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Conversion effects of PD-1 inhibitor camrelizumab combined with Nab-POF regimen in patients with initially unresectable locally advanced or limited metastatic gastric or gastroesophageal junction adenocarcinoma: FDZL-GC001

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Abstract

Background: We conducted this prospective, single-arm, phase II trial to improve conversion efficacy by PD-1 antibody camrelizumab (Cam) combined with Nab-POF regimen in patients with initially unresectable locally advanced or limited metastatic gastric or gastroesophageal (G/GEJ) adenocarcinoma.

Objective: Patients with initially unresectable locally advanced or limited metastatic gastric or gastroesophageal junction adenocarcinoma were enrolled.

Design: Eligible patients received Cam 200mg, nab-paclitaxel 125 mg/m2, oxaliplatin 85 mg/m2 or with trastuzumab if Her2 positive, followed by fluorouracil 2400 mg/m2 as a 48-hour continuous infusion every 2 weeks. Tumor response and surgical feasibility were assessed every 3 cycles. If confirmed feasible for surgical resection after 6 cycles, patients would undergo surgery. The primary endpoint was R0 resection rate.

Results: A total of 53 patients was enrolled and 52 were evaluable. The R0 resection rate was 75.0% (39/52), meeting the primary endpoint. ORR was 88.5% (46/52). The total CR rate was 23.1% (12/52). The median PFS and OS were not reached. The 3-year PFS and OS rates were 56.9% (95% CI = 45.7%-86.3%) and 62.8% (95% CI = 41.6%-78.0%), respectively. Patients tolerated treatment well. Grade 3/4 AEs were 42.3% (22/52) and neutrophil decrease was the most common at 36.5%. [68Ga]Ga-NOTA-GSI PET/CT scan demonstrated that patients with elevated SUV value of metastatic lesion had significantly longer PFS (P = 0.019) and a tendency of longer OS (P = 0.111).

Conclusion: Cam combined with Nab-POF regimen chemotherapy provides a new conversion strategy for patients with initially unresectable locally advanced or limited metastatic G/GEJ cancer.

Introduction

Gastric cancer (GC) is one of the most common types of malignant tumors affecting the digestive system, particularly in East Asia, posing a significant threat to human health. In China, most patients with GC have locally advanced or metastatic disease at the time of diagnosis, rendering them ineligible for radical surgery. The prognosis for these patients is poor, and palliative systemic drug treatment is typically the only viable option for extending life and improving quality of life.[1] To improve the outcomes for advanced GC patients, new therapeutic strategies must be explored.

The prospective phase III REGATTA Study revealed that palliative primary resection did not improve long-term survival for stage IV GC patients.[2] However, several retrospective reports have suggested that certain patients with advanced GC may experience long-term survival by achieving margin-free (R0) resection in conjunction with effective drug treatment[3–5]. The phase II FLOT3 study observed the favorable survival in the group of patients with limited metastatic disease who received FLOT chemotherapy and subsequently underwent surgery with both primary tumor and metastatic lesions

resection[6]. These results provide a rationale for the potential use of conversion surgery in the treatment of advanced GC. Conversion surgery is adopted to achieve a radical cure after effective induction therapy and therefore, differs from salvage surgery. We conducted the conversion study based on the FLOT3 trial.

In the recent years, immune checkpoint antibodies targeting Programmed Cell Death 1 (PD-1) and Programmed Death-Ligand 1(PD-L1) has opened a new field of cancer treatment. Checkmate-649[7] and ORIENT-16[8] studies showed that the addition of PD-1 antibodies to the first-line treatment of advanced gastric or gastroesophageal junction(G/GEJ) adenocarcinoma increased the overall response rate (ORR) by 10% or more, suggesting that PD-1 antibodies are suitable for conversion therapy. In our conversion study, we added the PD-1 antibody camrelizumab (Cam) to the chemotherapy. The efficacy of Cam in the treatment of liver cancer has been confirmed in phase III clinical trials and approved for indications[9]. It has shown preliminary efficacy in phase I/II[10, 11] trials of first-line treatment for advanced G/GEJ cancer. It has also shown preliminary efficacy in improving pathological complete response (pCR) in neoadjuvant therapy for initially resectable G/GEJ cancer[12]. We combined Cam with chemotherapy in our study expecting to further improve conversion efficacy.

