First-Line Nivolumab and Relatlimab Plus Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma: The Phase II RELATIVITY-060 Study

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ABSTRACT

PURPOSE Open-label phase II study (RELATIVITY-060) to investigate the efficacy and safety of first-line nivolumab, a PD-1–blocking antibody, plus relatlimab, a lymphocyte-activation gene 3 (LAG-3)–blocking antibody, plus chemotherapy in patients with previously untreated advanced gastric cancer (GC) or gastroesophageal junction cancer (GEJC).

METHODS Patients with unresectable, locally advanced or metastatic GC/GEJC were randomly assigned 1:1 to nivolumab + relatlimab (fixed-dose combination) + chemotherapy or nivolumab + chemotherapy. The primary end point was objective response rate (ORR; per RECIST v1.1 by blinded independent central review [BICR]) in patients whose tumors had LAG-3 expression ≥1%.

RESULTS Of 274 patients, 138 were randomly assigned to nivolumab + relatlimab + chemotherapy and 136 to nivolumab + chemotherapy. Median follow-up was 11.9 months. In patients with LAG-3 expression ≥1%, BICR-assessed ORR (95% CI) was 48% (38 to 59) in the nivolumab + relatlimab + chemotherapy arm and 61% (51 to 71) in the nivolumab + chemotherapy arm; median progression-free survival (95% CI) by BICR was 7.0 months (5.8 to 8.4) versus 8.3 months (6.9 to 12.1; hazard ratio [HR], 1.41 [95% CI, 0.97 to 2.05]), and median overall survival (95% CI) was 13.5 months (11.9 to 19.1) versus 16.0 months (10.9 to not estimable; HR, 1.04 [95% CI, 0.70 to 1.54]), respectively. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 69% and 61% of all treated patients, and 42% and 36% of patients discontinued because of any-grade TRAEs in the nivolumab + relatlimab + chemotherapy and nivolumab + chemotherapy arms, respectively.

CONCLUSION RELATIVITY-060 did not meet its primary end point of improved ORR in patients with LAG-3 expression ≥1% when relatlimab was added to nivolumab + chemotherapy compared with nivolumab + chemotherapy. Further studies are needed to address whether adding anti–LAG-3 to anti–PD-1 plus chemotherapy can benefit specific GC/GEJC patient subgroups.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Gastric cancer (GC), including gastroesophageal junction cancer (GEJC), is the fourth leading cause of cancer-related death worldwide each year, with a 5-year relative survival rate of 6% or less for patients with metastatic disease.[1]

Nivolumab, a PD-1–blocking antibody, plus oxaliplatin-based chemotherapy demonstrated superior overall survival (OS) and progression-free survival (PFS) benefit and maintained health-related quality of life with an acceptable safety profile compared with chemotherapy in previously untreated patients with non–human epidermal growth factor receptor 2 (HER2)–positive gastroesophageal adenocarcinoma in the CheckMate 649 trial.[2,3] On the basis of these results, nivolumab + chemotherapy was approved as a first-line treatment for unresectable advanced or metastatic GC/GEJC/esophageal adenocarcinoma in many countries including the United States.[4]

CONTEXT

Key Objective

Does the combination of relatlimab, a lymphocyte-activation gene 3 (LAG-3)–blocking antibody, and nivolumab, a PD-1–blocking antibody, plus chemotherapy provide clinical benefit in patients with previously untreated advanced gastric or gastroesophageal junction cancer?

Knowledge Generated

RELATIVITY-060 did not meet its primary end point of improved objective response rate with nivolumab + relatlimab + chemotherapy compared with nivolumab + chemotherapy in patients whose tumors had LAG-3 expression ≥1%. Median progression-free survival and median overall survival were also not improved; however, disease control rate was comparable. The safety profile of nivolumab + relatlimab + chemotherapy was acceptable and consistent with the known safety profiles of the immunotherapy and chemotherapy components.

Relevance *(E.M. O'Reilly)*

The results from the RELATIVITY-060 trial endorse a current standard of care (chemotherapy/anti-PD-1 antibody) as the addition of LAG-3 blockade in untreated upper esophagogastric cancers does not add significant benefit.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

Dual immunotherapies, such as nivolumab plus ipilimumab, a cytotoxic T lymphocyte antigen-4–blocking antibody, have resulted in clinical benefit versus chemotherapy for the treatment of multiple tumor types, suggesting that combining nivolumab with other checkpoint inhibitors, such as relatlimab, a lymphocyte-activation gene 3 (LAG-3)–blocking antibody, has the potential for a synergistic effect.[5-11] The distinct immune checkpoints PD-1 and LAG-3 are often coexpressed on tumor-infiltrating lymphocytes and contribute to T-cell dysfunction.[12] The combination of nivolumab + relatlimab demonstrated significant PFS benefit compared with nivolumab alone with a manageable safety profile in patients with previously untreated metastatic or unresectable melanoma in the RELATIVITY-047 study.[13] On the basis of these results, nivolumab + relatlimab as a fixed-dose combination (FDC) was approved for the treatment of unresectable or metastatic melanoma.[14]

Here, we present the results from the RELATIVITY-060 study of nivolumab + relatlimab + chemotherapy versus nivolumab + chemotherapy as first-line therapy for patients with unresectable, locally advanced or metastatic GC/GEJC.

METHODS

Study Design and Eligibility

RELATIVITY-060 is a randomized, open-label, multicenter, phase II study conducted at 70 centers across 17 countries in Asia, Europe, North America, South America, and Australia. Eligible patients were at least age 18 years with histologically/cytologically confirmed unresectable and either locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma and had not previously received systemic treatment. Adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy were permitted if given at least 6 months before random assignment. Patients had an Eastern Cooperative Oncology Group performance status score of 0 or 1; at least one measurable lesion per RECIST v1.1; and tumor tissue for biomarker analyses.[15] Patients with HER2-positive status were excluded. Additional details are provided in the protocol.

This study was conducted in accordance with Good Clinical Practice guidelines as defined by the International Council for Harmonisation. The institutional review board or independent ethics committee approved the study protocol and subsequent amendments at each site. All patients provided written informed consent on the basis of the principles of the Declaration of Helsinki.

Randomization and Blinding

Patients were randomly assigned 1:1 to nivolumab + relatlimab + investigator's (INV's) choice of oxaliplatin-based chemotherapy (oxaliplatin + capecitabine [XELOX], oxaliplatin + leucovorin + fluorouracil [FOLFOX], or oxaliplatin + tegafur/gimeracil/oteracil potassium [SOX] regimen; additional details are provided in the protocol) or nivolumab + INV's choice of oxaliplatin-based chemotherapy, using interactive web response technology (block size of 2). Randomization was stratified according to LAG-3 expression (≥1% *v* <1%) and PD-L1 combined positive score (CPS; <1 [including indeterminate] *v* ≥1 to <5 *v* ≥5). Geographic region (Japan/Taiwan *v* rest of the world) was planned as a stratification factor but was not used because of lack of

patients enrolled from Japan and Taiwan. INVs were not blinded to treatment allocation.

