Pathologic Response of Phase III Study: Perioperative Camrelizumab Plus Rivoceranib and Chemotherapy Versus Chemotherapy for Locally Advanced Gastric Cancer (DRAGON IV/CAP 05)

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ABSTRACT

PURPOSE This multicenter, randomized phase III trial evaluated the efficacy and safety of perioperative camrelizumab (an anti–PD-1 antibody) plus low-dose rivoceranib (a VEGFR-2 inhibitor) and S-1 and oxaliplatin (SOX) (SOXRC), high-dose rivoceranib plus SOX (SOXR), and SOX alone (SOX) for locally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

METHODS Patients with T3-4aN + M0 G/GEJ adenocarcinoma were randomly assigned (1:1:1) to receive perioperative treatment with SOXRC, SOXR, or SOX. The primary end points were pathologic complete response (pCR) and event-free survival. The Independent Data Monitoring Committee recommended stopping enrollment in the SOXR group on the basis of the safety data of the first 103 randomly assigned patients in the three groups. The patients were then randomly assigned 1:1 to the SOXRC or SOX groups. This report presents the pCR results obtained per protocol for the first 360 randomly assigned patients who had the opportunity for surgery in the SOXRC and SOX groups.

RESULTS In the SOXRC and SOX groups, of the 180 patients in each group, 99% and 98% of patients received neoadjuvant therapy, 91% and 94% completed planned neoadjuvant therapy, and 86% and 87% underwent surgery, respectively. The pCR was significantly higher in the SOXRC group at 18.3% (95% CI, 13.0 to 24.8) compared with 5.0% (95% CI, 2.3 to 9.3) in the SOX group (difference of 13.7%; 95% CI, 7.2 to 20.1; odds ratio of 4.5 [95% CI, 2.1 to 9.9]). The one-sided *P* value was <.0001, crossing the prespecified statistical significance threshold of $P = .005$. Surgical complications and grade ≥3 neoadjuvant treatment-related adverse events were 27% versus 33% and 34% versus 17% for SOXRC and SOX, respectively.

CONCLUSION The SOXRC regimen significantly improved pCR compared with SOX alone in patients with G/GEJ adenocarcinoma with a tolerable safety profile.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Gastric cancer represents a major global health issue, with more than one million new cases and 769,000 deaths reported in 2020.[1] For locally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma, perioperative chemotherapy significantly improved overall survival (OS) compared with surgery alone.[2] A phase II randomized study found no significant difference in pathologic response between neoadjuvant fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) and S-1 and oxaliplatin (SOX).[3] Additionally, the RESOLVE and FOCUS trials demonstrated that perioperative SOX had tolerable toxicity and was superior to adjuvant CAPOX in the RESOLVE trial and

CONTEXT

Key Objective

To investigate whether adding an anti–PD-1 antibody and a VEGFR2 inhibitor to chemotherapy improves pathologic complete response (pCR) compared with chemotherapy alone for locally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Knowledge Generated

Combining camrelizumab and rivoceranib with S-1 and oxaliplatin (SOX) significantly improved pCR compared with SOX alone, with a manageable safety profile and without impeding surgery.

Relevance statement *(A.H. Ko)*

While combined PD-1/VEGFR inhibition plus chemotherapy is not ready for routine use in the neoadjuvant setting for G/GEJ cancers, these study findings offer an encouraging early signal of efficacy. Longer-term data focused on oncologic outcomes will determine whether this enhanced strategy has the potential to be adopted into clinical practice.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

noninferior to FOLFOX in the FOCUS trial.[4,5] However, clinical outcomes in patients receiving perioperative chemotherapy need further improvement.[4,6]

Randomized trials, including the phase II DANTE and NEOSUMMIT-01 trials, and the phase III KEYNOTE-585 and MATTERHORN trials, showed an approximately 10% improvement in pathologic complete response (pCR) with chemotherapy plus PD-1/PD-L1 antibodies compared with chemotherapy alone.[7-10] Additionally, the KEYNOTE-585 trial showed a longer median event-free survival (EFS) with pembrolizumab plus chemotherapy versus placebo plus chemotherapy (44.4 *v* 25.3 months), although the difference was not statistically significant. The median OS was 60.7 versus 58.0 months.[9] Survival outcomes from other randomized trials are currently anticipated.

