Perioperative camrelizumab and apatinib combined with chemotherapy for locally advanced gastric cancer in China: three-year survival outcomes of phase 2 randomized controlled trial

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Summary

Background The Arise-FJ-G005 study compared the efficacy and safety of perioperative camrelizumab and apatinib combined with chemotherapy with those of perioperative chemotherapy alone for locally advanced gastric cancer (LAGC) and assessed its effect on major pathological response (MPR). Herein, we report the 3-year survival outcomes of this trial.

Methods Arise-FJ-G005 was a multicenter, open-label, phase 2, randomized controlled trial (NCT 04195828), conducted between June 2020 and March 2022. Patients with LAGC (clinical T2–4, N+, M0) were randomly assigned to receive perioperative CA-SAP (camrelizumab and apatinib combined with nab-paclitaxel plus S-1 [SAP]) or SAP alone for three cycles preoperatively and five cycles postoperatively. The primary endpoint was the MPR. This report focuses on the secondary endpoints of 3-year progression-free survival (PFS) and overall survival (OS).

Findings Between June 18, 2020, and March 31, 2022, 106 patients were randomly assigned to the CA-SAP or the SAP group in a 1:1 ratio, of whom 51 in the CA-SAP and 53 in the SAP group were included in the modified intention-to-treat analysis. The 3-year PFS was 64% (95% confidence [CI]: 52%–79%) and 48% (95% CI: 36%–64%) in the CA-SAP and SAP groups, respectively, with an adjusted hazard ratio (HR) of 0.512 (95% CI: 0.263–0.998). The 3-year OS was 63% (95% CI: 51%–78%) and 61% (95% CI: 49%–77%) in the CA-SAP and SAP groups, respectively (adjusted HR: 0.987, 95% CI: 0.481–2.026). Exploratory analysis revealed heterogeneity in the treatment effect among subgroups according to performance status.

Interpretation Adding camrelizumab and apatinib to perioperative chemotherapy did not result in a meaningful improvement in the 3-year OS of unselected patients with LAGC. Due to its suboptimal tolerability and effectiveness, future research should focus on identifying subpopulations that may benefit from this combination treatment strategy.

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Research in context

Evidence before this study

We searched PubMed and the abstracts of the American Society of Clinical Oncology, European Society for Medical Oncology, and Chinese Society of Clinical Oncology and other major oncology congresses with the keywords "gastric" OR "gastroesophageal junction", "neoadjuvant" OR "perioperative" as well as "PD-1" OR "PD-L1", for articles published between Jan 1, 2020, and June 30, 2025. We identified two phase 3 trials of perioperative PD-1/PD-L1 inhibitors combined with chemotherapy in patients with locally advanced gastric cancer: KEYNOTE-585 and MATTERHORN. The former reported that adding immunotherapy to perioperative chemotherapy did not significantly improve event-free survival, while the latter reported that perioperative immunochemotherapy significantly improved event-free survival compared to perioperative chemotherapy. Another phase 3 trial, DRAGON IV/CAP 05, reported that neoadjuvant chemotherapy combined with immunotherapy and antiangiogenic therapy significantly improved the pathological complete response rate in locally advanced gastric cancer compared to chemotherapy alone. Likely, our group previously demonstrated that neoadjuvant camrelizumab (immunotherapy) and apatinib (antiangiogenic therapy) combined with chemotherapy significantly increased the proportions of patients achieving major pathological response with acceptable safety compared with neoadjuvant chemotherapy alone.

Added value of this study

In this updated report of survival outcomes, for unselected patients with locally advanced gastric cancer, the addition of camrelizumab and apatinib to perioperative chemotherapy was associated with a modestly improved 3-year progression-free survival, but it did not improve the 3-year overall survival and showed suboptimal tolerability. Exploratory analysis revealed heterogeneity in the treatment effect among subgroups according to performance status.

Implications of all the available evidence

The failure of the "one-size-fits-all" strategy for this combination treatment underscores the urgent need for a reliable and precise method to stratify patients based on clinical, pathological, and molecular biomarkers, in order to enable optimal personalized treatment strategies for each individual.

Introduction

Radical surgical resection is the only curative treatment available for locally advanced gastric cancer (LAGC).[1] However, achieving a biologically complete resection without any residual cancer cells remains challenging due to the presence of micrometastases. To address this dilemma, a multidisciplinary treatment strategy, incorporating perioperative chemotherapy, has been adopted. Neoadjuvant chemotherapy enhances the chance of radical resection, eliminates micrometastases early, and enables an assessment of in-vivo response, making it the standard treatment for patients with LAGC in the Western countries and some countries in the Asia–Pacific region.[2–4] Nevertheless, more than half of the patients experience tumor relapse following perioperative chemotherapy and surgery,[5–7] highlighting the urgent need to develop more effective regimens.

Neoadjuvant immunotherapy, which involves administering an immune checkpoint inhibitor prior to surgical resection, represents an emerging strategy in oncology.[8] Compared with adjuvant immunotherapy, neoadjuvant immunotherapy can alleviate the immunosuppressive effects associated with surgical procedures.[9] Currently, neoadjuvant immunotherapy has shown survival benefits in multiple cancer types.[10,11] For LAGC, several randomized controlled trials (RCTs) have demonstrated that adding anti-PD-1/PD-L1 therapy to neoadjuvant chemotherapy significantly improves the pathological complete response (PCR) rate.[12–14] In the interim analysis of the KEYNOTE-585 study, although neoadjuvant immunochemotherapy prolonged the median event-free survival compared with that of neoadjuvant chemotherapy (44.4 vs. 25.3 months), this difference was not statistically significant.[13] The recently published MATTERHORN study reported encouraging results, showing that adding durvalumab to neoadjuvant chemotherapy significantly improved the 2-year event-free survival (67.4% vs. 58.5%).[15] The overall survival (OS) results are immature, and follow-up is still ongoing.

Vascular endothelial growth factor (VEGF) is a biological mediator that has simultaneous tumor angiogenesis and immunosuppressive effects. VEGF indirectly influences antitumor immunity by hindering the infiltration of immune effector cells into tumors. Additionally, it has direct local and systemic immunosuppressive effects. Anti-VEGF therapy has the potential to reverse these immunosuppressive mechanisms, thereby "normalizing" the tumor microenvironment

and enhancing sensitivity to immunotherapy.[16] Several clinical trials have demonstrated that the combined blockade of VEGF and the PD-1/PD-L1 axis has promising antitumor effects in solid tumors,[17–19] suggesting a novel combination strategy.

Anti-PD-1 therapy combined with anti-VEGF therapy and chemotherapy has been shown to have antitumor activity in metastatic gastric cancer,[20,21] but its effect on LAGC remains unclear. Therefore, we conducted a multicenter phase 2 RCT to explore the efficacy and safety of camrelizumab and apatinib combined with chemotherapy compared with chemotherapy alone in the perioperative treatment of LAGC. The primary report demonstrated that adding camrelizumab and apatinib to neoadjuvant chemotherapy significantly improved the major pathological response (MPR).[22] Herein, we report the 3-year survival outcomes.