From EXELOX study we know that the ORR of triplet regimen EOX was not significantly higher than that of doublet regimen XELOX in metastatic GC[13]. However, in the FLOT4 trial[14], the R0 resection rate was also higher, suggesting that FLOT may be a better conversion regimen. However, its greater toxicities, especially the myelosuppression of docetaxel, may be unfavorable to the combined PD-1 antibody, especially when lymphocytes are also reduced. Thus, we modified the regimen by replacing docetaxel with nanoparticle albumin-bound paclitaxel (Nab-PTX), which has less hematologic toxicity and then may result in better immune synergy. Moreover, a recent study found that Nab-PTX exhibits superior effects compared to paclitaxel in improving the immune microenvironment and activating T cells, thereby enhancing the efficacy of PD-1 antibody therapy[15]. Thus, we conducted the FDZL-GC001 trial, used the Nab-POF regimen (Nab-PTX, oxaliplatin, fluorouracil) in combination with the PD-1 antibody Cam to improve the conversion rate of patients with initially unresectable locally advanced and limited metastatic G/GEJ adenocarcinoma.

Materials and Methods

Participants

FDZL-GC001 was an open-label, single-center, phase II trial conducted at Fudan University Shanghai Cancer Center designed to investigate the efficacy and safety of the PD-1 antibody Cam in combination with Nab-POF regimen for conversion therapy in patients with unresectable locally advanced or limited metastatic G/GEJ adenocarcinoma. The study was registered at ClinicalTrial.gov (identifier: NCT04510064).

Eligible patients aged over 18 years old had histologically or cytologically confirmed advanced metastatic G/GEJ adenocarcinoma. Eligible patients had at least one measurable lesion according to RECIST1.1 criteria[16]. Patients should undergo computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Patients were enrolled with unresectable locally advanced (imaging stage T4b and/or second station lymph nodes > 3 cm or fused into a mass) or limited metastatic G/GEJ cancer with any of the following single-site metastases:

- Retroperitoneal lymph node metastasis (RPLM) and/or the following distant metastases.
- Unilateral or bilateral Kruckenberg neoplasm.
- 1–5 metastases to liver, with the maximum lesion diameter not exceeding 5 cm.
- 1–5 metastases to lung, with the maximum lesion diameter not exceeding 5 cm.
- Metastases to adrenals.
- Extra-abdominal metastases to lymph nodes such as supraclavicular, cervical, or mediastinal lymph nodes that can be included in one radiation field.
- Single-site metastases to peritoneum as confirmed by surgical exploration, such as P1.
- Other site metastases considered as limited by the investigator.

Full eligibility criteria are provided in the attached protocol. The full analysis set (FAS) included patients who met the eligibility criteria, received at least one cycle of chemotherapy, and underwent at least one tumor response evaluation.

Ethics Statement

The institutional review board and ethics committee at Fudan University Shanghai Cancer Center approved the protocol (No. 1912212-5-2411). The trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and Chinese law. All patients signed an informed consent form before enrollment in the trial.

Procedure and Treatment

All patients received a combination of Cam and Nab-POF regimen (Cam 200mg on day1, Nab-PTX 125 mg/m2 on day1, oxaliplatin 85 mg/m2 on day1 and fluorouracil 2400mg/m2 civ48h, every two weeks). Human Epidermal Growth Factor Receptor 2 (HER2) positive patients will receive additional treatment with trastuzumab. The regimen is repeated every 2 weeks. The dose modifications are detailed in the attached trial protocol. Efficacy will be assessed every 3 cycles using RECIST1.1 criteria[16].

For each patient, a multidisciplinary discussion will be held after 6 cycles, involving surgeons, radiologists and medical oncologists to assess whether the patient is eligible for radical surgery. Criteria for resection is that the tumor lesion has regressed and can be R0 resected. If confirmed feasible for surgical resection, surgery occurs within 3–6 weeks post-chemotherapy. If not feasible for resection,

extend conversion therapy by 3–6 cycles will be performed and resection will be re-evaluated. If still unresectable, they will continue to receive treatment based on palliative care principles. If the treatment response is complete response (CR), the investigator will adopt “wait and see” strategy detailed in the attached trial protocol, after patients’ consultation. Progressive disease (PD) at any evaluation leads to treatment failure and study withdrawal. Patients with good postoperative recovery will continue immunotherapy in combination with chemotherapy within 3–6 weeks, with a maximum of 12 cycles for chemotherapy and a maximum of 1 year for immunotherapy. For patients who cannot tolerate the triplet-regimen chemotherapy, doublet or single-agent regimen or early termination of chemotherapy will be adopted, or early termination of chemotherapy.

