV disease and adenocarcinoma.

All patients discontinued treatment at data cut-off, mostly because of disease progression (track 1: nivolumab plus ipilimumab, 65%; nivolumab plus relatlimab, 85%; nivolumab plus IDO1i, 74%; track 2: nivolumab plus ipilimumab, 57%; nivolumab plus relatlimab, 72%; nivolumab plus IDO1i, 91%). Fifty-five patients continued treatment after initial disease progression. Study drug toxicity led to treatment discontinuation in <9% of patients in all arms except for the track 2 nivolumab plus ipilimumab arm, where it was responsible for 30% of discontinuations.

Efficacy

ORR per investigator for nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i in track 1 was 4% (95% CI 0.1% to 21.9%), 5% (95% CI 0.1% to 24.9%), and 13% (95% CI 4.4% to 28.1%), respectively, and in track 2 was 9% (95% CI 1.1% to 28.0%), 6% (95% CI 0.7% to 18.7%), and 0% (95% CI 0% to 15.4%), respectively (Table 2). All six treatment arms were terminated for futility, as they all failed to meet the prespecified stopping boundaries. DOR has been reported for each individual patient with a response due to the small number of responders in each treatment arm (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104107). At data cut-off, none of the responders had ongoing responses, 55% of responders had responses lasting at least 12 months, and 63% were alive (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.104107). Median PFS in track 1 was 1.7 months (95% CI 1.2-1.9 months), 1.7 months (95% CI 1.4-1.7 months), and 1.8 months (95% CI 1.6-3.5 months), and in track 2 was 1.9 months (95% CI 1.5-5.3 months), 1.9 months

Table 2. Response and disease control rate

	Track 1			Track 2		
	NIVO + IPI (n = 23)	NIVO + RELA (n = 20)	NIVO + IDO1i (n = 38)	NIVO + IPI (n = 23)	NIVO + RELA (n = 36)	NIVO + IDO1i (n = 22)
Objective response rate, n (%)	1 (4)	1 (5)	5 (13)	2 (9)	2 (6)	0
95% CI	0.1-21.9	0.1-24.9	4.4-28.1	1.1-28.0	0.7-18.7	0.0-15.4
Best overall response, n (%)						
Complete response	0	0	0	0	0	0
Partial response	1 (4)	1 (5)	5 (13)	2 (9)	2 (6)	0
Stable disease	4 (17)	0	6 (16)	5 (22)	6 (17)	3 (14)
Progressive disease	11 (48)	17 (85)	21 (55)	11 (48)	21 (58)	17 (77)
Not evaluable	5 (22)	1 (5)	5 (13)	4 (17)	6 (17)	2 (9)
Not available	2 (9)	1 (5)	1 (3)	1 (4)	1 (3)	0
Disease control rate, n (%)	5 (22)	1 (5)	11 (29)	7 (30)	8 (22)	3 (14)
95% CI	7.5-43.7	0.1-24.9	15.4-45.9	13.2-52.9	10.1-39.2	2.9-34.9

All responses were assessed according to the Response Evaluation Criteria in Solid Tumors, v1.1. CIs based on the Clopper and Pearson method.
CI, confidence interval; IDO1i, BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor; IPI, ipilimumab; NIVO, nivolumab; RELA, relatlimab.

(95% CI 1.5-3.4 months), and 1.7 months (95% CI 1.6-1.8 months) for nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i, respectively (Figure 1). The PFS rate at 24 weeks was 24% (95% CI 11% to 39%) for patients receiving nivolumab plus IDO1i in track 1 and 17% (95% CI 6% to 32%) for patients receiving nivolumab plus relatlimab in track 2. The PFS rate at 24 weeks was not calculated for the other treatment arms due to small numbers of patients at risk at this time point. Median OS in track 1 was 3.2 months (95% CI 1.7-8.8 months), 8.3 months (95% CI 2.6-13.1 months), and 8.4 months (95% CI 5.9-11.5 months) for nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i, respectively, and in track 2 was 7.4 months (95% CI 4.5-11.1 months), 9.2 months (95% CI 4.6-14.9 months), and 9.1 months (95% CI 3.6-15.8 months), respectively (Figure 2). Of the 130 patients who had a target lesion at baseline and at least one post-baseline tumor assessment, 20 patients experienced a tumor burden reduction of 30% or more (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.104107).