Methods

Study design and population

Arise-FJ-G005 is a multicenter, open-label, phase 2 RCT conducted in China from June 18, 2020 to March 31, 2022. Details on the eligibility criteria have been reported previously.[22] Briefly, participants were treatment-naive patients with histopathologically confirmed gastric adenocarcinoma, clinically staged as cT2-4, N+, M0, with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1). Additional eligibility criteria included age between 18 and 75 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1, and no active autoimmune disease or history of autoimmune disease. Full inclusion and exclusion criteria are in the protocol. This study was registered with ClinicalTrials.gov (NCT04195828). The results were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Ethics

The study was approved by the ethics committee of the Fujian Medical University Union Hospital (approval number: 2020YF013) and was conducted in adherence to the Declaration of Helsinki. All participants provided written informed consent before undergoing any experimental treatment.

Randomization

After enrollment, participants were randomly assigned in a 1:1 ratio to receive perioperative camrelizumab and apatinib combined with chemotherapy or perioperative chemotherapy alone. Simple randomization was performed, without block or stratification. The randomization sequence was generated by an independent statistician using SAS software, version 9.2 (SAS Institute, Cary, NC, USA). An independent data manager maintained this sequence and communicated the randomization results to clinicians via phone or text message. Both the participants and care providers were aware of the treatment allocation, but the outcome assessors, staff involved in follow-up, and statisticians were blinded to the treatment assignment.

Procedures

All participants underwent a perioperative treatment consisting of three neoadjuvant cycles and five adjuvant cycles, with each cycle lasting 21 days. Any incomplete neoadjuvant cycles were continued postoperatively to complete a total of eight cycles. Chemotherapy consisted of nab-paclitaxel 125 mg/m^2 intravenously on days 1 and 8 combined with S-1 40–60 mg orally twice daily, with the dose based on body surface area, on days 1–14 (SAP group). The CA-SAP group received the same chemotherapy as that of the SAP group, with the addition of camrelizumab (200 mg intravenously on day 1) and apatinib (250 mg orally once daily on days 1–21). D2 gastrectomy was performed by experienced surgeons. During the perioperative treatment, dose modifications (e.g., dose interruption, skip, delay, or reduction) were allowed in cases of grade 3–4 treatment-related adverse events (TRAE) or intolerable grade 2 non-hematologic adverse events. Up to two dose reductions of nab-paclitaxel and S-1 were allowed. Dose escalation was not permitted in participants who had undergone a dose reduction. Dose adjustments of camrelizumab and apatinib were not permitted. The criteria for discontinuation included patient request, disease progression or death, investigator decision, and intolerable adverse events despite dose modification.

The follow-up period started on completion of all study medications. The follow-up procedures included physical examinations, laboratory tests (including measurements of tumor markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen), and imaging (using chest radiography or computed tomography [CT], abdominal ultrasound or CT, and endoscopy). In the first 2 years after surgery, follow-up was conducted every 3 months, and from the third year onwards, follow-up was performed every 6 months. Information on survival status and subsequent treatment was collected through outpatient visits or telephone calls to participants, their family members, or local physicians, until the endpoint of death, loss to follow-up, or study termination. According to the study protocol, all surviving participants were followed up for 3 years after randomization. The evaluation of adverse events continued until 90 days after the last administration of camrelizumab and 30 days after the last administration of the other trial medications. Subsequent antitumor treatments were determined by the investigators and based on the most recent clinical practice guidelines, in particular the 2018 Japanese

gastric cancer treatment guidelines[23] and its later versions. Since SAP was used as the chemotherapy regimen, paclitaxel-based regimens were not recommended as subsequent-line therapy in either group; instead, platinum-based regimens were permitted. Immunotherapy was allowed upon disease progression in both groups.

Endpoints

The primary endpoint was the centrally assessed MPR rate. Tumor regression was graded according to Becker's criteria by two blinded pathologists at the main institution. MPR was defined as TRG 1a (no viable tumor cells) or TRG 1b (viable tumor cells <10%).[24] The primary endpoint and several secondary endpoints, including the R0 resection rate, radiologic response, and safety, have been reported previously.[22] This report focuses on 3-year survival outcomes, including OS and progression-free survival (PFS). OS was defined as the time from the date of randomization to the last follow-up or death from any cause. PFS was defined as the time from randomization to the first documented progression or recurrence or the last follow-up, whichever occurred first.

Statistical analysis

The calculation of sample size has been reported previously.[22] All efficacy analyses were conducted in both the modified intent-to-treat (mITT) population and the per protocol (PP) population. The mITT population included all participants who were randomly assigned and received at least one dose of the allocated treatment, whereas the PP population included participants in the mITT population who were treated without any major deviations from the protocol. The safety analysis population consisted of all participants who received at least one dose of allocated treatment.

Categorical variables were reported as frequencies (percentages) and compared using the X^2 test or Fisher's method, as appropriate. In the latter method, the two-tailed P value was calculated as two times the minimum of the left-tailed or right-tailed P value and 0.5. Continuous variables were reported as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Survival curves were plotted using the Kaplan–Meier method. Cox regression was used to compare survival rates between the CA-SAP and SAP groups, and hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated after adjusting for baseline clinicopathological characteristics. Several post-hoc sensitivity analyses were performed in the PP population. To minimize the potential impact of baseline occult metastases, analyses were repeated after excluding participants with intraoperatively confirmed peritoneal metastases following neoadjuvant treatment. Subsequent sensitivity analyses excluded participants in the CA-SAP group who did not resume postoperative camrelizumab or apatinib, to assess the impact of early discontinuation. Heterogeneity in treatment effect was evaluated by creating interaction terms between treatment assignment and baseline characteristics. An additional analysis was performed to compare survival outcomes between the SAP group and a historical series treated with perioperative oxaliplatin plus S-1 (SOX). To reduce bias, we applied a target trial emulation analysis[25] and overlap weighting.[26] Further details are provided in the Supplementary Methods. The survival analyses were descriptive and exploratory; therefore, adjustments for multiple comparisons were not performed. Statistical significance was set at a two-tailed $P < 0.05$. All statistical analyses were conducted using R software (version 4.4.0; The R Foundation for Statistical Computing, Vienna, Austria).

Role of funding source

The funder had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Results

Study population and perioperative treatments

Between June 18, 2020, and March 31, 2022, a total of 106 patients with LAGC were randomly assigned to the CA-SAP group or the SAP group. After excluding 2 participants who withdrew their consent after random assignment, 51 participants in the CA-SAP group, and 53 participants in the SAP group were included in the mITT analysis (Fig. 1). The baseline characteristics were generally balanced between the two groups (Table 1).

Forty-nine of the 51 participants in the CA-SAP group and 50 of the 53 participants in the SAP group received surgery (including one participant with an unresectable tumor who underwent exploratory surgery). These 99 participants constituted the PP population. Postoperatively, 44 participants in the CA-SAP group and 47 in the SAP group received adjuvant treatment (Fig. 1).