Preclinical evidence suggests that abnormal tumor vasculature, which leads to hypoxia and acidosis, can hinder drug delivery and create an immunosuppressive tumor microenvironment (TME). This environment suppresses immune effector cells and promotes immunosuppressive cells.[11,12] Unlike high doses of antiangiogenic agents, which disrupt the vasculature and worsen immunosuppression, low doses can normalize tumor blood vessels and improve drug delivery, immune cell infiltration, and antitumor activity.[13,14] Antiangiogenic agents combined with PD-1/PD-L1 antibodies are recommended for several cancers, including renal cell carcinoma, non–small cell lung cancer, and hepatocellular carcinoma.[15-21]

Rivoceranib, also known as apatinib, is a tyrosine kinase inhibitor that specifically targets VEGFR2. It exhibits both antitumor and antiangiogenic effects while mitigating TME immunosuppression.[22] In gastric cancer models, rivoceranib reduces tumor-associated neutrophils and enhances the efficacy of nivolumab.[23] Therefore, we hypothesized that low-dose rivoceranib can convert the immunosuppressive TME into an immunostimulatory one, thereby improving immunotherapeutic responses. This could potentially expand the patient population that responds to immunotherapy plus chemotherapy. For instance, the CheckMate 649 trial demonstrated no significant survival benefit between nivolumab plus chemotherapy and chemotherapy alone in the PD-L1 combined positive score (CPS) <1 and <5 subgroups.[24]

Several phase II studies have shown promising results for rivoceranib or camrelizumab (an anti–PD-1 antibody) in combination with chemotherapy or all three in the neoadjuvant setting for gastric cancer.[25-30] However, large-scale confirmatory studies are lacking in this regard. This randomized phase III trial evaluated the efficacy and safety of perioperative low-dose rivoceranib plus camrelizumab and SOX (SOXRC), high-dose rivoceranib plus SOX (SOXR), and SOX alone (SOX) in patients with G/GEJ adenocarcinoma. The Independent Data Monitoring Committee recommended stopping SOXR group enrollment on the basis of the safety data of the first 103 randomly assigned patients in the three groups. Subsequent eligible patients were randomly assigned 1:1 to the SOXRC and SOX groups. We present the pCR results for the first 360 randomly assigned patients in the SOXRC and SOX groups, as prespecified by the protocol. Safety analysis included patients who received the study treatment among the first 360 randomly assigned patients.

METHODS

Patients

Patients who met the following criteria were enrolled in this study: they were age 18-75 years, had pathologically confirmed G/GEJ adenocarcinoma, had an Eastern Cooperative

Oncology Group performance status score of 0-1, had adequate organ function, were clinically staged as T3-4aN + M0 by computed tomography (CT) or magnetic resonance imaging (MRI), were eligible for curative resection by CT or MRI, had not received any previous antitumor treatment, and had an expected survival of ≥12 months. The exclusion criteria included known human epidermal growth factor receptor 2 positivity. Exploratory laparoscopy and peritoneal lavage cytology were not mandatory and were performed at the investigators' discretion. The trial protocol was approved by the responsible ethics committees and all patients provided written informed consent.

Treatments

The patients were randomly assigned in a 1:1:1 ratio using a stratified block permutation randomization method to the SOXRC, SOXR, and SOX groups. Stratification factors included tumor site (stomach *v* GEJ) and bulky nodal status (yes *v* no). After stopping enrollment in the SOXR group, subsequent eligible patients were randomly assigned 1:1 to the SOXRC and SOX groups. The pathologic and safety results in the SOXR group are shown in the Data Supplement (Tables S1 and S2, online only).

The patients received three cycles of neoadjuvant therapy, followed by D2 radical gastrectomy 3-6 weeks after completion of the last dose of neoadjuvant therapy. In the SOX group, patients were administered oxaliplatin intravenously on day 1 (130 mg/m^2) and S-1 orally twice daily for 14 days (40 mg for body surface area [BSA] <1.25 m^2, 50 mg for BSA 1.25-1.5 m^2, or 60 mg for BSA ≥1.5 m^2), once every 3 weeks. In the SOXRC group, patients received camrelizumab intravenously on day 1 (200 mg), rivoceranib orally once daily on days 1-21 (250 mg), and the SOX regimen, once every 3 weeks. In the SOXR group, patients received rivoceranib orally once daily on days 1-21 (500 mg) and the SOX regimen, once every 3 weeks. Notably, in both the SOXRC and SOXR groups, rivoceranib was administered for only 14 days during the third cycle of neoadjuvant therapy.

Patients received three cycles of adjuvant therapy 4-6 weeks after surgery, using the same regimen as their neoadjuvant therapy. Subsequently, patients in the SOXRC group received three additional cycles of camrelizumab plus rivoceranib, while those in the SOXR group received three additional cycles of rivoceranib. After these treatments, investigators could decide whether to continue rivoceranib plus camrelizumab or rivoceranib, with a maximum duration of 1 year for rivoceranib and 17 doses for camrelizumab during the entire course of therapy. In the SOX groups, investigators could decide whether to continue S-1 for up to 1 year during the entire treatment course.

End Points and Assessments

The primary end points were the rate of pCR (ypT0) assessed by a blinded independent review committee (BIRC) and EFS assessed by investigators. Secondary end points included major pathologic response (MPR) and total pCR (ypT0N0) assessed by BIRC, lymph node status after neoadjuvant therapy (ypN staging), R0 resection rate, disease-free survival, OS, and safety. An exploratory end point was to evaluate potential predictive biomarkers for treatment response. Definitions of end points, detailed assessments, and biomarker analyses are provided in the Data Supplement.