Biomarker analyses

Overall, 78 (96%) patients in track 1 [immuno-oncology (IO)-naïve] and 48 (59%) patients in track 2 (IO-experienced) had evaluable tumor cell PD-L1 data. The prevalence of tumor cell PD-L1 $\geq$1% trended higher in track 2 [12 of 48 (25%) assessable patients] than in track 1 [10 of 78 (13%) assessable patients]. Response by PD-L1 expression is summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104107. Interpretation of investigator-assessed objective responses by PD-L1 expression was difficult due to the low number of responders. Meaningful analysis of ORR by MSI status was precluded due to the very low number of patients reporting MSI status per local testing [40 of 162 (25%) patients reported MSI and/or MMR status]. A higher baseline level of IDO1 expression was observed in track 2 as compared with track 1. The majority of patients in track 1 had increased IDO1 expression after treatment for all arms regardless of response status, which was not observed in track 2, with the exception of some patients receiving nivolumab plus ipilimumab (Supplementary Figure S4A, available at https://doi.org/10.1016/j.esmoop.2024.104107). No significant difference was observed in the baseline tumor density of CD8 T cells between tracks 1 and 2. The majority of patients in track 1 had increased CD8 T cells after treatment for all treatment arms regardless of response status, which was not observed in track 2, with the exception of those receiving nivolumab plus ipilimumab (Supplementary Figure S4B, available at https://doi.org/10.1016/j.esmoop.2024.104107). Baseline tumor density of LAG-3+ cells trended higher in track 2 compared with track 1. Most patients in track 1 had increased tumor density of LAG-3+ cells after treatment for all treatment groups regardless of response status, as did some of the patients in track 2 receiving nivolumab plus ipilimumab and nivolumab plus relatlimab (Supplementary Figure S3C, available at https://doi.org/10.1016/j.esmoop.2024.104107). The limited number of responders precludes meaningful analysis of biomarker association with efficacy.

Exposure and safety

The median duration of therapy was between 0.9 and 2 months across all arms, with 74%-96% of patients achieving a relative dose intensity between 90% and 110% (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.104107). Any-grade TRAEs were reported in 17 (74%), 12 (60%), and 23 (61%) patients receiving nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i in track 1 and in 19 (83%), 18 (50%), and 13 (60%) patients in track 2, respectively. Grade 3 or 4 TRAEs were reported in 5 (22%), 1 (5%), and 7 (18%) patients receiving nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i in track 1 and in 8 (35%), 4 (11%), and 4 (18%) patients in track 2, respectively (Table 3). The most common grade 3 or 4 TRAEs across both tracks were diarrhea (n = 3, 7%), autoimmune hepatitis (n = 3, 7%), colitis (n = 2, 4%), increased aspartate aminotransferase (n = 2, 4%), increased lipase (n = 2, 4%), and hepatitis (n = 2, 4%) for nivolumab plus