Overall, 26 of the 51 participants (51%) in the CA-SAP group completed all eight cycles of perioperative treatment. Specifically, 25 participants (49%) completed eight cycles of chemotherapy and immunotherapy. Reasons for discontinuation included disease progression or recurrence (chemotherapy: n = 2; immunotherapy: n = 2), adverse events (chemotherapy: n = 12; immunotherapy: n = 9), patient refusal (chemotherapy: n = 6; immunotherapy: n = 9), and other reasons (chemotherapy: n = 6; immunotherapy: n = 6). Only seven participants (14%) completed full cycles of apatinib, with reasons

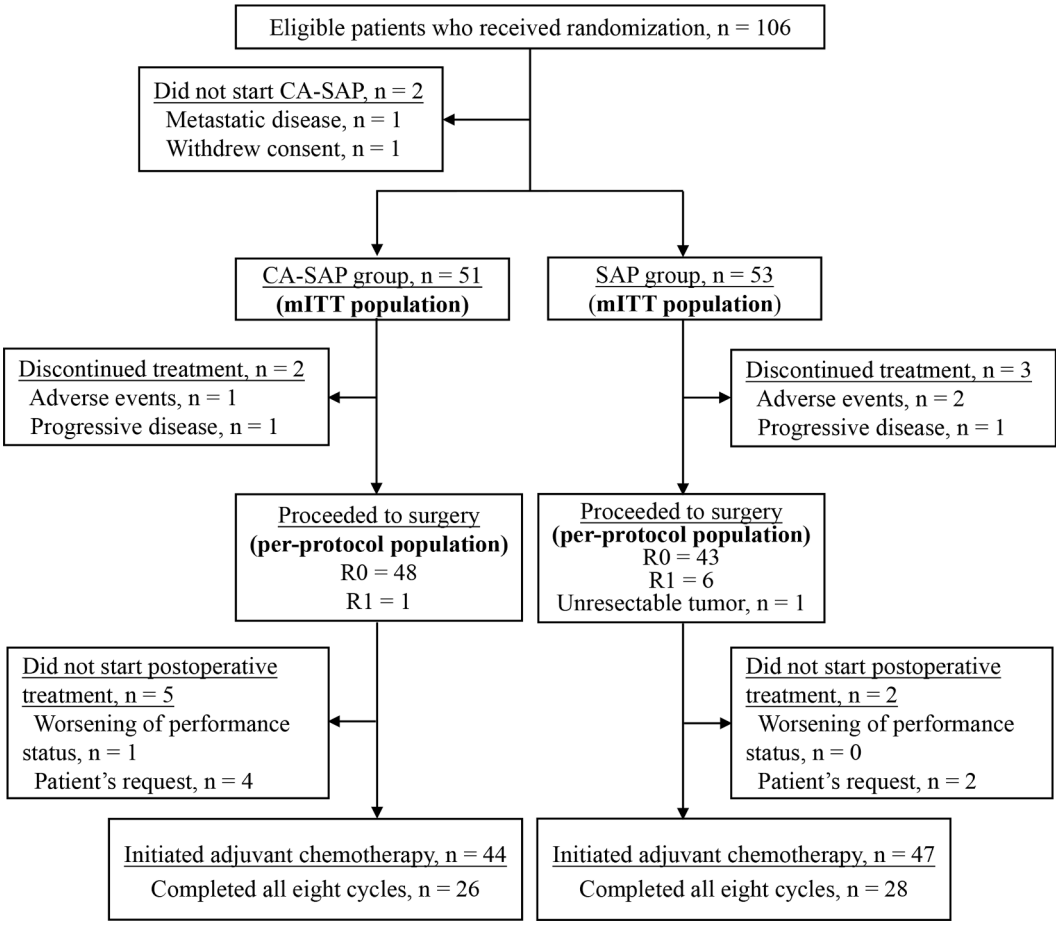


Fig. 1: Trial Profile. R0 indicates complete resection without macroscopic or microscopic residual disease, whereas R1 indicates gross removal of tumors with microscopic resection margin involvement. CA-SAP = camrelizumab, apatinib, nab-paclitaxel, and S-1; SAP = nab-paclitaxel and S-1; mITT = modified intention-to-treat.

for discontinuation including disease progression or recurrence (n = 1), adverse events (n = 25), patient refusal (n = 7), and other reasons (n = 11). In the SAP group, 28 of the 53 participants (53%) completed all eight cycles of perioperative treatment. The reasons for discontinuation were disease progression or recurrence (n = 6), adverse events (n = 13), patient refusal (n = 3), and other reasons (n = 3) (Table S1). Additionally, 32 of the 51 participants (63%) in the CA-SAP group and 24 of the 53 participants (45%) in the SAP group underwent TRAE-related dose modifications; 10 participants (20%) in the CA-SAP group and 4 participants (8%) in the SAP group received at least one dose reduction.

Primary endpoint: MPR

As previously reported,[22] the MPR rates in the CA-SAP group and the SAP group were 33% (17/51) vs. 17% (9/53) in the mITT population and 35% (17/50) vs. 18% (9/49) in the PP population, with significant differences of 16% (95% CI: 0–33%) and 17% (95% CI: 0–34%), respectively. The prespecified subgroup analysis revealed a significant interaction between treatment assignment and ECOG PS (P for interaction = 0.042 and 0.031, respectively, in the mITT and PP analyses) (Figure S1).

Secondary endpoint: 3-year survival outcomes

As of March 24, 2025, all surviving participants except one participant in the CA-SAP group, had completed the 3-year follow-up. The mITT analysis showed disease progression or recurrence occurred in 17 of the 51 participants (33%) in the CA-SAP group and 26 of the 53 participants (49%) in the SAP group. The 3-year PFS rates for the CA-SAP and SAP groups were 64% (95% CI: 52%–79%) and 48% (95% CI: 36%–64%), respectively, with an adjusted HR of 0.512 (95% CI: 0.263–0.998, P = 0.049) (Fig. 2A). In the PP population, the 3-year PFS rates in the CA-SAP and SAP groups were 66% (95% CI: 53%–81%) and 49% (95% CI: 37%–65%), respectively, with an adjusted HR of 0.462 (95% CI: 0.229–0.934, P = 0.032) (Figure S2A).