Procedures

Patients assigned to XELOX received nivolumab + relatlimab FDC (nivolumab 360 mg and relatlimab 120 mg) or nivolumab 360 mg administered intravenously (IV) over 60 or 30 minutes, respectively, on days 1 and 22 of each 6-week treatment cycle. Oxaliplatin 130 mg/m² was administered IV on days 1 and 22 of each cycle, and capecitabine 1,000 mg/m² was administered orally twice daily on days 1-14 and days 22-35 of each cycle. Patients assigned to FOLFOX received nivolumab + relatlimab FDC (nivolumab 480 mg and relatlimab 160 mg) or nivolumab 480 mg administered IV over 60 or 30 minutes, respectively, on days 1 and 29 of every odd-numbered 6-week treatment cycle and day 15 of every even-numbered 6-week cycle. Oxaliplatin 85 mg/m², leucovorin 400 mg/m², and fluorouracil 400 mg/m² were administered IV on days 1, 15, and 29 of each cycle, and fluorouracil 1,200 mg/m² IV continuous infusion over 24 hours (or per local standard) on days 1, 2, 15, 16, 29, and 30 of each cycle. SOX treatment details are provided in the Data Supplement (online only). Treatment continued until progressive disease, unacceptable toxicity, withdrawal of consent, or study end. Additional details are in the protocol. Treatment was permitted beyond initial RECIST v1.1–defined progressive disease, on the basis of INV assessment. Dose escalations or reductions of nivolumab + relatlimab or nivolumab were not allowed. Dose modifications, delays, and discontinuation of chemotherapy components could be modified separately and were permitted according to local standards.

Biomarker Analyses

LAG-3 expression was determined using an analytically validated immunohistochemistry assay. LAG-3 expression was reported as the percent of LAG-3–positive cells resembling lymphocytes, relative to all nucleated cells within the tumor region.[16] PD-L1 expression was assessed using the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay (Dako, Agilent) assay. CPS was defined as the number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells and multiplied by 100.[17] Additional details are shown in the Data Supplement.

Assessments

The primary end point was objective response rate (ORR) by blinded independent central review (BICR) in patients with LAG-3 expression ≥1% per RECIST v1.1.[15] Secondary end points included safety; ORR (BICR) in patients with LAG-3 expression <1% and all randomly assigned patients; and ORR as assessed per INV, duration of response (DOR; BICR and INV), PFS (BICR and INV), and OS, all in patients with LAG-3 expression ≥1% and <1% and all randomly assigned patients. Key exploratory end points included pharmacokinetic, biomarker, and immunogenicity analyses (Data Supplement). Additional details are described in the Data Supplement.

Safety

Adverse events (AEs) were reported up to 100 days after the last treatment dose according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (INV). Immune-mediated AEs (IMAEs) were consistent with immune-mediated mechanisms or components for which noninflammatory etiologies have been ruled out. Definitions of treatment-related AEs (TRAEs) and additional methods are described in the protocol.

Statistical Analyses

Sample size of the study was determined on the basis of the primary objective, and calculations were based on the methodology of Fleiss et al.[18] Assuming a 40% prevalence of LAG-3 positivity, randomization of approximately 250 patients in a 1:1 ratio would ensure that 100 patients with LAG-3 expression ≥1% were enrolled. This would provide approximately 71% power for testing the ORR difference between the two arms, with a 0.15 one-sided (0.30 two-sided) significance level, assuming ORRs of 75% (nivolumab + relatlimab + chemotherapy) and 60% (nivolumab + chemotherapy). The maximum width of the two-sided 70% CI for the ORR difference would be 0.192. ORR and corresponding 95% CIs were determined using the Clopper-Pearson method. ORR difference (and 70% CI) in patients with LAG-3 expression ≥1% and the associated *P* value was compared between arms using a two-sided Cochran-Mantel-Haenszel test. Two-sided 95% CI for unweighted difference was calculated using Newcombe method. Additional details are described in the Data Supplement. Safety was analyzed by descriptive statistics using NCI CTCAE v5.0 by treatment group.

RESULTS

Patient Baseline Characteristics

From October 16, 2018, to November 4, 2019, 461 patients were assessed for eligibility, and of these, 274 patients were randomly assigned to the nivolumab + relatlimab + chemotherapy arm (n = 138) or the nivolumab + chemotherapy arm (n = 136); 271 patients received one or more doses of the assigned treatment (136 and 135 patients, respectively; Fig 1). At the data cutoff on August 27, 2020, the median follow-up (time from randomization date to the last known date alive or death date) was 11.9 months. The baseline characteristics were balanced across the treatment groups (Table 1). Twenty-two (16%) and 29 (21%) patients had received previous systemic therapy in the nivolumab + relatlimab + chemotherapy and nivolumab + chemotherapy arms, respectively (Table 1).