Statistical Analysis

The graphical method was used to control the family-wise type I error rate (one-sided alpha = .025) across the pCR and EFS. An initial one-sided alpha of .005 and .02 was allocated to pCR and EFS, respectively. If the between-group difference in pCR was significant, a comparison of EFS would be performed at a one-sided alpha of .025. With a pCR rate of 5% anticipated in the SOX group,[4] the SOXRC group was projected to reach 17%. To detect this difference with a minimum of 80% power at a one-sided alpha of .005, 153 patients were required per group. Considering a 15% dropout rate, enrollment needed to be 180 patients per group, totaling 360 for prespecified pCR analysis. Assuming the median EFS for SOX at 25 months and hypothesizing 0.7 hazard ratio of SOXRC compared with SOX, approximately 268 events would achieve 80% power to discriminate the difference in EFS at a one-sided alpha of .02. Including an estimated 15% dropout rate, the overall enrollment had to include 512 patients. This report emphasizes the pCR analysis, with at least 80% power ensured by 360 patients who had the opportunity for surgery in the SOXRC and SOX groups, with the current cutoff for reported data being April 19, 2023. Interim EFS assessment is scheduled. The other statistical methods are detailed in the Data Supplement.

RESULTS

Patients

Between December 18, 2019 and December 31, 2022, patients were randomly allocated into either the SOXRC group (n = 180) or the SOX group (n = 180). In the SOXRC group, 179 patients (99%) received neoadjuvant therapy, 164 (91%) completed all three cycles of neoadjuvant therapy, and 155 (86%) underwent surgery. In the SOX group, 177 patients (98%) received neoadjuvant therapy, 169 (94%) completed the planned neoadjuvant therapy, and 156 (87%) underwent surgery (Fig 1). A summary of the neoadjuvant therapy is presented in the Data Supplement (Table S3). Among the patients who did not undergo surgery, the main reasons were refusal (15 [8%] patients in the SOXRC group *v* 12 [7%] in the SOX group) and imaging evaluation indicating that surgery was not feasible (6 [3%] *v* 11 [6%]).

The baseline characteristics were balanced between the two groups. Most patients had the stomach as the primary tumor site (125 patients [69%] in the SOXRC group and 132 [73%] in