Variable	CA-SAP group	SAP group
Patient characteristics	**N = 51**	**N = 53**
Age, median (Q1-Q3), years	63 (57–68)	63 (56–68)
Sex, No. (%)		
Male	42 (82)	35 (66)
Female	9 (18)	18 (34)
ECOG performance status, No. (%)		
0	33 (65)	36 (68)
1	18 (35)	17 (32)
Baseline tumor characteristics	**N = 51**	**N = 53**
Lauren classification, No. (%)		
Intestinal	11 (22)	10 (19)
Diffuse	39 (77)	42 (79)
Unknown	1 (2)	1 (2)
Tumor location, No. (%)		
Upper 1/3	22 (43)	29 (55)
Middle 1/3	10 (20)	6 (11)
Lower 1/3	11 (22)	11 (21)
Mixed	8 (16)	7 (13)
Tumor size, median (Q1-Q3), mm	65 (45–80)	60 (50–75)
Borrmann type, No. (%)		
II-III	43 (84)	48 (91)
IV	8 (16)	5 (9)
cT stage, No. (%)		
T3	5 (10)	8 (15)
T4	46 (90)	45 (85)
PD-L1 expression (CPS), No. (%)		
<1	23 (45)	23 (43)
≥1	27 (53)	28 (53)
Unknown	1 (2)	2 (4)
MMR status, No. (%)		
pMMR	47 (92)	48 (91)
dMMR	3 (6)	3 (6)
Unknown	1 (2)	2 (4)
Pathological findings	**N = 49**	**N = 49**
ypT stage, No. (%)		
T0	8 (16)	3 (6)
T1	4 (8)	5 (10)
T2	5 (10)	5 (10)
T3	23 (47)	23 (47)
T4a	9 (18)	13 (27)
ypN stage, No. (%)		
N0	18 (37)	21 (43)
N1	12 (25)	8 (16)
N2	7 (14)	7 (14)
N3	12 (25)	13 (27)
ypM stage, No. (%)		
M0	49 (100)	47 (96)
M1	0 (0)	2 (4)
Lymphovascular invasion, No. (%)		
No	25 (51)	28 (57)
Yes	24 (49)	21 (43)
Neural invasion, No. (%)		
No	21 (43)	19 (39)
Yes	28 (57)	30 (61)
(Continued from previous column)		
R category, No. (%)		
R0	48 (98)	43 (88)
R1	1 (2)	6 (12)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; MMR = mismatch repair; dMMR = deficient mismatch repair; pMMR = proficient mismatch repair.

Table 1: **Baseline characteristics and pathological findings.**

Among the mITT population, 18 of the 51 participants (35%) in the CA-SAP group and 20 of the 53 participants (38%) in the SAP group died before the final follow-up. The 3-year OS in the CA-SAP and SAP groups was 63% (95% CI: 51%–78%) and 61% (95% CI: 49%–76.5%), respectively, with an adjusted HR of 0.987 (95% CI: 0.481–2.026, P = 0.97) (Fig. 2B). Similar results were obtained in the PP population (Figure S2B).

In the mITT population, dose modifications were not significantly associated with PFS (unadjusted HR 0.764, 95% CI 0.420–1.389, P = 0.38) or OS (unadjusted HR 0.899, 95% CI 0.472–1.714, P = 0.75), with similar findings in the PP population (Figure S3). No significant interaction was observed between treatment assignment and dose modification (P for interaction = 0.26 for OS and 0.13 for PFS) (Figure S4).

We conducted three sensitivity analyses in the PP population. First, we excluded three participants with intraoperatively confirmed peritoneal metastases, resulting in adjusted HRs of 0.514 (95% CI: 0.255–1.037, P = 0.063) for PFS and 0.899 (95% CI: 0.432–1.873, P = 0.78) for OS. Then, we excluded participants who received camrelizumab or apatinib only in the preoperative setting, and the results remained consistent with the primary analysis (Figure S5).

In participants who underwent gastrectomy, the 3-year cumulative recurrence rates were 33% (16 of 49) in the CA-SAP group and 49% (24 of 49) in the SAP group. The most common site of recurrence in both the CA-SAP and SAP groups was the peritoneum, with 3-year cumulative recurrence rates of 12% and 17%, respectively. The cumulative recurrence rates of other sites were similar in the two groups (Table S2). After recurrence, 9 of the 16 participants (56%) in the CA-SAP group and 17 of the 24 participants (71%) in the SAP group received a subsequent line of antitumor treatment. Most participants received second-line platinum-based chemotherapy. In the SAP group, 13 of the 24 participants (54%) received second-line immunotherapy, whereas only 2 of the 16 participants (13%) in the CA-SAP group received second-line immunotherapy (P = 0.017) (Table S3). The median post-recurrence survival in the CA-SAP and SAP groups

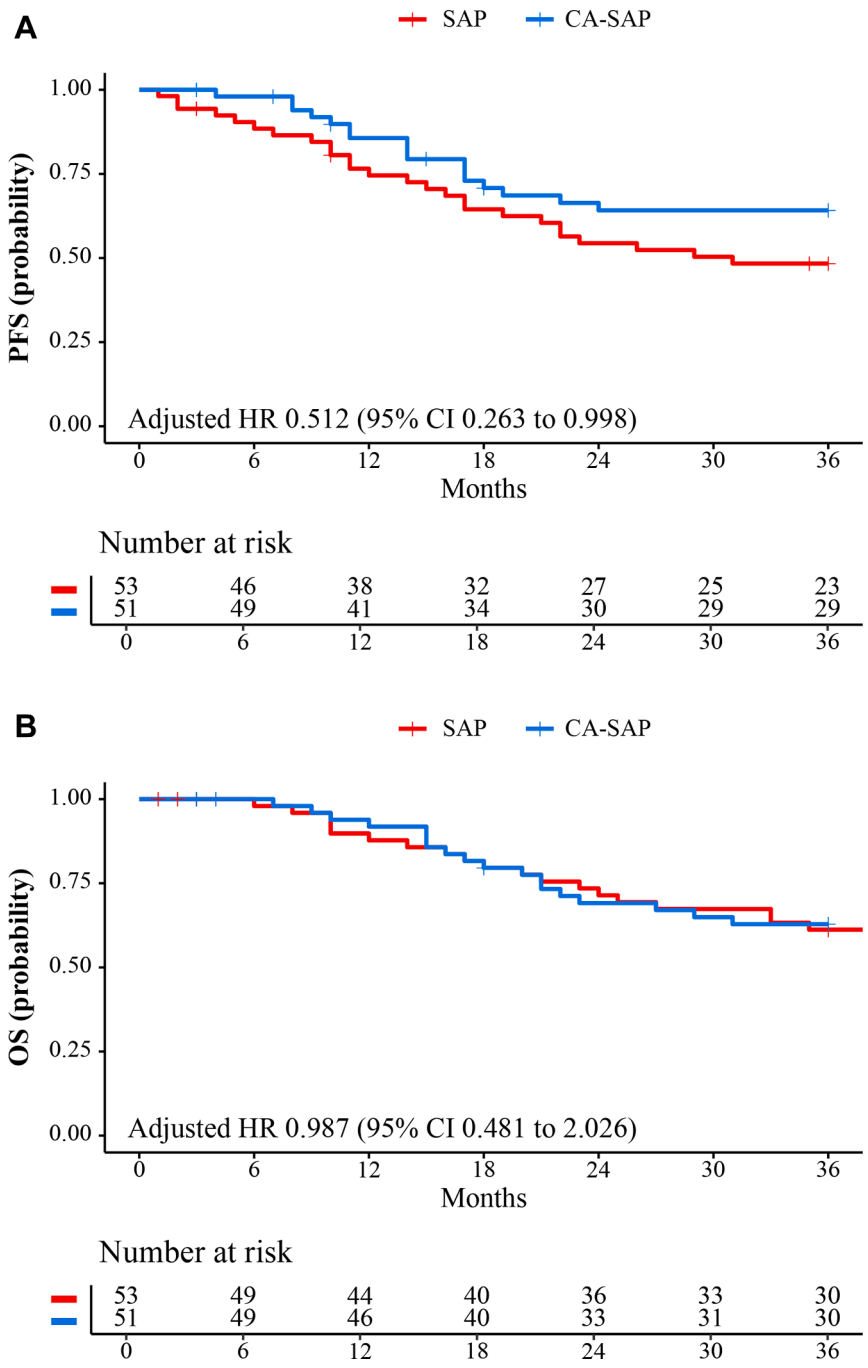


Fig. 2: Kaplan–Meier estimates of progression-free survival (PFS) (A) and overall survival (OS) (B) in the modified intention-to-treat population. Hazard ratios (HRs) of CA-SAP vs. SAP were adjusted for baseline characteristics.