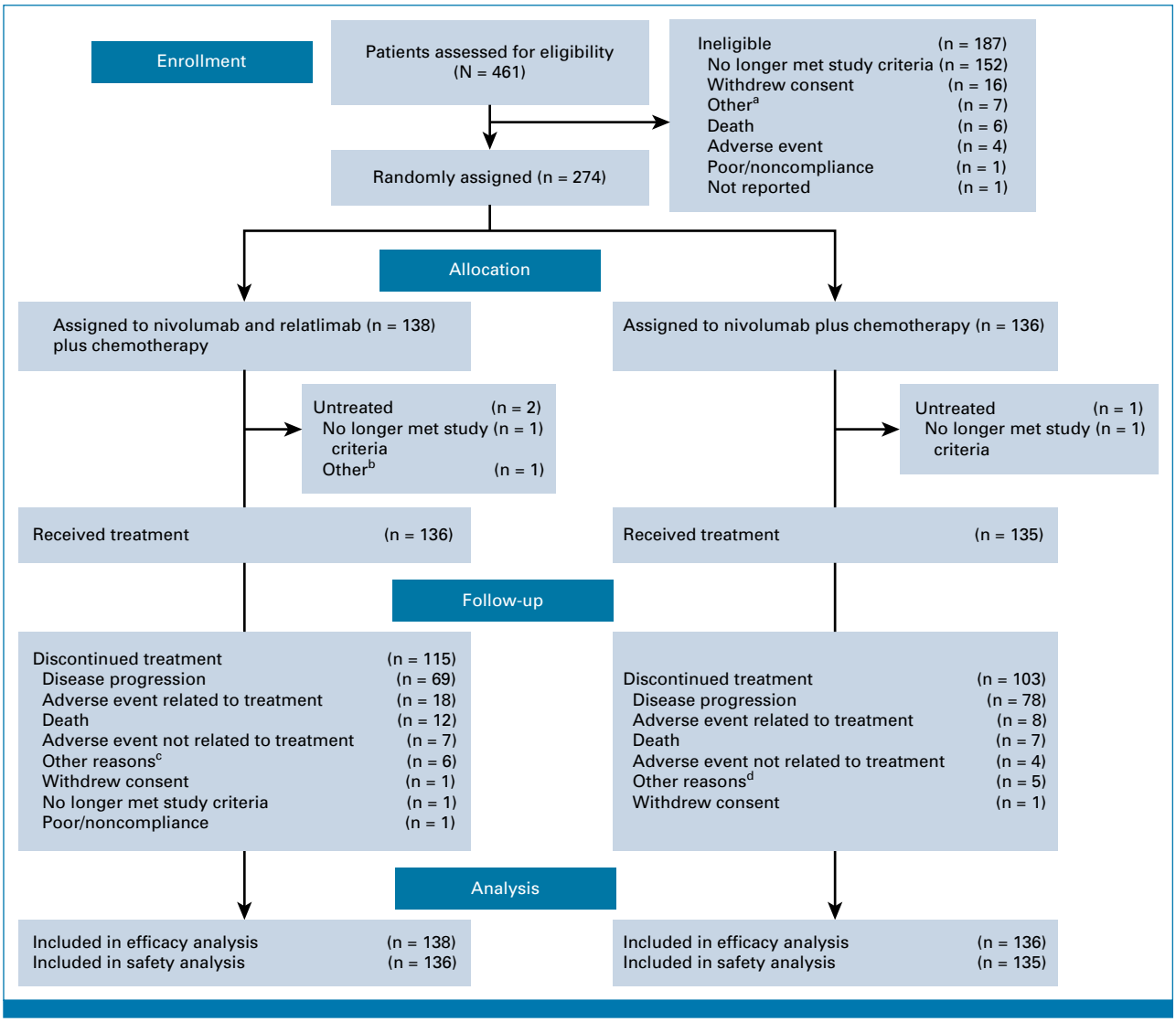

FIG 1. CONSORT diagram. [a]Other reasons included clinical progression (n = 2), and one each of patient could not wait for centralized review, patient went for laparoscopic surgery, patient did not meet eligibility criteria, rapid progression of malignant neoplasm disease, and not possible to obtain a tumor sample. [b]Other reason was patient had myocardial infarction (n = 1). [c]Other reasons included one each of INV decision, patient request, physician decision, total gastric surgery, clinical progression, and additional reasons. [d]Other reasons included patient request (n = 2), and one each of INV decision, clinical progression, and bedridden patient. AE, adverse event; INV, investigator.

Patient Disposition and Study Drug Exposure

At data cutoff, 15% of patients in the nivolumab + relatlimab + chemotherapy arm and 21% in the nivolumab + chemotherapy arm were still receiving study treatment, with a median (range) duration of therapy of 6.1 months (0.1-19.9) and 7.4 months (0.5-20.6), respectively (Data Supplement, Table S1). Disease progression was the most common reason for discontinuation in both treatment arms (51% *v* 58%, respectively; Data Supplement, Table S1).

The majority of patients received ≥90% of the planned relative dose intensity for nivolumab + relatlimab FDC (66%) and nivolumab (65%) regardless of the chemotherapy regimens; the cumulative and relative dose intensity of the chemotherapy component was lower in patients treated with nivolumab + relatlimab + chemotherapy relative to patients treated with nivolumab + chemotherapy for both XELOX and FOLFOX treatment regimens. Cumulative dose and dose delays are shown in the Data Supplement (Table S2).

In both arms, 34% of patients received subsequent anticancer therapy, including radiotherapy (6% *v* 7%), surgery (4% *v* 4%), and systemic therapy (29% *v* 26%; Data Supplement, Table S3).

Response

In patients with LAG-3 expression ≥1%, BICR-assessed ORR (95% CI) was 48% (38 to 59) with nivolumab +

TABLE 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	NIVO + RELA + Chemo (n = 138)	NIVO + Chemo (n = 136)
Age, years, median (range)	62 (24-79)	63 (23-84)
Sex, No. (%)		
Male	94 (68)	98 (72)
Female	44 (32)	38 (28)
Race, No. (%)		
White	128 (93)	122 (90)
Asian	5 (4)	8 (6)
Black	0	1 (<1)
Other	5 (4)	5 (4)
Geographic region, No. (%)		
Europe	71 (51)	77 (57)
United States and Canada	22 (16)	22 (16)
Asia	2 (1)	3 (2)
Rest of world	43 (31)	34 (25)
ECOG PS,[a] No. (%)		
0	55 (40)	61 (45)
1	83 (60)	74 (54)
Primary tumor location at initial diagnosis, No. (%)		
GC	68 (49)	70 (51)
GEJC	70 (51)	66 (49)
Lauren classification, No. (%)		
Intestinal	33 (24)	42 (31)
Diffuse	36 (26)	31 (23)
Mixed	7 (5)	8 (6)
Unknown	62 (45)	55 (40)
Signet ring cell carcinoma, No. (%)	20 (14)	27 (20)
Disease stage, No. (%)		
Metastatic	128 (93)	122 (90)
Unresectable locally advanced	6 (4)	9 (7)
Locally recurrent	4 (3)	5 (4)
Site of metastasis, No. (%)		
Liver	63 (46)	51 (38)
Peritoneal	56 (41)	59 (43)
Helicobacter pylori infection,[b] No. (%)	15 (11)	19 (14)
LAG-3 expression, No. (%)		
<1%	41 (30)	38 (28)
≥1%	97 (70)	98 (72)
PD-L1 CPS, No. (%)		
<1 or indeterminate	29 (21)	33 (24)
≥1 to <5	35 (25)	28 (21)
≥5	74 (54)	75 (55)
Chemo received on study,[c,d] No. (%)		
FOLFOX	103 (75)	97 (71)
XELOX	34 (25)	38 (28)
Previous systemic therapy,[e] No. (%)	22 (16)	29 (21)
Adjuvant therapy	4 (3)	11 (8)
Neoadjuvant	18 (13)	21 (15)
Locally advanced	1 (<1)	1 (<1)
Previous radiotherapy, No. (%)	21 (15)	23 (17)
Previous surgery, No. (%)	45 (33)	47 (35)

NOTE. Percentages may not add up to 100 because of rounding.
Abbreviations: chemo, chemotherapy; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, oxaliplatin + leucovorin + fluorouracil; GC, gastric cancer; GEJC, gastroesophageal junction cancer; LAG-3, lymphocyte-activation gene 3; NIVO, nivolumab; RELA, relatlimab; SOX, oxaliplatin + tegafur/gimeracil/oteracil potassium; XELOX, oxaliplatin + capecitabine.
[a]Not reported, n = 1 (NIVO + chemo).
[b]Unknown, n = 79 (NIVO + RELA + chemo, n = 43; NIVO + chemo, n = 36).
[c]Patients who received at least one dose of assigned treatment.
[d]One patient in each arm received SOX.
[e]Patient may have received more than one type of therapy.

relatlimab + chemotherapy versus 61% (51 to 71) with nivolumab + chemotherapy, and the difference in ORR (nivolumab + relatlimab + chemotherapy over nivolumab + chemotherapy) was −13 (70% CI, −20 to −6; P = .0711; Table 2). In patients with LAG-3 expression <1%, BICR-assessed ORR (95% CI) was 32% (18 to 48) for nivolumab + relatlimab + chemotherapy versus 55% (38 to 71) for nivolumab + chemotherapy, and in all randomly assigned patients, BICR-assessed ORR (95% CI) was 44% (35 to 52) versus 60% (51 to 68), respectively. Concordance rates between BICR- and INV-assessed ORR were 83% for the nivolumab + relatlimab + chemotherapy arm and 78% for the nivolumab + chemotherapy arm. BICR-assessed ORR favored nivolumab + chemotherapy over nivolumab + relatlimab + chemotherapy across most prespecified subgroups (Fig 2).