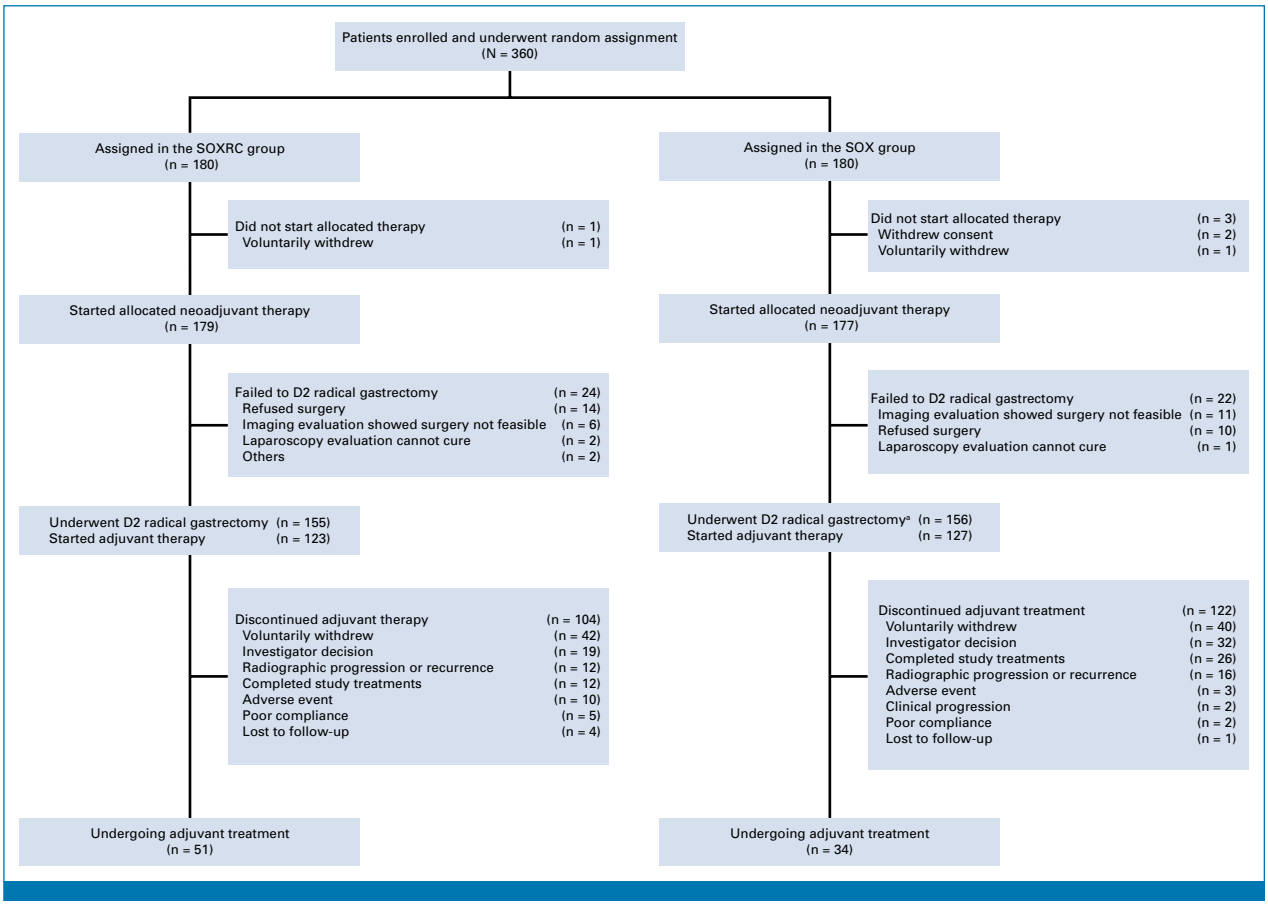

FIG 1. CONSORT diagram. [a]One patient in the SOX group did not receive the study drugs but underwent D2 radical resection for gastric cancer. SOX, S-1 and oxaliplatin; SOXRC, perioperative low-dose rivoceranib plus camrelizumab and SOX.

the SOX group) and had T4a stage tumor (117 [65%] *v* 121 [67%]). Additionally, in the SOXRC and SOX groups, 85 (47%) and 92 (51%) patients had PD-L1 CPS ≥1, 38 (21%) and 42 (23%) had PD-L1 CPS ≥5, 16 (9%) and 14 (8%) patients had deficient mismatch repair (dMMR), and 32 (18%) and 20 (11%) had signet-ring cell carcinoma, respectively (Table 1).

Efficacy

The pCR (ypT0) analysis was conducted in the intention-to-treat population at the cut-off date of April 19, 2023. The SOXRC group had a statistically significantly higher pCR rate than the SOX group assessed by the BIRC: 18.3% (33/180; 95% CI, 13.0 to 24.8) versus 5.0% (9/180; 95% CI, 2.3 to 9.3), with a difference of 13.7% (95% CI, 7.2 to 20.1) and an odds ratio of 4.5 (95% CI, 2.1 to 9.9). The one-sided *P* value was <.0001, which crossed the prespecified statistical criterion of $P = .005$ (Fig 2). Similarly, the SOXRC group had a higher MPR rate than the SOX group: 51.1% (92/180; 95% CI, 43.6 to 58.6) versus 37.8% (68/180; 95% CI, 30.7 to 45.3), with a difference of 13.6% (95% CI, 3.4 to 23.8). Higher total pCR (ypT0N0) rates were observed in the SOXRC group (16.7% [30/180]; 95% CI, 11.5 to 22.9) than in the SOX group (4.4% [8/180]; 1.9 to 8.6; Table 2).

The subgroup analysis of pCR on the basis of baseline characteristics showed similar trends to those of the primary analysis. For PD-L1 CPS <1, the pCR rate was 19.0% versus 0; for PD-L1 CPS <5, 16.2% versus 4.0%; and for PD-L1 CPS ≥5, 28.9% versus 7.1%. In the dMMR subgroup, the pCR rate was 43.8% versus 7.1%, and in the proficient mismatch repair (pMMR) subgroup, it was 16.5% versus 4.8%. For Epstein-Barr virus (EBV)–positive patients, pCR rates were 25.0% versus 0%, and for EBV-negative patients, pCR rates were 18.1% versus 5.1% (Fig 2).

Among patients who underwent surgery, in the SOXRC and SOX groups, the pCR was 21.3% (33/155; 95% CI, 15.1 to 28.6) and 5.8% (9/156; 95% CI, 2.7 to 10.7), the total pCR rate was 19.4% (30/155; 95% CI, 13.5 to 26.5) and 5.1% (8/156; 95% CI, 2.2 to 9.9), and the MPR rate was 59.4% (92/155; 95% CI, 51.2 to 67.2) and 43.6% (68/156; 95% CI, 35.7 to 51.8), respectively. Moreover, the R0 resection rate was 99% (153/155) in the SOXRC group versus 94% (147/156) in the SOX group, and the D2 lymphadenectomy rate was 96% (149/155) versus 97% (151/156) in the respective groups. Similar surgical outcomes were observed between the two groups in terms of the type of surgery, surgical duration, number of lymph nodes removed, and length of hospitalization (Table 2).