was 4 (IQR: 2 to 10) months and 8 (IQR: 4 to 16) months, respectively, with an adjusted HR of 3.306 (95% CI 1.078–10.141, P = 0.037) (Figure S6). Additionally, the 3-year cancer-specific death rates were 31% (15 of 49) in the CA-SAP group and 37% (18 of 49) in the SAP group. Two participants in the CA-SAP group died due to strangulated intestinal obstruction at 8 months and 1 year after surgery, without preoperative and intraoperative evidence of recurrence; one participant died due to cerebral infarction (drug withdrawal over 90 days at the time of onset). In the SAP group, two participants died, one due to cerebral infarction (drug withdrawal over 30 days at the time of onset) and one due to an accidental event (Table S2).

Among these 98 participants, we explored the prognostic value of postoperative pathological characteristics. Multivariable analysis revealed that MPR was not an independent prognostic factor for either PFS (HR: 0.271, 95% CI: 0.045–1.639, P = 0.16) or OS (HR: 0.477, 95% CI: 0.073–3.107, P = 0.44). Instead, the ypN stage (lymph node status after neoadjuvant therapy) was the only independent prognostic factor identified for PFS and for OS (both P < 0.0001) (Figure S7).

Subgroup analysis for 3-year survival

In the PP population, the treatment effect of CA-SAP was consistent across most subgroups (P for interaction >0.05), but heterogeneity was observed among subgroups with different ECOG PS scores. In participants with an ECOG PS of 0, the 3-year OS in the CA-SAP group and SAP group was 71% (95% CI: 57%–89%) and 53% (95% CI: 39%–73%), respectively; however, in participants with an ECOG PS of 1, the 3-year OS in the CA-SAP group and SAP group was 48% (95% CI: 29%–79%) and 80% (95% CI: 62%–100%), suggesting a significant interaction effect (P for interaction = 0.018) (Fig. 3). A significant interaction was also observed between treatment assignment and ECOG PS on 3-year PFS (P for interaction = 0.032) (Fig. 4). Similar results were obtained in the mITT population (Figures S8–S9).

We further evaluated the association between the ECOG PS and treatment effect in the PP population. After adjusting for patient characteristics, the interaction between treatment assignment and ECOG PS remained significant (P for interaction = 0.0064 for OS and 0.023 for PFS); however, this interaction was no longer significant after adjustment for both patient and tumor characteristics (P for interaction = 0.074 for OS and 0.26 for PFS) (Figure S10). Two additional sensitivity analyses, which excluded participants with intraoperatively confirmed peritoneal metastases and those with deficient MMR (dMMR), supported this interaction effect (all P for interaction <0.05) (Figure S11).

We also investigated the association between combined positive score (CPS, a scoring method used to quantify the expression of PD-L1 in tumor tissue samples), mismatch repair (MMR) status, and survival outcomes. Interaction analyses showed that there was no heterogeneity of the treatment effect in subgroups with different CPS (all P for interaction >0.05) (Figs. 3 and 4, Figures S8–S9). Additionally, three participants with dMMR in the CA-SAP group survived without recurrence until the end of follow-up, whereas two of the three participants with dMMR in the SAP group experienced recurrence.

Safety

TRAEs during perioperative treatment for the safety analysis population are summarized in Table 2. The most common TRAEs in both groups were leukopenia (80% [41 of 51] and 83% [44 of 53] in the CA-SAP and SAP group, respectively) and neutropenia (59% [30 of 51] and 64% [34 of 53], respectively). Grade 3 or 4 adverse events occurred in 22 participants (43%) in the CA-SAP group and 17 participants (32%) in the SAP group. In the CA-SAP group, the most common grade 3 or 4 adverse event was leukopenia (n = 10, 20%), followed by neutropenia (n = 7, 14%) and elevated alanine transaminase (ALT) (n = 5, 10%). In the SAP group, the most common grade 3 or 4 adverse events were leukopenia (n = 5, 9%) and neutropenia (n = 5, 9%), followed by elevated ALT (n = 3, 6%) and elevated aspartate aminotransferase (AST) (n = 3, 6%). Additionally, 17 participants (33%) in the CA-SAP group experienced immune-related adverse events (irAEs), with hypothyroidism being the most common (n = 8, 16%). Except for one case of grade 3 disseminated intravascular coagulation, all other irAEs were grade 1 or 2 (Table S4).

Historical comparison between SAP and SOX

An additional analysis was performed including a historical cohort of patients treated with perioperative SOX for comparison with the SAP group. After weighting, the 3-year PFS (52% [95% CI: 39%–69%] vs. 45% [95% CI: 36%–56%]) and 3-year OS (67% [95% CI: 55%–82%] vs. 52% [95% CI: 43%–64%]) were comparable between the SAP group and the historical (SOX) cohort (P = 0.40 and 0.14, respectively) (Supplementary Methods).

Discussion

The Arise-FJ-G005 study evaluated the efficacy and safety of adding anti-PD-1 and anti-VEGF therapies to perioperative chemotherapy in patients with LAGC. An analysis of the short-term efficacy showed that the MPR rate in the CA-SAP group was significantly higher than that in the SAP group (33% [17 of 51] vs. 17% [9 of 53]), achieving the primary endpoint.[22] In the analysis of 3-year survival, the 3-year PFS was higher in the CA-SAP group than in the SAP group, with the emergence of a characteristic tail plateau. However, the advantages in MPR and PFS did not achieved a clinically significant improvement in OS.