Outcomes

The primary endpoint was R0 resection rate (R0 resection refers to the absence of residual tumor cells in the proximal, distal, and circumferential margins under a microscope after resection of the primary gastric lesion, and negative microscopic margins of simultaneously resected metastatic lesions, or complete ablation of metastatic lesions after local treatment such as radiofrequency ablation/SBRT [lesion disappearance or no enhancement on enhanced CT/MRI]). The secondary endpoints included total CR rate: the proportion of the patients with pCR or cCR (pCR refers to the absence of residual cancer cells in the primary lesion, regional lymph nodes, and simultaneously resected metastatic lesions; cCR refers to the disappearance of tumor lesions as assessed by imaging, absence of cancer cells detected in endoscopic biopsy), pCR, major pathological response (MPR, pathological complete regression or < 10% residual tumor per tumor bed) rate, objective response rate(ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AE) including surgery complications were classified and graded using the Common Terminology Criteria for Adverse Events (version 5.0)[17].

[68Ga]Ga-NOTA-GSI PET/CT

For [68Ga] Ga-NOTA-GSI (Granzyme B specific Inhibitor) PET/CT scanning[18] was performed with the PET/CT scanner (Biograph 16 HR, Siemens Medical Systems, Erlangen, Germany). PET images were performed from the head to the thigh, 6–8 weeks after the first cycle of treatment.

Exploration for efficacy predictors

The detailed methods of exsome, RNA extraction, RNA sequencing, immunohistochemistry (IHC) and gut microbiome analysis are in Supplementary document 1.

Statistical Analysis

According to the FLOT3 study, which used the FLOT regimen for conversion therapy and achieved an R0 resection rate of 48% (29/60). We will adopt the Nab-POF regimen in combination with Cam in the

present study and aim to increase the R0 resection rate to 70%. Based on the rate comparison of PASS software, with a power of 0.8 and a significance level of 0.05 in a two-sided test, we will need a sample size of 39 cases, and assuming a dropout rate of 10%, we will need a sample size of 43 cases. Since the FLOT3 study did not specify the HER2 positive or negative status of the enrolled patients, we will ensure that 43 patients with HER2-negative status are enrolled, with no limit on the number of HER2-positive patients.

OS and PFS were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the stratified Cox proportional hazards model. The statistical significance level was set to 0.05. Statistical methods were all analyzed using the Stata statistical software (version 12.0; StataCorp, College Station, TX).

Results

Patients and Treatment

Between January 6, 2021 and January 31, 2024, 43 HER2 negative and 10 HER2 positive cases were enrolled. One patient withdrew the informed consent. A total of 52 evaluable patients constructed the FAS set (Fig. 1). The baseline characteristics of FAS set were illustrated (Table 1). 41 patients (78.8%) had metastasis, and 11 patients (21.2%) had locally advanced G/GEJ.

Table 1
Baseline clinicopathologic characteristics of patients in the FAS set.

Characteristic	cases (%)
Total	52
Sex	
Male	38 (73.1)
Female	14 (26.9)
Age	
< 65 years	26 (50.0)
≥ 65 years	26 (50.0)
ECOG PS	
0–1	52 (100.0)
2	0 (0.0)
Metastatic status	
Locally advanced	11 (21.2)
Metastatic	41 (78.8)
Primary tumor location	
Proximal gastric	18 (34.6)
Gastric body	12 (23.1)
Distal gastric	18 (34.6)
Multicentric	4 (7.7)
Liver metastasis	
Yes	24 (46.2)
No	28 (53.8)
Lung metastasis	
Yes	0 (0.0)
No	52 (100.0)
Retroperitoneal lymphatic metastasis	
Yes	21 (40.4)

Characteristic	cases (%)
No	31 (59.6)
Ovarian metastasis	
Yes	3 (5.8)
No	49 (94.2)
Pathologic type	
Adenocarcinoma	43 (82.7)
SRCC	9(17.3)
Histologic grade	
Well differentiated	0 (0.0)
Moderately differentiated	15 (28.8)
Poorly differentiated	37 (71.2)
HER2	
Positive	10 (19.2)
Negative	42 (80.8)
MSI/MMR	
MSI-H/dMMR	4 (7.7)
MSS/pMMR	48 (92.3)
PD-L1 CPS	
CPS < 5	14 (27.0)
CPS ≥ 5	19 (36.5)
Unknown	19 (36.5)

All of the 52 patients received at least 6 courses of treatment with Cam combined with Nab-POF regimen. Thirteen patients (25%) received 7 to 9 courses. Among the 39 surgical patients, nine patients (23.1%) received 7 to 9 doses of medication before surgery and three patients stopped PD-1 antibody treatment after only 3 cycles of immunotherapy because of immune hepatitis or dermatitis.