TABLE 1. Baseline Characteristics

Characteristic	SOXRC Group (n = 180)	SOX Group (n = 180)
Age, years		
<65, No. (%)	101 (56)	112 (62)
≥65, No. (%)	79 (44)	68 (38)
Median (range)	63.0 (28.0-75.0)	63.0 (34.0-75.0)
Sex, No. (%)		
Male	151 (84)	145 (81)
Female	29 (16)	35 (19)
ECOG performance status, No. (%)		
0	101 (56)	93 (52)
1	79 (44)	87 (48)
Primary tumor location, No. (%)		
Gastroesophageal junction	55 (31)	48 (27)
Stomach	125 (69)	132 (73)
Bulky nodal status, No. (%)		
Yes	6 (3)	7 (4)
No	174 (97)	173 (96)
Adenocarcinoma, No. (%)	180 (100)	180 (100)
Signet-ring cell carcinoma	32 (18)	20 (11)
Clinical T stage, No. (%)		
T3	61 (34)	59 (33)
T4a	117 (65)	121 (67)
T4b	2 (1)	0
Clinical N stage, No. (%)		
N1	92 (51)	85 (47)
N2	76 (42)	77 (43)
N3	12 (7)	18 (10)
PD-L1 CPS, No. (%)		
<1	58 (32)	50 (28)
≥1	85 (47)	92 (51)
≥5	38 (21)	42 (23)
≥10	18 (10)	22 (12)
Unknown	37 (21)	38 (21)
EBV status, No. (%)		
Positive	8 (4)	6 (3)
Negative	138 (77)	137 (76)
Unknown	34 (19)	37 (21)
MMR status, No. (%)		
pMMR	127 (71)	124 (69)
dMMR	16 (9)	14 (8)
Unknown	37 (21)	42 (23)
Exploratory laparoscopy, No. (%)		
Yes	76 (42)	92[a] (51)
No	104 (58)	88 (49)
Peritoneal lavage cytology, No. (%)		
Yes	76 (42)	89 (49)
No	104 (58)	91 (51)

Abbreviations: CPS, combined positive score; dMMR, deficient mismatch repair; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; N stage, nodal stage; pMMR, proficient mismatch repair; SOX, S-1 and oxaliplatin; SOXRC, perioperative low-dose rivoceranib plus camrelizumab and SOX; T stage, tumor stage.

[a]In the SOX group, three patients underwent only exploratory laparoscopy and did not undergo peritoneal lavage cytology.