The primary objective of the Arise-FJ-G005 study was to determine whether the addition of immunotherapy and antiangiogenic therapy to neoadjuvant chemotherapy could effectively improve the MPR, and consequently, prognosis. Although this combination treatment modality significantly increased the MPR by almost 100% compared with treatment with chemotherapy alone, the improvement in short-term efficacy did not translate into a marked improvement in the 3-year OS. The topic whether pathological response can serve as a surrogate endpoint for OS in neoadjuvant clinical trials is the subject of ongoing debate. In the context of LAGC, the findings of the AIO-FLOT4 study

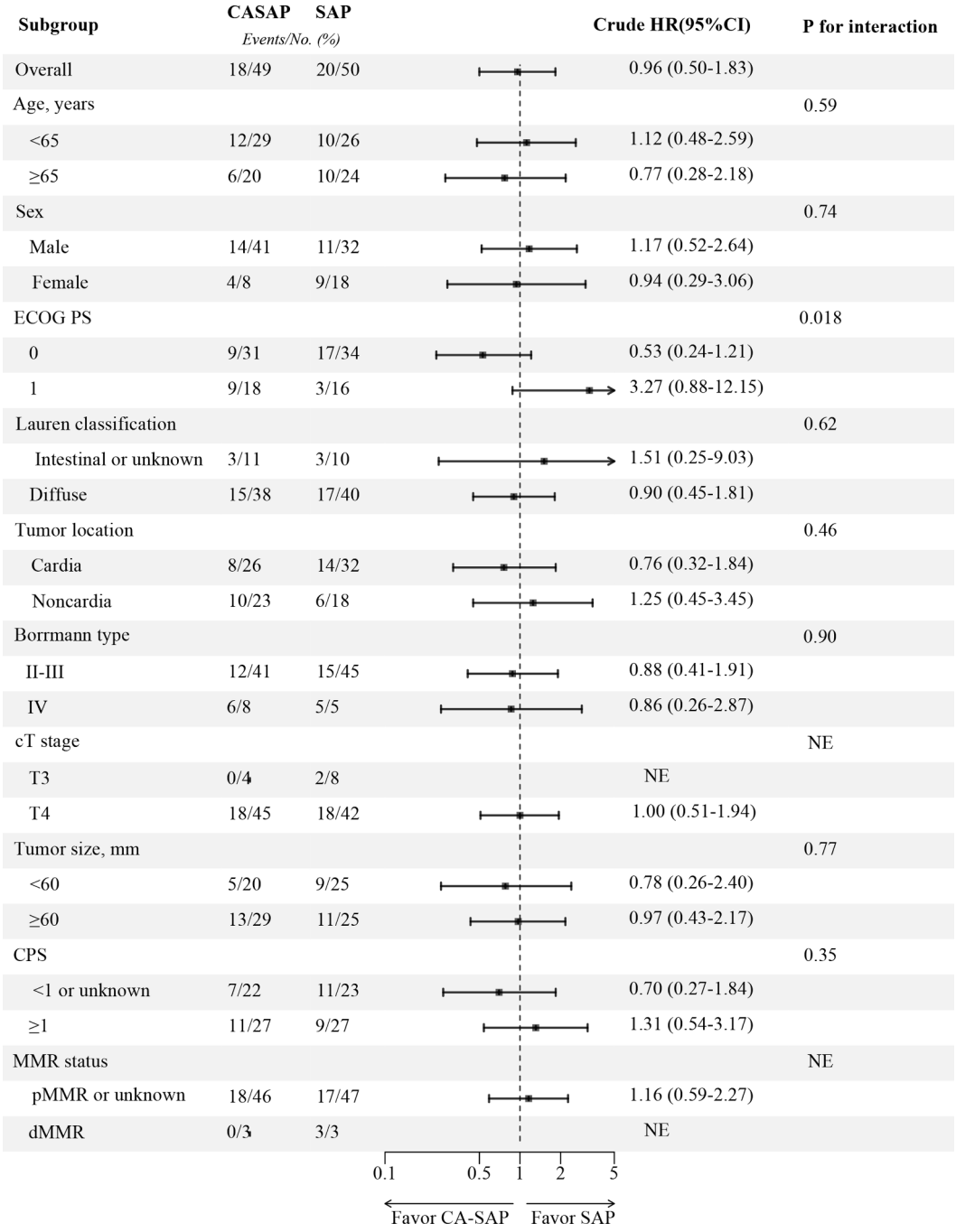


Fig. 3: Overall survival in subgroups on the basis of the baseline characteristics in the per protocol population. NE (i.e., not evaluable) indicates estimates could not be obtained because of the small sample size and low number of events.

suggested that an increase in PCR rate could lead to improved OS.[5] However, both the TOPGEAR[27] and KEYNOTE-585[13] studies demonstrated that an increase in PCR rate did not result in survival benefits. This may be primarily because of the current evaluation system of using pathological response, which mainly measures the primary tumor. Micrometastasis, as an important factor influencing recurrence, is itself the major target of neoadjuvant treatment[28]; however, it is rarely evaluated in clinical practice. Gastric cancer is highly heterogeneous, and previous evidence has shown variability in the effects of neoadjuvant treatment on

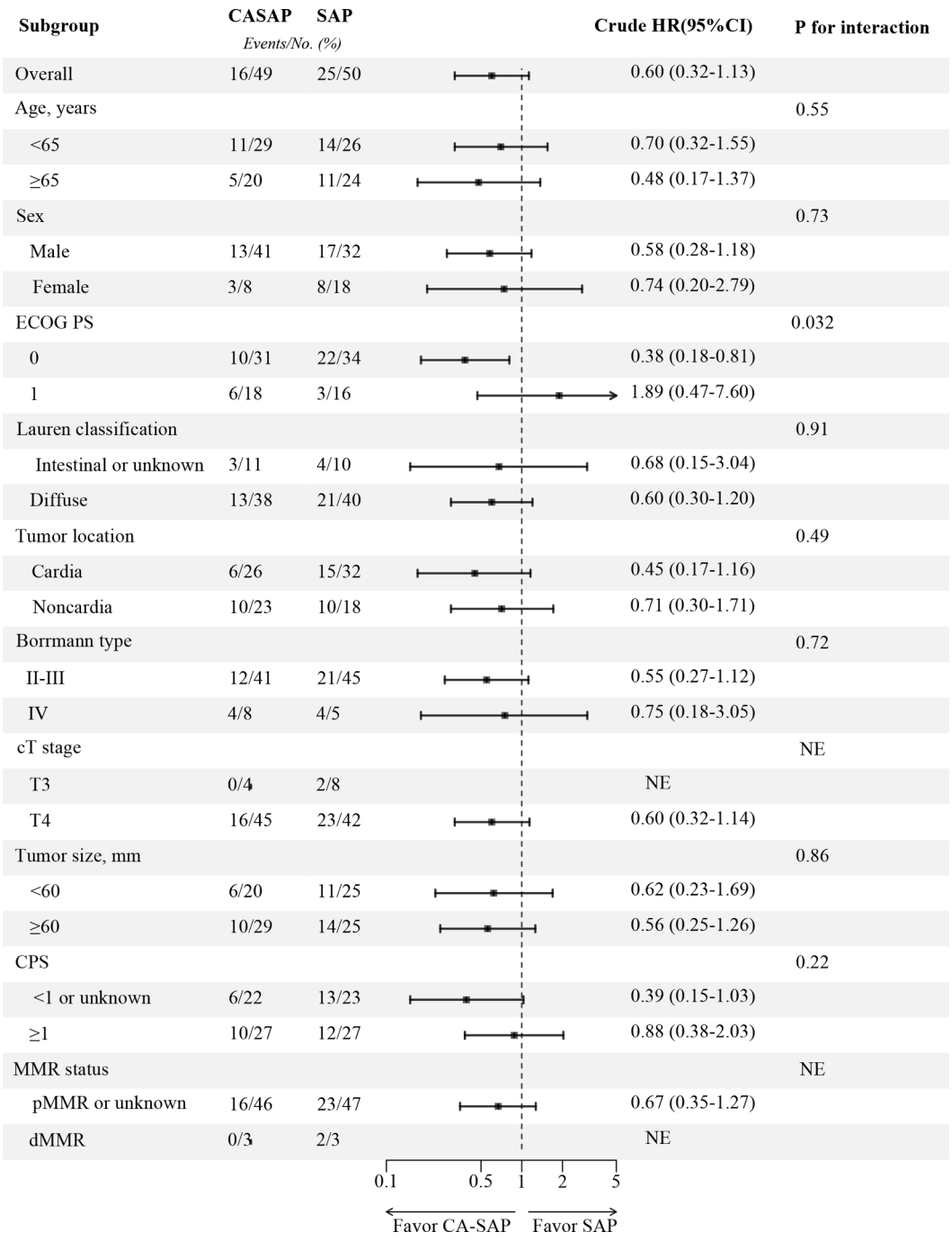


Fig. 4: Progression-free survival in subgroups on the basis of the baseline characteristics in the per protocol population. NE (i.e., not evaluable) indicates estimates could not be obtained because of the small sample size and low number of events.