Median time to response was similar between treatment arms (Table 2). BICR-assessed median (95% CI) DOR in the nivolumab + relatlimab + chemotherapy and nivolumab + chemotherapy arms was 5.7 months (4.4 to 10.0) versus 10.1 months (6.4 to 13.3) in patients with LAG-3 expression ≥1%, 5.4 months (3.3 to 7.0) versus 8.5 months (5.3 to 13.6) in patients with LAG-3 expression <1%, and 5.6 months (5.1 to 7.0) versus 9.7 months (6.7 to 12.5) in all responders. For patients with LAG-3 expression ≥1%,

TABLE 2. Response, Disease Control, and PFS

Outcome	LAG-3 ≥1%		LAG-3 <1%		All Randomly Assigned	
	NIVO + RELA + Chemo (n = 97)	NIVO + Chemo (n = 98)	NIVO + RELA + Chemo (n = 41)	NIVO + Chemo (n = 38)	NIVO + RELA + Chemo (n = 138)	NIVO + Chemo (n = 136)
BICR-assessed						
ORR[a,b]						
No. (%)	47 (48)	60 (61)	13 (32)	21 (55)	60 (43)	81 (60)
[95% CI]	38 to 59	51 to 71	18 to 48	38 to 71	35 to 52	51 to 68
Difference of ORR[c] (70% CI)	−13 (−20 to −6)		−25 (−36 to −15)		−17 (−23 to −10)	
P[d]	.0711		NA		NA	
Best overall response,[a] No. (%)						
CR	6 (6)	10 (10)	2 (5)	0	8 (6)	10 (7)
PR	41 (42)	50 (51)	11 (27)	21 (55)	52 (38)	71 (52)
SD	34 (35)	18 (18)	11 (27)	7 (18)	45 (33)	25 (18)
PD	1 (1)	10 (10)	2 (5)	4 (11)	3 (2)	14 (10)
Unable to determine	7 (7)	5 (5)	7 (17)	0	14 (10)	5 (4)
DCR[a]						
No. (%)	89 (92)	83 (85)	32 (78)	34 (89)	121 (88)	117 (86)
95% CI	84 to 96	76 to 91	62 to 89	75 to 97	81 to 93	79 to 91
TTR, months,[e] median (range)	1.5 (1.2-5.3)	1.5 (1.2-5.6)	1.6 (1.3-4.0)	2.8 (1.2-7.2)	1.5 (1.2-5.3)	2.0 (1.2-7.2)
DOR, months,[e] median (95% CI)	5.7 (4.4 to 10.0)	10.1 (6.4 to 13.3)	5.4 (3.3 to 7.0)	8.5 (5.3 to 13.6)	5.6 (5.1 to 7.0)	9.7 (6.7 to 12.5)
PFS, months, median (95% CI)	7.0 (5.8 to 8.4)	8.3 (6.9 to 12.1)	6.6 (4.7 to 7.1)	9.7 (6.9 to 13.7)	6.8 (5.8 to 7.3)	9.4 (7.0 to 11.5)
INV-assessed						
ORR[a,b]						
No. (%)	51 (53)	55 (56)	13 (32)	16 (42)	64 (46)	71 (52)
95% CI	42 to 63	46 to 66	18 to 48	26 to 59	38 to 55	43.5 to 61
Best overall response,[a] No. (%)						
CR	3 (3)	5 (5)	0	0	3 (2)	5 (4)
PR	48 (49)	50 (51)	13 (32)	16 (42)	61 (44)	66 (49)
SD	33 (34)	27 (28)	19 (46)	18 (47)	52 (38)	45 (33)
PD	6 (6)	12 (12)	2 (5)	4 (11)	8 (6)	16 (12)
Unable to determine	7 (7)	4 (4)	7 (17)	0	14 (10)	4 (3)
DCR[a]						
No. (%)	84 (87)	82 (84)	32 (78)	34 (89)	116 (84)	116 (85)
95% CI	78 to 93	75 to 90	62 to 89	75 to 97	77 to 90	78 to 91
TTR, months,[f] median (range)	1.6 (0.9-5.5)	1.4 (1.2-8.5)	1.5 (1.2-4.1)	2.3 (1.0-16.6)	1.6 (0.9-5.5)	1.5 (1.0-16.6)
DOR, months,[f] median (95% CI)	6.9 (4.4 to 8.3)	8.3 (6.9 to 12.45)	5.5 (3.0 to 6.9)	7.5 (5.6 to 13.6)	5.9 (4.4 to 7.3)	8.3 (6.9 to 11.1)
PFS, months, median (95% CI)	7.0 (5.8 to 8.4)	8.3 (5.9 to 9.7)	5.4 (4.2 to 7.6)	11.0 (6.9 to 13.7)	6.6 (5.4 to 7.6)	8.3 (6.9 to 9.7)

Abbreviations: BICR, blinded independent central review; chemo, chemotherapy; CR, complete response; DCR, disease control rate; DOR, duration of response; INV, investigator; LAG-3, lymphocyte-activation gene 3; NA, not applicable; NIVO, nivolumab; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RELA, relatlimab; SD, stable disease; TTR, time to response.

[a]Per RECIST 1.1.

[b]CI on the basis of the Clopper-Pearson method.

[c]Strata adjusted difference in ORR (NIVO + RELA + chemo over NIVO + chemo) on the basis of the Cochran-Mantel-Haenszel method of weighting.

[d]On the basis of two-sided stratified Cochran-Mantel-Haenszel test.

[e]Number of responders: LAG-3 ≥1%, NIVO + RELA + chemo (n = 47) and NIVO + chemo (n = 60); LAG-3 <1%, NIVO + RELA + chemo (n = 13) and NIVO + chemo (n = 21); all randomly assigned NIVO + RELA + chemo (n = 60) and NIVO + chemo (n = 81).

[f]Number of responders: LAG-3 ≥1%, NIVO + RELA + chemo (n = 51) and NIVO + chemo (n = 55); LAG-3 <1%, NIVO + RELA + chemo (n = 13) and NIVO + chemo (n = 16); all randomly assigned NIVO + RELA + chemo (n = 64) and NIVO + chemo (n = 71).