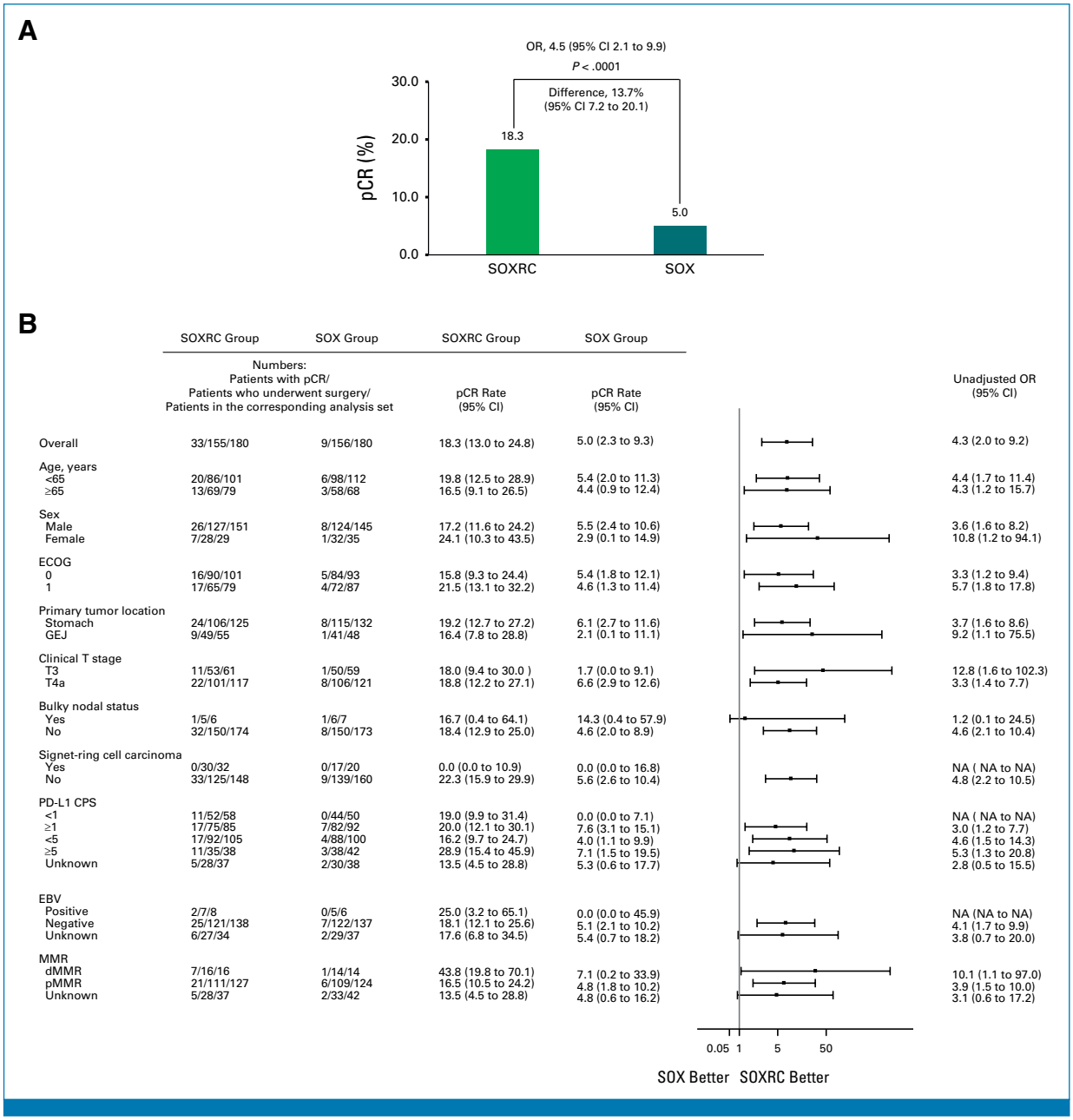

FIG 2. Pathologic complete response in the intention-to-treat population as assessed by the blinded independent review committee. (A) The analysis of pathologic complete response, and the difference between the two groups was calculated using a stratified Cochran-Mantel-Haenszel method. (B) Pathologic complete response in prespecified subgroups on the basis of the baseline characteristics. CPS, combined positive score; dMMR, deficient mismatch repair; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; MMR, mismatch repair; NA, not available; OR, odds ratio; pCR, pathologic complete response; pMMR, proficient mismatch repair; SOX, S-1 and oxaliplatin; SOXRC, perioperative low-dose rivoceranib plus camrelizumab and SOX.

Safety

In the neoadjuvant phase, treatment-related adverse events (TRAEs) of any grade occurred in 157 patients (88%) in the SOXRC group and in 142 patients (80%) in the SOX group; grade ≥3 TRAEs occurred in 60 (34%) and 30 (17%) in the respective groups. These TRAEs resulted in interruption/delay/dose reduction of any study drug in 74 patients (41%) versus 47 patients (26%); permanent discontinuation of any study drug occurred in nine (5%) versus one (1%), respectively. TRAEs did not result in any death in either group (Table 3).

Immune-related adverse events (irAEs) were only reported in the SOXRC group. During neoadjuvant therapy, any grade irAEs occurred in 40 patients (22%), with grade 1-2 irAEs

TABLE 2. Pathologic and Surgical Outcomes

Intention-to-Treat Population	SOXRC Group (n = 180)	SOX Group (n = 180)
Pathologic complete response (ypT0) rate	18.3% (95% CI, 13.0 to 24.8)	5.0% (95% CI, 2.3 to 9.3)
Total pathologic complete response (ypT0N0) rate	16.7% (95% CI, 11.5 to 22.9)	4.4% (95% CI, 1.9 to 8.6)
Major pathologic response rate	51.1% (95% CI, 43.6 to 58.6)	37.8% (95% CI, 30.7 to 45.3)
Pathologic tumor regression grade, No. (%)		
Grade 1a	33 (18)	9 (5)
Grade 1b	59 (33)	59 (33)
Grade 2	40 (22)	47 (26)
Grade 3	14 (8)	35 (19)
Not evaluable[a]	9 (5)	6 (3)
ypT stage and ypN stage, No. (%)		
ypT0	33 (18)	9 (5)
ypT1	19 (11)	20 (11)
ypT2	8 (4)	27 (15)
ypT3	63 (35)	66 (37)
ypT4a	22 (12)	27 (15)
ypT4b	1 (1)	1 (1)
ypN0	83 (46)	66 (37)
ypN1	23 (13)	35 (19)
ypN2	20 (11)	22 (12)
ypN3	20 (11)	27 (15)
Not evaluable[a]	9 (5)	6 (3)

The Surgical Population	SOXRC Group (n = 155)	SOX Group (n = 156)
Type of surgery, No. (%)		
Distal gastrectomy	92 (59)	106 (68)
Proximal gastrectomy	4 (3)	1 (1)
Total gastrectomy	59 (38)	49 (31)
Lymphadenectomy, No. (%)		
D2	149 (96)	151 (97)
Others	6 (4)	5 (3)
Resection, No. (%)		
R0	153 (99)	147 (94)
R1	1 (1)	4 (3)
R2	1 (1)	5 (3)
Surgery duration, hours		
Median	3.5	3.5
Minimum-maximum	1.9-7.0	1.6-8.4
Length of hospitalization, days		
Median	10	11
Minimum-maximum	6-60	6-67
No. of lymph nodes removed		
Median	32	29
Minimum-maximum	8-125	8-91

NOTE. The tumor regression grade was evaluated according to the Becker classification system. ypT and ypN staging were assessed according to the eighth edition of the AJCC guidelines.