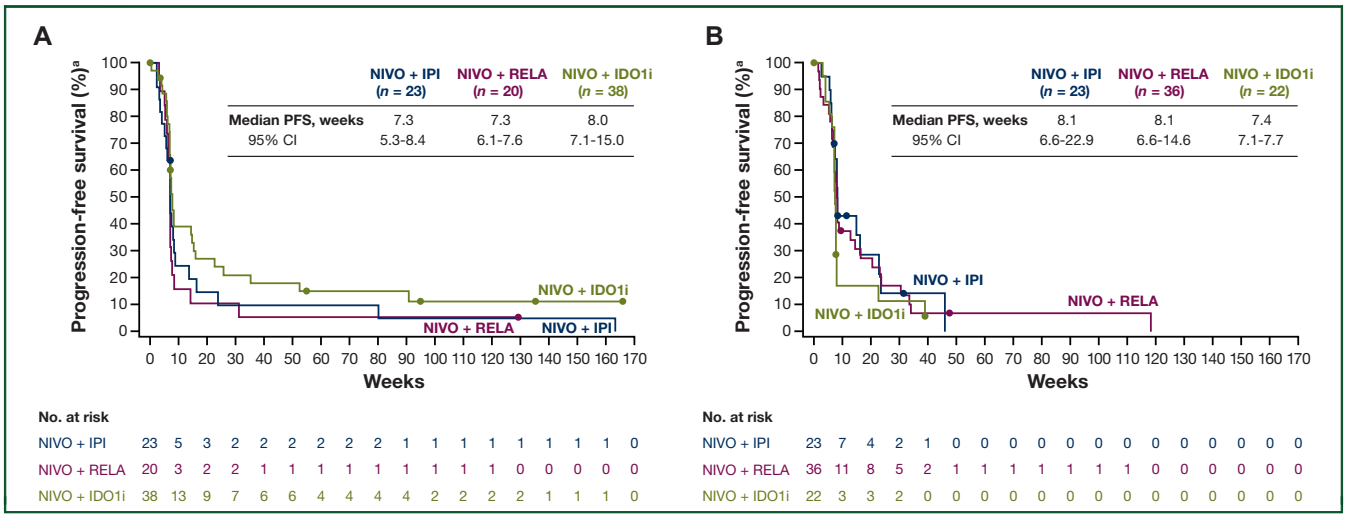

Figure 1. Kaplan–Meier plots of progression-free survival per investigator. (A) track 1 and (B) track 2. Symbols represent censored observations.
CI, confidence interval; IDO1i, BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; RELA, relatlimab.
[a]Assessed by investigator according to the Response Evaluation Criteria in Solid Tumors, v1.1.

ipilimumab; increased aspartate aminotransferase ($n = 2$, 4%) for nivolumab plus relatlimab; and increased lipase ($n = 2$, 3%) for nivolumab plus IDO1i. Eighteen patients across both tracks discontinued treatment due to any-grade TRAEs (10 for nivolumab plus ipilimumab, four for nivolumab plus relatlimab, and four for nivolumab plus IDO1i), 17 of whom discontinued due to grade 3 or 4 TRAEs. The most common TRAEs leading to discontinuation were diarrhea ($n = 3$, 7%), hepatitis ($n = 2$, 4%), and increased aspartate aminotransferase ($n = 2$, 4%) for nivolumab plus ipilimumab; adrenal insufficiency (2%), secondary adrenocortical insufficiency ($n = 1$, 2%), autoimmune hepatitis ($n = 1$, 2%), and increased hepatic enzyme ($n = 1$, 2%) for nivolumab plus relatlimab; and increased alanine aminotransferase ($n = 1$, 2%), increased aspartate aminotransferase ($n = 1$, 2%), increased hepatic enzyme ($n = 1$, 2%), adrenal insufficiency ($n = 1$, 2%), nausea ($n = 1$, 2%), vomiting ($n = 1$, 2%) and decreased appetite ($n = 1$, 2%) for nivolumab plus IDO1i. Serious TRAEs occurred in four (17%), one (5%), and five (13%) patients receiving nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i in track 1 and in seven (30%), three (8%) and zero (0%) patients in track 2, respectively. Serious grade 3 or 4 TRAEs were reported in one (4%), one (5%), and four (11%) patients receiving nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i in track 1 and in seven (30%), three (8%), and zero (0%) patients in track 2, respectively. Of the 118 deaths across tracks 1 and 2, 111 (94%) were due to disease progression and none were due to study drug toxicity.

DISCUSSION

In the adaptive-design FRACTION-GC randomized trial, multiple regimens, including nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i, were