primary tumors and lymph node metastases.[29] Therefore, merely evaluating the degree of regression in the primary tumor does not fully reflect the impact of neoadjuvant treatment on the overall tumor burden. The current evaluation system provides inadequate information about even the primary tumor. For example, patients with residual tumors concentrated in the serosal layer have more heterogenous prognosis than those with residual tumors concentrated in the mucosal layer.[30] Future neoadjuvant clinical trials in

LAGC should avoid setting the pathological response as the only primary endpoint and instead consider other validated surrogate endpoints.[31]

MPR not only failed to serve as a surrogate marker for OS at the trial level but also lacked independent prognostic value at the patient level. In contrast, ypN staging demonstrated an ability to independently predict both OS and PFS. Similarly, a pooled analysis of four RCTs revealed that the prognostic value of ypN staging was significantly better than that of MPR.[32] Although the CA-SAP group had significantly better MPR, this did not significantly increase the N downstaging rate (26% [13 of 51] vs. 17% [9 of 53]). This may be why the improvement in MPR did not translate into OS benefits. Moreover, we observed that post-recurrence survival was better in the SAP group compared with the CA-SAP group, which could be another significant factor contributing to the similar OS between the two groups. Consistent with the findings of this study, the ATTRACTON-4 study showed that although the addition of nivolumab to first-line chemotherapy significantly improved PFS, it did not significantly improve OS.[33] Boku et al.[33] attributed this phenomenon to the higher utilization of immunotherapy as a subsequent treatment in the chemotherapy-only group. Similarly, in this study, a larger proportion of patients in the SAP group who experienced recurrence received immunotherapy as their subsequent-line treatment. Of note, the proportion of patients receiving subsequent-line treatment was lower in the CA-SAP group than in the SAP group (56% [9 of 16] vs. 71% [17 of 24]). A similar phenomenon was observed in the double-blinded KEYNOTE-585[13] and MATTERHORN[15] studies, which may partly reflect the impact of residual toxicity from the combination therapy on subsequent treatment choices. Further optimization of subsequent treatment strategies following CA-SAP may represent a feasible approach to enhance its survival benefit.

We selected paclitaxel-based chemotherapy as the control regimen. This decision was made based on our previous study which demonstrated higher MPR and PCR rates with SAP than with SOX for LAGC.[34] Several RCTs have also demonstrated that paclitaxel-based chemotherapy is noninferior to platinum-based chemotherapy.[35–37] Additionally, apatinib combined with SOX has shown a high incidence of thrombocytopenia in previous studies,[38–40] which may be associated with the combined use of oxaliplatin and apatinib.[41] The frequent occurrence of thrombocytopenia may have a negatively effect on treatment outcomes.[42] Based on this evidence and the principle of the patient's best interests, this study chose SAP, which is associated with a lower incidence of thrombocytopenia,[35] non-inferior efficacy, and synergistic effects with anti-PD-1 and anti-VEGF therapies[43,44] as the chemotherapy regimen. The DRAGON IV/CAP 05 study compared the efficacy of SOX combined with camrelizumab and apatinib (SOXRC) with SOX alone in the neoadjuvant treatment of LAGC,[45] which was similar with our study. The results showed that the PCR rates of SOXRC and SOX were 18.3% and 5.0%, respectively, which were similar to the PCR rates of CA-SAP and SAP (16% [8 of 51] and 6% [3 of 53], respectively); however, the MPR rates of SOXRC and SOX were 51.1% and 37.8%, respectively, which were higher than those of CA-SAP and SAP (33% [17 of 51] and 17% [9 of 53], respectively). This discrepancy may be attributed to the higher proportion of cT4-stage patients in our study. The incidence of any grade thrombocytopenia during neoadjuvant SOXRC and SOX was 37% and 31%, respectively, which was higher than those with CA-SAP and SAP (16% [8 of 51] and 4% [2 of 53], respectively), indirectly indicating the rationality of our selected regimen. Additionally, 20 of the 53 patients (38%) in the SAP group died within 3 years, which was similar to the 3-year survival outcome of the perioperative-SOX group in the RESOLVE study (38.7% of patients died within 3 years), with similar baseline stages.[6] A comparison between the SAP group in this study and the historical SOX cohort from the participating centers also demonstrated comparable 3-year

Adverse events	CA-SAP group (n = 51)		SAP group (n = 53)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Hematologic				
Neutropenia	22 (43)	8 (16)	29 (55)	5 (9)
Leukopenia	31 (61)	10 (20)	39 (76)	5 (9)
Thrombocytopenia	11 (22)	1 (2)	4 (8)	2 (4)
Anemia	19 (37)	1 (2)	28 (53)	0 (0)
Gastrointestinal				
Nausea	21 (41)	2 (4)	24 (45)	2 (4)
Vomiting	11 (22)	1 (2)	15 (28)	1 (2)
Anorexia	12 (24)	1 (2)	12 (23)	1 (2)
Diarrhea	16 (31)	3 (6)	10 (19)	2 (4)
Bleeding	8 (16)	1 (2)	8 (15)	1 (2)
Liver				
AST elevation	15 (29)	3 (6)	13 (26)	3 (6)
ALT elevation	14 (28)	5 (10)	12 (23)	3 (6)
Bilirubin increased	15 (29)	0 (0)	10 (19)	0 (0)
Cardio-renal				
Hypertension	12 (24)	1 (2)	2 (4)	0 (0)
Proteinuria	10 (20)	0 (0)	1 (2)	0 (0)
Dermatologic				
Rash	11 (22)	1 (2)	5 (9)	0 (0)
Hand–foot syndrome	10 (20)	0 (0)	1 (2)	0 (0)
Systemic				
Fatigue	15 (29)	2 (4)	21 (31)	2 (4)
Fever	11 (22)	0 (0)	6 (11)	0 (0)
Others				
Peripheral sensory neuropathy	6 (12)	0 (0)	8 (15)	1 (2)
Stomatitis	10 (20)	1 (2)	5 (9)	0 (0)

Table 2: **Adverse events graded based on CTCAE 5.0 during perioperative therapy.**

survival outcomes (Supplementary Methods). Given this evidence, SAP appears to be noninferior to SOX. However, high-level evidence supporting the use of SAP as a first-line treatment remains limited, and it has not been established as a standard neoadjuvant chemotherapy option. Therefore, the findings of this study should be interpreted with caution.