Abbreviations: AJCC, American Joint Committee on Cancer; SOX, S-1 and oxaliplatin; SOXRC, perioperative low-dose rivoceranib plus camrelizumab and SOX.

[a]Pathologic results were not available for patients who underwent surgery.

TABLE 3. TRAEs With Neoadjuvant Therapy

	SOXRC Group (n = 179), No. (%)			SOX Group (n = 178), No. (%)		
TRAE	Any Grade	Grade 1-2	Grade ≥3	Any Grade	Grade 1-2	Grade ≥3
Any adverse event	157 (88)	97 (54)	60 (34)	142 (80)	112 (63)	30 (17)
Neutrophil count decreased	89 (50)	68 (38)	21 (12)	53 (30)	45 (25)	8 (4)
WBC count decreased	88 (49)	83 (46)	5 (3)	49 (28)	48 (27)	1 (1)
Platelet count decreased	66 (37)	51 (28)	15 (8)	56 (31)	43 (24)	13 (7)
Nausea	38 (21)	35 (20)	3 (2)	23 (13)	23 (13)	0
Vomiting	31 (17)	30 (17)	1 (1)	37 (21)	37 (21)	0
AST increased	30 (17)	28 (16)	2 (1)	37 (21)	36 (20)	1 (1)
Diarrhea	27 (15)	25 (14)	2 (1)	22 (12)	18 (10)	4 (2)
Anemia	25 (14)	21 (12)	4 (2)	24 (13)	22 (12)	2 (1)
Decreased appetite	25 (14)	25 (14)	0	18 (10)	18 (10)	0
Blood lactate dehydrogenase increased	23 (13)	23 (13)	0	20 (11)	20 (11)	0
Hypertension	23 (13)	15 (8)	8 (4)	0	0	0
ALT increased	20 (11)	20 (11)	0	24 (13)	24 (13)	
Proteinuria	20 (11)	20 (11)	0	0	0	0
Blood bilirubin increased	19 (11)	19 (11)	0	10 (6)	10 (6)	0
Asthenia	17 (9)	16 (9)	1 (1)	18 (10)	18 (10)	0

NOTE. The table shows TRAEs that occurred in at least 10% of the patients in the two groups. TRAEs were graded according to the Common Terminology Criteria for Adverse Events (version 5.0).
Abbreviations: SOX, S-1 and oxaliplatin; SOXRC, perioperative low-dose rivoceranib plus camrelizumab and SOX; TRAEs, treatment-related adverse events.

occurring in 29 (16%), and grade ≥3 irAEs occurring in 11 (6%) (Data Supplement, Table S4). Surgical complications of any grade occurred in 42 patients (27%) in the SOXRC group and 52 (33%) in the SOX group; 10 (6%) and seven (4%) in the respective groups had complications of grade ≥3. Most surgical complications were mild or moderate (Data Supplement, Table S5). As of the cutoff date, TRAEs and irAEs throughout the treatment period were analyzed. Details of the AE incidence are provided in the Data Supplement (Tables S6 and S7).

DISCUSSION

The DRAGON IV/CAP 05 trial showed that adding low-dose rivoceranib and camrelizumab to SOX significantly improved pCR compared with SOX alone, meeting the end point of pCR. Additionally, this regimen was well tolerated and did not compromise the surgical feasibility.

In this trial, the pCR rate in the SOX group was consistent with the rates in the SOX groups of the RESOLVE and FOCUS trials,[4,5] suggesting the validity of the control group in this trial. Notably, the pCR rate in the SOXRC group was higher than that in the historical data for neoadjuvant camrelizumab plus SOX (10.3%) or rivoceranib plus SOX (13.8% or 6.3%).[27,28,31] It was similar to rivoceranib plus camrelizumab and chemotherapy (15.8% in a single-arm phase II study and 15.7% in a randomized phase II study versus 6.7% in the camrelizumab plus chemotherapy group versus 5.7% in the chemotherapy group).[29,30] Moreover, the SOXRC group showed higher rates of total pCR, MPR, and a higher proportion of patients with ypN0 stage disease than the SOX group.