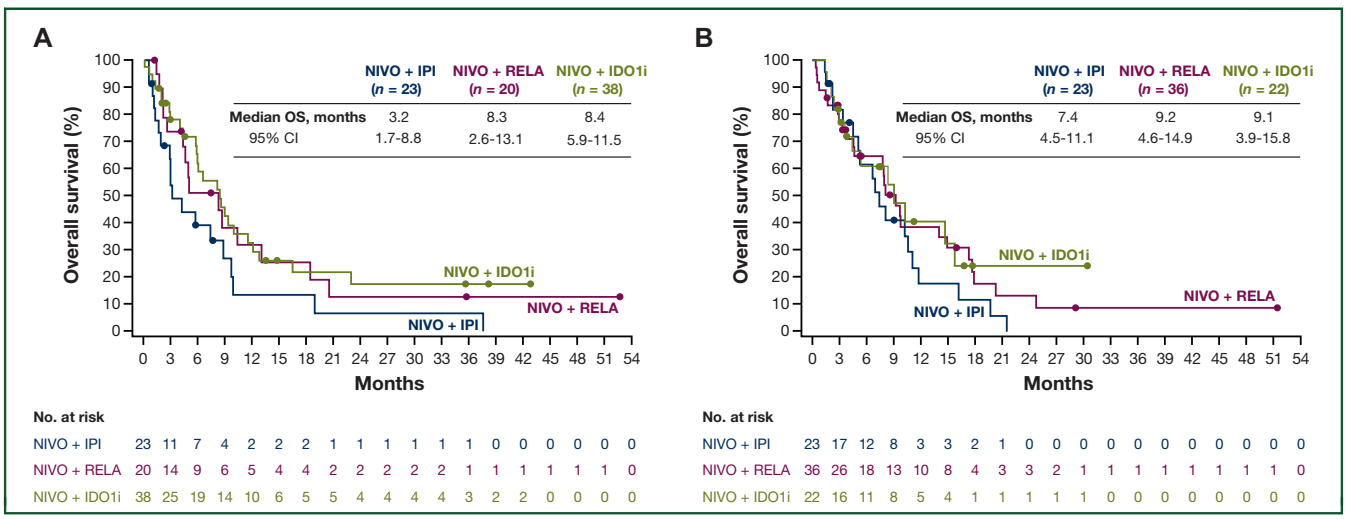

Figure 2. Kaplan–Meier plots of overall survival. (A) track 1 and (B) track 2. Symbols represent censored observations.
CI, confidence interval; IDO1i, BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; RELA, relatlimab.

Table 3. Summary of treatment-related adverse events in all treated patients

	Track 1			Track 2		
	NIVO + IPI (n = 23)[a]	NIVO + RELA (n = 20)	NIVO + IDO1i (n = 38)	NIVO + IPI (n = 23)	NIVO + RELA (n = 36)	NIVO + IDO1i (n = 22)
Any TRAEs	17 (74)	12 (60)	23 (61)	19 (83)	18 (50)	13 (59)
Grade 3/4 events	5 (22)	1 (5)	7 (18)	8 (35)	4 (11)	4 (18)
Serious TRAEs	4 (17)	1 (5)	5 (13)	4 (17)	3 (8)	0 (0)
Grade 3/4 events	1 (4)	1 (5)	4 (11)	1 (4)	3 (8)	0 (0)
TRAEs leading to discontinuation	3 (13)	1 (5)	4 (11)	7 (30)	3 (8)	0 (0)
Grade 3/4 events	3 (13)	1 (5)	3 (8)	7 (30)	3 (8)	0 (0)
Events in 10% or more of treated patients[b]						
Fatigue	7 (30)	5 (25)	14 (37)	5 (22)	7 (19)	4 (18)
Rash maculopapular	4 (17)	1 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Rash papular	3 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pyrexia	3 (13)	1 (5)	1 (3)	2 (9)	0 (0)	0 (0)
Diarrhea	2 (9)	1 (5)	4 (11)	5 (22)	2 (6)	0 (0)
Lipase increased	1 (4)	0 (0)	2 (5)	1 (4)	0 (0)	3 (14)
Hypothyroidism	1 (4)	2 (10)	3 (8)	3 (13)	0 (0)	1 (5)
Decreased appetite	1 (4)	2 (10)	4 (11)	1 (4)	3 (8)	2 (9)
Nausea	1 (4)	1 (5)	7 (18)	1 (4)	2 (6)	0 (0)
Aspartate aminotransferase increased	0 (0)	1 (5)	6 (16)	4 (17)	2 (6)	1 (5)
Alanine aminotransferase increased	0 (0)	1 (5)	5 (13)	2 (9)	2 (6)	0 (0)
Constipation	0 (0)	2 (10)	2 (5)	0 (0)	1 (3)	1 (5)
Pruritus	0 (0)	1 (5)	0 (0)	4 (17)	3 (8)	2 (9)
Blood alkaline phosphatase increased	0 (0)	0 (0)	2 (5)	3 (13)	1 (3)	1 (5)
Lipase increased	1 (4)	0 (0)	2 (5)	1 (4)	0 (0)	3 (14)

All values expressed as n (%). Patients received at least one dose of the assigned treatment. Includes events reported between the first dose and 30 days after the last dose of trial therapy. Treatment refers to nivolumab, at least one treatment component, or both. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, and Medical Dictionary for Regulatory Activities, v23.0.

IDO1i, BMS986205, an indoleamine 2,3-dioxygenase 1 inhibitor; IPI, ipilimumab; NIVO, nivolumab; RELA, relatlimab; TRAE, treatment-related adverse event.

[a]One patient's death was initially reported in the track 1 nivolumab plus ipilimumab arm as a grade 5 TRAE, but reconciliation after the database lock determined that this death was assessed by the investigator to be due to disease and not related to study treatment.