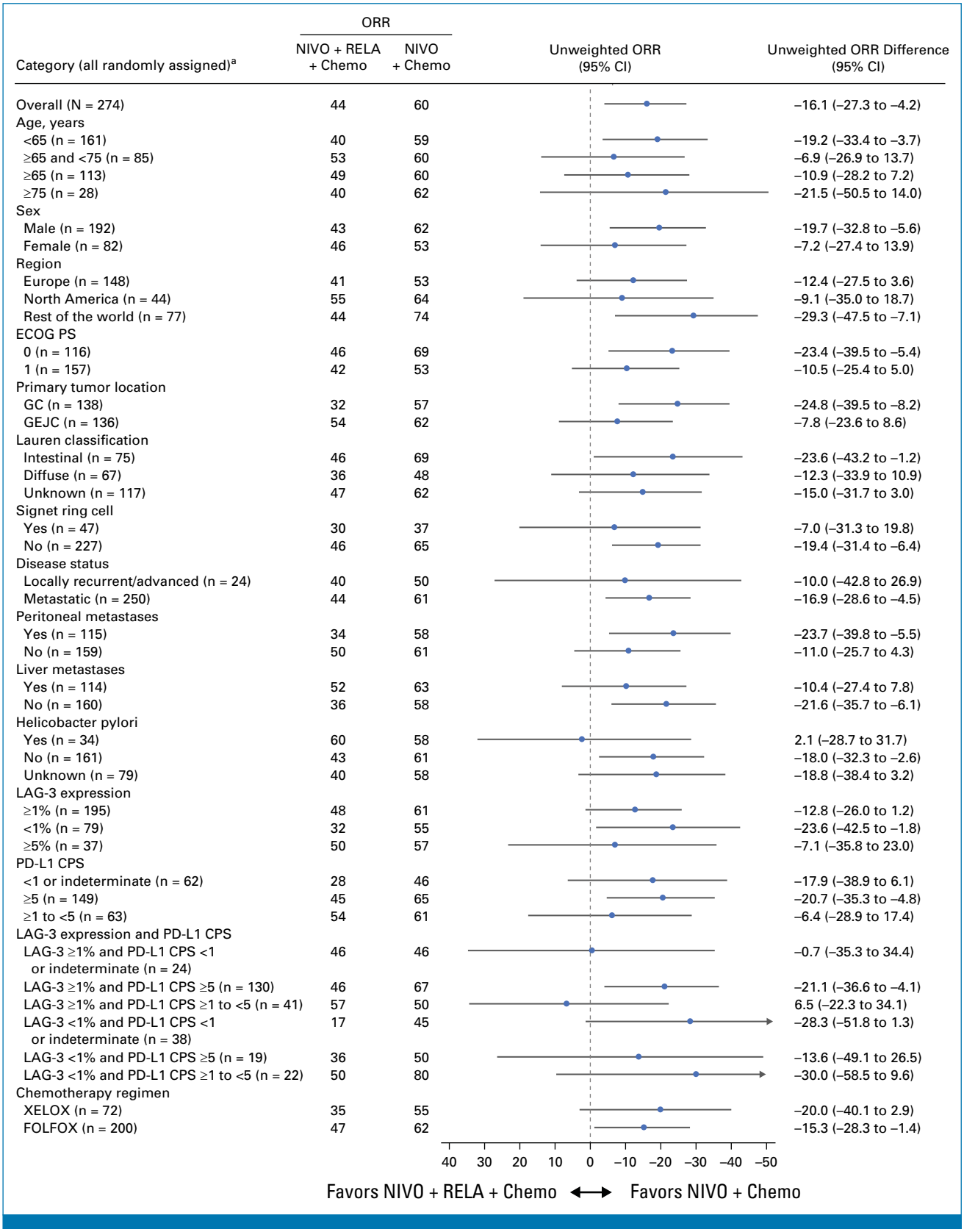

FIG 2. Subgroup analysis of unweighted ORR difference per BICR in all randomly assigned patients. Two-sided 95% CI for unweighted difference was calculated using Newcombe method. ORR difference is not computed for subsets with <10 patients in at least one treatment group. ORR difference: NIVO plus RELA minus NIVO. [a]ORR difference was not computed for (continued on following page)

FIG 2. (Continued). subset category with <10 patients in at least one treatment group. BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, oxaliplatin + leucovorin + fluorouracil; GC, gastric cancer; GEJC, gastroesophageal junction cancer; LAG-3, lymphocyte-activation gene 3; NIVO, nivolumab; ORR, objective response rate; RELA, relatlimab; XELOX, oxaliplatin + capecitabine.

BICR-assessed disease control rate (DCR) was 92% in the nivolumab + relatlimab + chemotherapy arm and 85% in the nivolumab + chemotherapy arm, and patients with LAG-3 expression <1% had DCR of 78% and 89%, respectively (Table 2). Results per INV are shown in Table 2.

PFS and OS

Median PFS (mPFS; 95% CI) by BICR in the nivolumab + relatlimab + chemotherapy arm versus the nivolumab + chemotherapy arm, respectively, was 7.0 months (5.8 to 8.4) versus 8.3 months (6.9 to 12.1) for patients with LAG-3 expression ≥1% (hazard ratio [HR], 1.41 [95% CI, 0.97 to 2.05]; Fig 3A), 6.6 months (4.7 to 7.1) versus 9.7 months (6.9 to 13.7) for patients with LAG-3 expression <1% (HR, 2.15 [95% CI, 1.23 to 3.76]; Fig 3B), and 6.8 months (5.8 to 7.3) versus 9.4 months (7.0 to 11.5) for all randomly assigned patients (HR, 1.61 [95% CI, 1.18 to 2.20]; Fig 3C). Similar results were observed for PFS by INV (Table 2). BICR-assessed PFS favored nivolumab + chemotherapy over nivolumab + relatlimab + chemotherapy across the majority of prespecified subgroups (Data Supplement, Fig S1A).

Median OS (mOS; 95% CI) in the nivolumab + relatlimab + chemotherapy arm versus the nivolumab + chemotherapy arm, respectively, was 13.5 months (11.9 to 19.1) versus 16.0 months (10.9 to not estimable) for patients with LAG-3 expression ≥1% (HR, 1.04 [95% CI, 0.70 to 1.54]; Fig 4A), 9.7 months (6.6 to 12.8) versus 16.8 months (11.4 to 17.6) for patients with LAG-3 expression <1% (HR, 2.16 [95% CI, 1.23 to 3.82]; Fig 4B), and 12.4 months (10.7 to 14.4) versus 15.5 months (11.8 to 17.2) for all randomly assigned patients (HR, 1.32 [95% CI, 0.96 to 1.83]; Fig 4C). OS favored nivolumab + chemotherapy over nivolumab + relatlimab + chemotherapy across the majority of prespecified subgroups (Data Supplement, Fig S1B).