Four randomized trials investigating perioperative PD-1/PD-L1 antibody plus chemotherapy for gastric cancer have reported pathologic outcomes. A randomized phase II study indicated that the combination of toripalimab and chemotherapy resulted in a pCR of 22.2% compared with 7.4% for chemotherapy alone.[8] The phase II portion of the randomized phase II/3 DANTE trial also demonstrated superior pCR for perioperative atezolizumab plus chemotherapy, as opposed to chemotherapy (24% *v* 15%).[7] Furthermore, the phase III KEYNOTE-585 and MATTERHORN trials showed enhanced pCR when pembrolizumab and durvalumab were combined with chemotherapy, respectively, in comparison with placebo plus chemotherapy (12.9% *v* 2.0% and 19% *v* 7%).[9,10] This trial and the phase III MATTERHORN trial achieved superior pCR, but this trial had a higher odds ratio between the experimental and control groups than the MATTERHORN trial (4.5 *v* 3.08).[10] However, cross-comparisons between different trials should be made with cautious interpretation because of inherent differences in study design, patient populations, and other potential confounding factors. Definitive conclusions regarding the superiority of any regimen over another require further investigation.

Although pCR is a promising early indicator of treatment efficacy, it is imperative to highlight that survival outcomes

are the ultimate measure of clinical efficacy. In the FLOT4 trial, the superior performance of FLOT in terms of pCR eventually translated into a significant OS benefit.[32] The KEYNOTE-585 trial, which demonstrated improved pCR with pembrolizumab plus chemotherapy, did not show a statistically significant increase in the EFS.[9] We emphasize that future survival analyses in this study will be crucial for definitively assessing the clinical benefits of the current regimen.

Moreover, the phase III portion of the DANTE trial is enrolling only patients with specific biomarkers (PD-L1 CPS ≥1, MSI-high status, EBV-positive status, or high tumor mutational burden).[33] This decision was based on phase II results, where these groups showed better responses to atezolizumab plus chemotherapy compared with chemotherapy alone (33% *v* 12% in the PD-L1 CPS >10 subgroup, 63% *v* 27% in the MSI-high status subgroup).[7] In the phase III KEYNOTE-585 and MATTERHORN trials, pCR showed no obvious improvement in patients with a PD-L1 CPS <1.[9,10] This trial indicated a trend toward enhanced pCR with rivoceranib plus camrelizumab and SOX compared with SOX alone, regardless of PD-L1 expression. However, the highest odds ratio for pCR was observed in the PD-L1 CPS ≥5 subgroup, while the odds ratio in the PD-L1 CPS <1 subgroup was not estimated because no patients in the SOX group achieved pCR. Additionally, besides patients with dMMR and EBV-positive status, improvement in pCR was observed in patients with pMMR and EBV-negative status. However, given the limited sample size of these subgroups, these results should be interpreted with caution.

The SOXRC and SOX groups in this trial had similar rates of completion of three cycles of neoadjuvant treatment (91% *v* 94%) and surgery (86% *v* 87%). Therefore, the addition of camrelizumab and rivoceranib may contribute to a significant improvement in pCR. Moreover, this trial showed comparable surgical outcomes and postoperative complications between the two groups, consistent with the findings of the RESOLVE, FOCUS, and KEYNOTE-585 trials.[4,5,9] The SOXRC group had a higher incidence of grade ≥3 neoadjuvant TRAEs (34% *v* 17%) than the SOX group, but they were all manageable. This increase was associated with higher incidences of neutrophil count decrease (12% *v* 4%) and hypertension (4% *v* 0%) in the SOXRC group. The increased neutrophil count decrease was likely because of the combined use of targeted, immune, and chemotherapeutic agents, while the increased hypertension was likely because it is a TRAE of special interest for rivoceranib.[34] Furthermore, most of the neoadjuvant irAEs that occurred in the SOXRC group were grade 1-2. Reactive cutaneous capillary endothelial proliferation (RCCEP), the most common camrelizumab-related irAE, had a low incidence, and all cases were grade 1 or 2. Its incidence was lower than that reported for camrelizumab monotherapy,[35,36] but similar to that of camrelizumab plus rivoceranib and chemotherapy.[29,30,37] Rivoceranib may prevent RCCEP by improving vascular normalization and reducing vascular occlusion.[38,39] These results showed that camrelizumab combined with rivoceranib and chemotherapy was well tolerated.

The DRAGON IV/CAP 05 trial had some limitations. First, it lacked a camrelizumab plus SOX group, which would have better evaluated the contribution of rivoceranib to the improved pCR, although the combination of camrelizumab, rivoceranib, and SOX achieved a higher pCR than camrelizumab plus chemotherapy (10.3%) in a phase II study.[25] Second, this trial had an open-label design, which could lead to bias in treatment assignment and assessment. Therefore, BIRC conducted the pathologic evaluation. Third, this trial enrolled patients only from China and did not include older patients (older than 75 years), which limits the generalizability of the results, particularly to those in Western countries and older patients.

In conclusion, the DRAGON IV/CAP 05 trial showed that the addition of camrelizumab and low-dose rivoceranib to SOX improved the pathologic response in patients with G/GEJ adenocarcinoma. This trial is ongoing to evaluate EFS according to the protocol.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pathologic Response of Phase III Study: Perioperative Camrelizumab Plus Rivoceranib and Chemotherapy Versus Chemotherapy for Locally Advanced Gastric Cancer (DRAGON IV/CAP 05)

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