For patients receiving neoadjuvant immunotherapy, there is currently no consensus on whether to continue immunotherapy postoperatively or whether to proceed with maintenance immunotherapy. Theoretically, neoadjuvant immunotherapy can elicit a stronger systemic antitumor response than that of adjuvant immunotherapy, because tumors carrying neoantigens and antitumor T-cells within the lesions have not been surgically removed.[8] In this study, the CA-SAP group was intended to receive five cycles of adjuvant immunotherapy combined with chemotherapy and antiangiogenic therapy. The DRAGON IV/CAP 05 study continued with three cycles of camrelizumab and apatinib maintenance therapies following three cycles of adjuvant SOXCA,[45] while the KEYNOTE-585 study administered a total of 14 cycles of immunotherapy postoperatively (with 11 cycles as maintenance therapy).[13] Notably, our sensitivity analysis did not indicate that continued postoperative camrelizumab or apatinib treatment conferred additional benefit to the CA-SAP group. Likewise, current evidence has not demonstrated a survival benefit of adjuvant immunotherapy in gastric cancer.[46,47] Further investigation is needed to determine whether differences in adjuvant treatment affect the overall efficacy.

The exploratory subgroup analysis suggested improved survival with CA-SAP compared with SAP among patients with an ECOG PS of 0. This corresponds to the short-term efficacy, that is, an ECOG PS of 0 was associated with greater MPR benefit from CA-SAP over SAP.[22] Similarly, in the KEYNOTE-059,[48] KEYNOTE-061,[49] and ORIENT-16[50] studies, patients with an ECOG PS of 0 were more likely to benefit from immunochemotherapy. However, in the DRAGON IV/CAP 05[45] and KEYNOTE-585[13] studies, neoadjuvant immunochemotherapy with or without antiangiogenic therapy significantly improved the PCR compared with neoadjuvant chemotherapy alone, regardless of the ECOG PS score. The effect of poor PS on immunotherapy remains controversial. Various factors such as older age, comorbidities, and advanced staging can contribute to a decline in patients' physical conditions, resulting in significant heterogeneity among this population. Moreover, the assessment of physical condition is relatively subjective, potentially leading to interobserver variation.[51] In this study, patients with different ECOG PS scores showed differences in baseline characteristics, especially age (Table S5). Additionally, the interaction between treatment assignment and ECOG PS was not significant after controlling for tumor characteristics. Further exploration is needed to understand the relationship between physical condition and the efficacy of immunotherapy in patients with gastric cancer.

For advanced gastric cancer, patients with a high PD-L1 expression were more likely to benefit from immunochemotherapy.[52–54] However, in this study, the effect of CPS on long-term treatment effect was not heterogenous, which was similar to the findings of the KEYNOTE-585[13] and the MATTERHORN[15] studies. Interestingly, we observed heterogeneity in the effect of CPS on short-term treatment effect, with greater benefit from CA-SAP over SAP in the CPS $\geq$1 subgroup compared with the CPS <1 subgroup (absolute MPR difference: 22% vs. 10%).[22] A similar phenomenon was also observed in the KEYNOTE-585 study (absolute PCR difference: 12.1% vs. 4.2% for CPS $\geq$1 and < 1 subgroups, respectively) and the MATTERHORN study (absolute PCR difference: 13.4% vs. 0% for CPS $\geq$1 and < 1 subgroups, respectively). This may be attributed to heterogeneity in the response of primary tumors and micrometastases to immunotherapy. On one hand, PD-L1 expression can differ between primary tumors and micrometastases[55]; on the other hand, the low immunogenicity of micrometastases impairs their ability to induce an adaptive immune response in the context of immunotherapy, especially after the removal of the primary tumor.[56] Additionally, we found that patients with dMMR appeared to benefit more from immunotherapy. Given the small sample size, this result should be interpreted with caution and requires validation in larger cohorts.

Consistent with our previous report,[22] the most common grade 3 or 4 adverse advent with perioperative CA-SAP was myelosuppression. Additionally, the adverse events related to antiangiogenic agents (e.g., hypertension, proteinuria, and hand-foot syndrome) and irAEs was mild, which were consistent with the results of the DRAGON IV/CAP 05[45] and the SPACE[57] studies. Notably, dose modifications were more common in the CA-SAP group than in the SAP group. Moreover, only 14% of patients (7 of 51) in the CA-SAP group completed the full cycle of apatinib treatment, suggesting that the tolerability of this combination regimen may be suboptimal. Although tolerability did not appear to impact survival outcomes, further investigations are needed to explore more optimal combination strategies, such as alternative administration routes for antiangiogenic agents, to improve treatment compliance.

The Arise-FJ-G005 study has some limitations. First, as a two-arm design, it cannot prove whether the CA-SAP is superior to camrelizumab combined with chemotherapy or apatinib combined with chemotherapy. The open-label design may have influenced patient willingness and investigators' decisions, potentially biasing post-progression treatment (e.g.,

subsequent immunotherapy) and survival. Second, most enrolled patients had advanced stages, but laparoscopic staging and peritoneal lavage cytology were not routinely performed before neoadjuvant treatment. Therefore, it cannot be ruled out that some patients may have had occult metastatic lesions that were difficult to identify by baseline examinations. Based on our sensitivity analyses, this limitation likely had minimal impact on the overall results. Third, given that all survival analyses and subgroup analyses are descriptive and exploratory, results from a large-scale, international, phase 3 RCT are expected to further validate our findings.

In conclusion, for unselected patients with LAGC, the addition of camrelizumab and apatinib to perioperative chemotherapy was associated with a modestly improved 3-year PFS, but it did not improve the 3-year OS and showed suboptimal tolerability. The failure of the "one-size-fits-all" strategy underscores the urgent need for a reliable and precise method to stratify patients based on clinical, pathological, and molecular biomarkers, in order to enable optimal personalized treatment strategies for each individual. Moreover, the forthcoming long-term survival results from the DRAGON IV/CAP 05 study are anticipated to provide further insights into this treatment strategy.

Contributors

Huang CM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Huang CM and Lin JX obtained funding, conceived of and designed the study, and supervised the whole study. Huang ZN, Tang YH, Ye K, Wang ZF, Cai LS, Lin W, Li P, Xie JW, Wang JB, Chen QY, Cao LL, and Zheng CH acquired the data, were responsible for study administration, and provided technical and material support. Huang CM and Lin JX accessed and verified the underlying data. Huang ZN interpreted and analyzed the data. Tang YH drafted the manuscript. Huang CM, Lin JX, and Huang ZN critically revised the manuscript. All authors reviewed the manuscript and agreed to submit it for publication.

Data sharing statement

The datasets used and analyzed during the current study are available from the corresponding author (C.M.-H.) on reasonable request.

Declaration of interests

There are no conflicts of interest or financial ties to disclose from any of author.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103568.

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