Safety

Any-grade TRAEs were reported for 124 (91%) patients (grade 3/4, n = 94 [69%]; grade 5, n = 0) in the nivolumab + relatlimab + chemotherapy arm and 129 (96%) patients (grade 3/4, n = 82 [61%]; grade 5, n = 1 [<1%]) in the nivolumab + chemotherapy arm (Table 3). The most frequently reported grade 3/4 TRAEs were neutropenia (21%), fatigue (7%), diarrhea (4%), peripheral neuropathy (4%), and anemia (4%) in the nivolumab + relatlimab + chemotherapy arm and neutropenia (17%), fatigue (7%), peripheral neuropathy (7%), and diarrhea (6%) in the nivolumab + chemotherapy arm. Serious any-grade TRAEs were reported in 38% (grade 3/4, 34%) of patients in the nivolumab + relatlimab + chemotherapy arm and 28% (grade 3/4, 26%; grade 5, <1%) of patients in the nivolumab + chemotherapy arm. Any-grade TRAEs leading to discontinuation were reported in 42% (grade 3/4, 21%) of patients in the nivolumab + relatlimab + chemotherapy arm and 36% (grade 3/4, 19%) of patients in the nivolumab + chemotherapy arm (Table 3). The most common any-grade TRAEs leading to discontinuation were peripheral neuropathy (7% *v* 10%) and peripheral sensory neuropathy (5% *v* 4%) in the nivolumab + relatlimab + chemotherapy arm and in the nivolumab + chemotherapy arm, respectively.

Most IMAEs were grade 1/2 in either treatment arm (Table 3). The most frequent grade 3/4 IMAEs were diarrhea/colitis (3%) for the nivolumab + relatlimab + chemotherapy arm and pneumonitis (4%) for the nivolumab + chemotherapy arm.

Three deaths (autoimmune encephalitis, lung infection, and acute renal failure) in the nivolumab + relatlimab + chemotherapy arm and one death (acute renal insufficiency) in the nivolumab + chemotherapy arm were considered treatment-related.

Exploratory Analyses

Exploratory analysis by LAG-3 and PD-L1 CPS status was performed. Results were consistent with the overall population, except for limited subgroups. Patients with LAG-3 expression ≥5% (n = 37) had mPFS per BICR of 13.1 months in the nivolumab + relatlimab + chemotherapy arm versus 6.9 months in the nivolumab + chemotherapy arm (unstratified HR, 0.75 [95% CI, 0.32 to 1.77]); mOS was not reached in both arms (Data Supplement, Fig S1). Patients with LAG-3 expression ≥1% combined with PD-L1 CPS ≥1 to <5 (n = 41) had mPFS of 8.3 months in the nivolumab + relatlimab + chemotherapy arm versus 8.3 months in the nivolumab + chemotherapy arm (unstratified HR, 0.69 [95% CI, 0.30 to 1.56]; Data Supplement, Fig S1A) and mOS of 15.0 months in the nivolumab + relatlimab + chemotherapy arm versus 11.2 months in the nivolumab + chemotherapy arm (unstratified HR, 0.66 [95% CI, 0.28 to 1.53]; Data Supplement, Fig S1B).

Previous reports demonstrated that LAG-3 can be present in soluble form; therefore, the pharmacodynamic (PD) effect of relatlimab on free soluble LAG-3 (sLAG-3) was

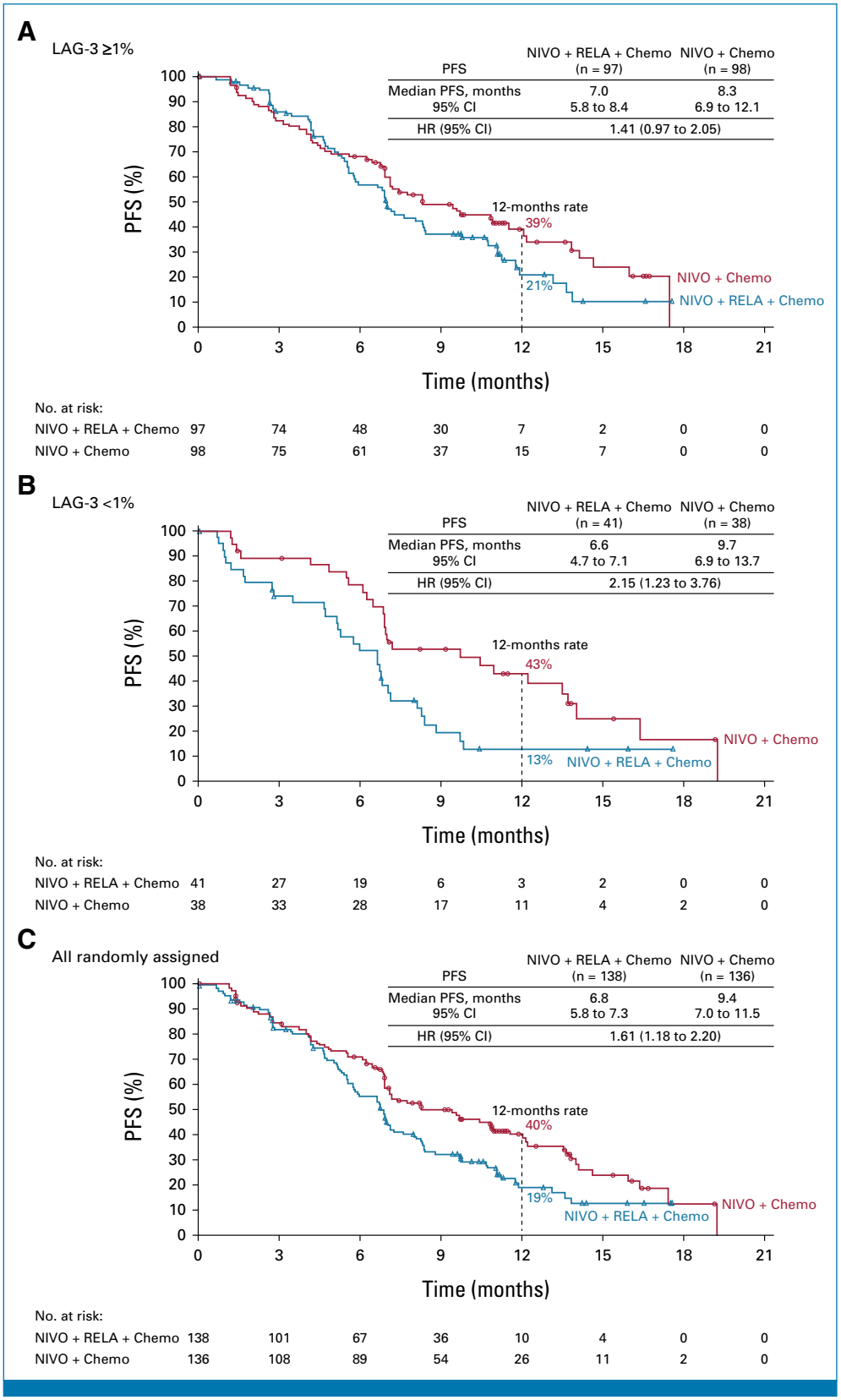

FIG 3. Kaplan-Meier estimates of PFS per BICR. (A) Patients with LAG-3 expression ≥1%; (B) patients with LAG-3 expression <1%; and (C) all randomly assigned patients. Symbols represent censored observations. BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; LAG-3, lymphocyte-activation gene 3; NIVO, nivolumab; PFS, progression-free survival; RELA, relatlimab.