[b]10% or more of patients in at least one treatment arm.

evaluated in patients with GC and GEJC, most of whom were pretreated. In patients who were naïve to immunotherapies (track 1), ORR did not meet the prespecified criteria for expansion to stage 2. In patients who had previously received immunotherapies (track 2), a small number of those treated with nivolumab plus ipilimumab and nivolumab plus relatlimab achieved an objective response, although no responses were observed in patients who received nivolumab plus IDO1i. Considering the low number of responders, interpretation of DOR results is limited. Median PFS was under 2 months for all arms and was slightly higher numerically in those who had previously received immunotherapy compared with those who had not, although the CIs overlapped. Most treatment arms had a median OS of 7.4-9.2 months, although in the nivolumab plus ipilimumab arm in immunotherapy-naïve patients, the median OS was shorter (3.2 months). This OS benefit despite a short median PFS and low ORR may be due to alteration of the immune microenvironment, which makes tumor cells respond favorably to subsequent cytotoxic agents or vascular endothelial growth factor inhibition.[24-27]

Despite the short median PFS, some patients did respond well to combination therapies. Although the ORR was low, tumor burden reduction in target lesions was seen in 15% of patients. Some of these patients may have experienced new and non-target lesions that prevented them from having a RECIST-confirmed ORR. It is possible that since patients in track 2 had been previously treated with anti-PD-1/anti-CTLA-4 therapies and survived, there may be unintended preselection for some level of immunosensitivity in track 2 patients. Overall, the ORRs observed in FRACTION-GC were low in contrast to contemporary later-line trials.[28-30] Differences in numerous factors, including baseline characteristics that were not accounted for despite the stringent eligibility criteria and the number of prior therapy lines, may have contributed to these relatively low response rates.

Safety profiles of these regimens are consistent with the known safety profiles of individual components of the regimens. Each of the treatment arms was well tolerated, with no new safety signals observed. Safety profiles were generally similar across treatment arms, with a slightly higher rate of TRAEs, serious TRAEs, and immune-mediated AEs in both track 1 and track 2 nivolumab plus ipilimumab arms. The highest rate of TRAEs (74%), grade 3 or 4 TRAEs (22%), and discontinuations due to TRAEs (22%) were in the nivolumab plus ipilimumab cohort.

Proportions of PD-L1+, IDO1+, and LAG-3+ cells in tumor tissue were generally higher at baseline in patients from the IO-experienced track 2 compared with IO-naïve track 1; it is possible that prior IO treatment may have increased the expression of these immune-related biomarkers. Most IO-naïve patients in track 1 demonstrated an increased expression of these biomarkers upon exposure to the treatment drugs. In the IO-experienced patients in track 2, such an increase was only observed for IDO1 and CD8 in response to

nivolumab plus ipilimumab, and for LAG-3 after nivolumab plus ipilimumab or nivolumab plus relatlimab treatment, suggesting that immune-related changes may be more readily induced in IO-naïve than IO-experienced patients. The low number of patients and limited number of responders preclude meaningful analysis of associations between efficacy and any specific biomarker. Additionally, the limited availability of MSI status reported per local testing precludes meaningful correlative analysis by MSI status.

Due to the exploratory nature of this study, ORR was selected as the criterion for a quick assessment at each stage. The minimum ORR for success was not reached in the treatment arms at stage 1, and median PFS was short; therefore, the study did not expand to the second stage. Ultimately, this study was limited by sample size, and due to a low number of responders, some estimates of efficacy such as DOR were difficult to assess. Although individual patients in the nivolumab plus relatlimab and nivolumab plus IDO1i arms had promising improvement in OS, this benefit was not further explored due to study termination. Future studies with similar adaptive experimental designs should incorporate novel biomarker and clinical data in order to allow for study continuation, despite low ORR and short PFS. As noted, FRACTION-GC had a very heterogeneous patient population, despite stringent eligibility criteria. Novel metrics such as the Gustave Roussy Immune Score[31] can be used in future studies to thoroughly evaluate baseline characteristics in such patient populations.

Nivolumab plus ipilimumab, nivolumab plus relatlimab, and nivolumab plus IDO1i demonstrated limited activity, as determined by ORR, in patients with advanced GC and GEJC. There were no new safety signals, and the observed safety was consistent with the individual contributing treatments.[16,20,21] This trial demonstrates a novel adaptive trial design that can be used in the future to rapidly evaluate combination immunotherapies in this and other indications. While the design of FRACTION-GC was necessarily complex because of the multiple tracks and treatment arms as well as enrollment of both immunotherapy-naïve and immunotherapy-experienced patients, the rapid accrual of patients to this international study shows the feasibility of enrolling patients into such an umbrella study. Given the low ORR and short PFS observed in FRACTION-GC, an unmet need for more effective therapies in these patients still exists despite recent studies that have led to the incorporation of anti-PD-1 antibodies into standard therapy for esophagogastric cancers.

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DATA SHARING

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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