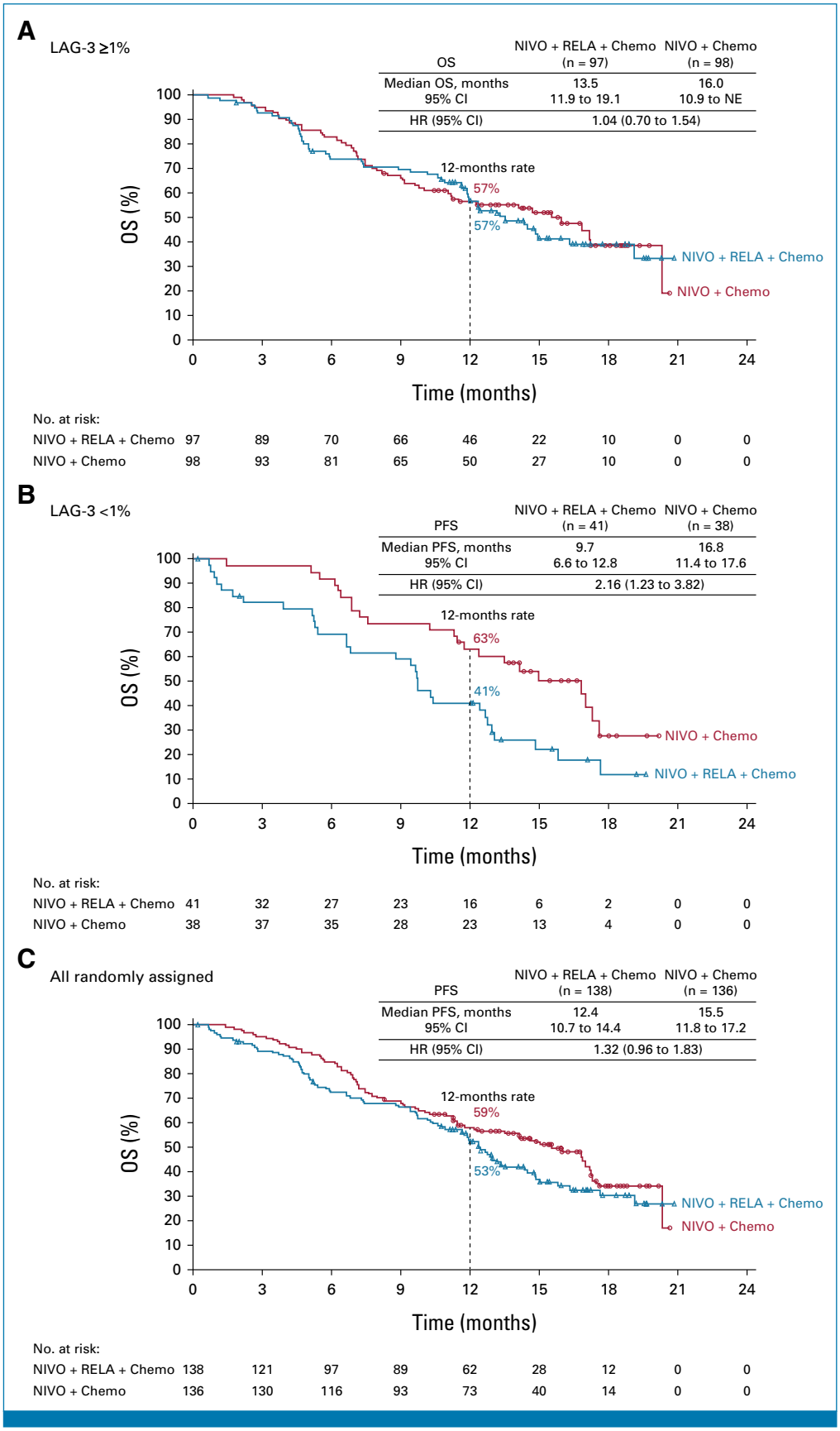

FIG 4. Kaplan-Meier estimates of OS. (A) Patients with LAG-3 expression ≥1%; (B) patients with LAG-3 expression <1%; and (C) all randomly assigned (continued on following page)

FIG 4. (Continued). patients. Symbols represent censored observations. Chemo, chemotherapy; HR, hazard ratio; LAG-3, lymphocyte-activation gene 3; NE, not estimable; NIVO, nivolumab; OS, overall survival; RELA, relatlimab.

investigated.[19,20] Free and total sLAG-3 were identified as relatlimab-specific PD biomarkers (Data Supplement, Figs S2A and S2B). Additionally, regardless of response, there was a trend of higher increase in interferon gamma, C-X-C motif chemokine ligand 9, and C-X-C motif chemokine ligand 10 after treatment with nivolumab + relatlimab + chemotherapy relative to nivolumab + chemotherapy (Data Supplement, Figs S2C-S2E).

TABLE 3. Summary of AEs in All Treated Patients

	NIVO + RELA + Chemo (n = 136), No. (%)		NIVO + Chemo (n = 135), No. (%)	
Patient	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any AE[a]	135 (99)	118 (87)	135 (100)	115 (85)
Serious AEs	95 (70)	84 (62)	82 (61)	71 (53)
AEs leading to discontinuation[b]	72 (53)	44 (32)	56 (41)	28 (21)
Any TRAE[a]	124 (91)	94 (69)	129 (96)	82 (61)
Serious TRAEs[a]	52 (38)	46 (34)	38 (28)	35 (26)
TRAEs leading to discontinuation[b]	57 (42)	29 (21)	48 (36)	25 (19)
TRAEs reported in ≥15% of patients in either arm				
Nausea	53 (39)	2 (1)	63 (47)	5 (4)
Fatigue	52 (38)	10 (7)	58 (43)	9 (7)
Diarrhea	41 (30)	5 (4)	45 (33)	8 (6)
Neutropenia	36 (26)	28 (21)	37 (27)	23 (17)
Neuropathy peripheral	30 (22)	5 (4)	43 (32)	10 (7)
Vomiting	28 (21)	0	34 (25)	4 (3)
Anemia	26 (19)	5 (4)	16 (12)	5 (4)
Peripheral sensory neuropathy	24 (18)	3 (2)	29 (21)	1 (<1)
Decreased appetite	23 (17)	3 (2)	23 (17)	0
Hypothyroidism	21 (15)	0	16 (12)	1 (<1)
Thrombocytopenia	18 (13)	1 (<1)	24 (18)	3 (2)
Platelet count decreased	12 (9)	1 (<1)	22 (16)	2 (1)
Immune-mediated AE[c]				
Hypothyroidism	19 (14)	0	15 (11)	1 (<1)
Rash	13 (10)	3 (2)	6 (4)	1 (<1)
Hyperthyroidism	8 (6)	1 (<1)	3 (2)	0
Diarrhea/colitis	5 (4)	4 (3)	5 (4)	3 (2)
Hepatitis	5 (4)	3 (2)	3 (2)	3 (2)
Adrenal insufficiency	4 (3)	2 (1)	1 (<1)	0
Pneumonitis	4 (3)	0	9 (7)	5 (4)
Hypophysitis	3 (2)	2 (1)	0	0
Diabetes mellitus	3 (2)	2 (1)	2 (1)	1 (<1)
Thyroiditis	2 (1)	1 (<1)	0	0

NOTE. Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of trial therapy. Treatment-relatedness was attributed to either nivolumab, relatlimab, or any of the chemotherapies, or all. Common Terminology Criteria for Adverse Events, version 5.0, and Medical Dictionary for Regulatory Activities, version 23.0.

Abbreviations: AE, adverse event; chemo, chemotherapy; NIVO, nivolumab; RELA, relatlimab; TRAE, treatment-related AE.

[a]Grade 5, n = 1 (NIVO + chemo).

[b]Discontinuation of any or all treatment components.

[c]Includes AEs of any grade occurring in ≥1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

There were no relatlimab treatment-emergent antidrug antibodies, and the incidence of nivolumab treatment-emergent antidrug antibodies was low.

Nivolumab C_{max} and C_{trough} were similar between nivolumab + relatlimab + chemotherapy and nivolumab + chemotherapy arms. Additional details are shown in the Data Supplement.

DISCUSSION

To our knowledge, this is the first report of a dual versus single immunotherapy in combination with chemotherapy in patients with GC/GEJC. RELATIVITY-060 did not meet its primary end point of improved ORR per BICR in patients with LAG-3 expression ≥1%, and ORR was numerically higher in the nivolumab + chemotherapy arm. Secondary end points were also not met, with no benefit for nivolumab + relatlimab + chemotherapy relative to nivolumab + chemotherapy for ORR, PFS, and OS in patients with LAG-3 expression ≥1% and <1% and in the all randomly assigned population. The lower cumulative dose intensity of the chemotherapy component in patients treated with nivolumab + relatlimab + chemotherapy relative to patients treated with nivolumab + chemotherapy may have influenced the efficacy results.

The safety profile of nivolumab + relatlimab + chemotherapy was manageable and consistent with the known safety profiles of immunotherapy and chemotherapy, and no new safety signals were identified. There was a small increase in AEs and IMAEs with the addition of a second immunotherapeutic agent.

Exploratory biomarker analyses identified some subgroups that showed numerical improvement in efficacy in the nivolumab + relatlimab + chemotherapy arm relative to the nivolumab + chemotherapy arm, such as mPFS in patients with LAG-3 expression ≥5% and mPFS and mOS in patients with LAG-3 expression ≥1% combined with PD-L1 CPS ≥1 to <5. In RELATIVITY-047, LAG-3 and PD-L1 expression did not appear to be predictive for clinical benefit with nivolumab + relatlimab over nivolumab monotherapy in patients with advanced melanoma; whether LAG-3 or PD-L1 expression is associated with clinical benefit from relatlimab in patients with gastroesophageal cancer will require further investigation. Melanoma is generally characterized by a high inflammatory tumor microenvironment, and tumors are frequently infiltrated with lymphocytes.[21] By contrast, GC is delineated by heterogeneous levels of inflammation and tumor-infiltrating lymphocytes.[22,23] Additionally, lymphocyte activation status and LAG-3 expression patterns vary among different types of tumor-infiltrating lymphocytes within the tumor microenvironment.[24] Interestingly, approximately 71% to 75% of the patients had LAG-3 expression ≥1% in the RELATIVITY-060 and RELATIVITY-047 studies; however, 14% and 36% of the patients had LAG-3 expression ≥5%, respectively, suggesting potentially different biology. In addition, tumor cell PD-L1 was used in RELATIVITY-047, whereas PD-L1 CPS was used in this study. Therefore, comparisons between the two studies should be made with caution.[25]

Separation of the PFS and OS curves in favor of nivolumab + chemotherapy was more pronounced in the population with LAG-3 expression <1% versus the population with LAG-3 expression ≥1%, possibly indicating a negative interaction when relatlimab was added to nivolumab + chemotherapy in patients with LAG-3 expression <1%. To some extent, this was overcome with higher levels of LAG-3 expression, with mPFS increasing from 6.6 months for patients with LAG-3 expression <1% to 13.1 months for patients with LAG-3 expression ≥5% in the nivolumab + relatlimab + chemotherapy arm.

Several preclinical studies and clinical trials have shown the efficacy of LAG-3–targeting agents on antitumor activity. Most of these studies combined anti–LAG-3 antibodies with additional immune checkpoint inhibitor targets, and studies combining anti–LAG-3 antibodies with chemotherapy are scarce.[24,26]

Our study has limitations that should be considered when interpreting these results. In this open-label phase II study, sample size was relatively small for correlation between biomarkers and efficacy analyses, and because of the exploratory nature, formal statistical comparisons between the arms were not performed.

In conclusion, adding relatlimab to nivolumab + chemotherapy, the current standard of care, did not show improved response in patients with GC/GEJC; however, a trend toward improved PFS in the small subgroup of patients with LAG-3 expression ≥5% was observed and may warrant further investigation. The safety profile of nivolumab + relatlimab + chemotherapy was manageable and consistent with the known safety profiles of dual immunotherapy and chemotherapy; no new safety signals were identified. Additional studies may identify subgroups of patients that could benefit from relatlimab-based therapies to treat unresectable, locally advanced or metastatic GC/GEJC.

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DATA SHARING STATEMENT

The Bristol Myers Squibb data sharing policy (https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html) is compliant with ICMJE guidelines. Bristol Myers Squibb will honor legitimate requests for clinical trial data from qualified researchers. Data will be shared with external researchers whose proposed use of the data has been approved. Complete deidentified patient data sets will be eligible for sharing 2 years after completion of the RELATIVITY-060 study. Before data are released, the researcher(s) must sign a Data Sharing Agreement, after which the deidentified and anonymized data sets can be accessed within a secured portal.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First-Line Nivolumab and Relatlimab Plus Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma: The Phase II RELATIVITY-060 Study

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Consulting or Advisory Role: Novartis, Lilly, AstraZeneca, Bristol Myers Squibb, Merck, Medscape, Takeda, Onc Live, Daiichi Sanyo, EMD Serono, Eisai, Peerview, Astellas Pharma, Ipsen, Philips Healthcare, Toray Industries, Novocure, Grail, Steris, Exact Sciences
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