One patient experienced PD after three courses of treatment. In two patients with SD, R0 resection was deemed not feasible. Four PR patients did not proceed with surgery because of disease progression due to epidemic-induced delay (n = 1), disease progression after six cycles treatments (n = 1), portal vein tumor thrombus assessed as technically unresectable (n = 1) and a death due to cerebrovascular

accident. Three PR patients who were evaluated as eligible for surgery refused the operation and three patients with cCR did not undergo surgery.

In this study, 17 patients received radical total gastrectomy, 12 radical partial gastrectomy, 9 radical gastrectomy combined with synchronous or staged resection of liver or ovarian metastatic lesions, and 1 radical gastrectomy combined with radiofrequency for liver metastatic lesions.

Postoperatively, most patients received doublet regimens (Nab-PTX or oxaliplatin combined with fluorouracil), or single-agent capecitabine or S1. The median number of cycles of Cam received by surgical patients was 10. Totally, 40.1% (16/39) received twelve cycles of Cam during the perioperative period. Besides, only one patient received one cycle of dose-reduced triplet regimen, one cycle of Nab-PTX and fluorouracil and one cycle of oral capecitabine due to intolerance of vomiting.

Efficacy

To the last follow-up of 06/2025, 20 patients relapsed, 14 died. The median follow-up time was 25.6 months.

Totally, the R0 resection rate was 75.0% (39/52). The pCR rate was 23.1% (9/39). The MPR rate was 46.2% (18/39). The ORR and DCR were 88.5% (46/52) and 98.1% (51/52) respectively. The total CR rate was 23.1% (12/52). 45 (86.5%) patients were assessed feasible for resection. The median OS and PFS were not reached (95% CI = 30.3-not evaluable [NE] months and 95% CI = 20.0-NE months respectively; Fig. 2A and Fig. 2B). The three-year OS and PFS rates were 66.6% (95% CI = 53.1%-83.4%) and 59.3% (95% CI = 46.8%-75.1%), respectively. Patients with cCR or MPR had a significantly longer OS (P = 0.011; Fig. 2C) and PFS (P = 0.002; Fig. 2D) than others. Patients who achieved cCR or R0 resection had a tendency of longer OS (P = 0.011; Fig. 2E) and significantly longer PFS (P = 0.000; Fig. 2F) than those who did not achieve cCR or R0 resection.

In a total of 42 patients with HER2 negative status, the R0 resection rate was 73.8% (31/42). The pCR rate was 19.4% (6/31) and the total CR rate was 21.4% (9/42). The MPR rate was 41.2% (13/31). The ORR and DCR were 85.7% (36/42) and 97.6% (41/42) respectively. The three-year OS and PFS rates were 63.5% (95% CI = 49.0%-82.3%) and 55.4% (95% CI = 41.9%-73.4%), respectively (Fig. 2G and Fig. 2H). Three HER2 negative cCR patients still alive and disease free, with survival periods of 27.0, 36.6, and 44.3 months, respectively.

In a total of 41 patients with metastasis, the R0 resection rate was 80.5% (33/41). The pCR rate was 24.2% (8/33). The MPR rate was 48.5% (16/33). The ORR and DCR were 87.8% (36/41) and 97.6% (40/41). The three-year OS and PFS rates were 60.1% (95% CI = 42.0%-86.0%) and 52.9% (95% CI = 36.4%-76.9%), respectively (Fig. 2K and Fig. 2L).

Safety

All patients experienced treatment-related adverse events (TRAEs). The most common AEs with an incidence of ≥ 5% are summarized in Table 2. The incidence of grade 3/4 AEs was 42.3% (22/52). White

blood cell decrease, and neutrophil decrease were the most common grade 3/4 AEs. Eight patients (15.4%) experienced immune related adverse events (irAE), and two of them experienced irAEs of grade 3 (Table 2). Reactive cutaneous capillary endothelial proliferation (RCCEP) occurred in 33 patients (63.5%), all of which were grade 1 or 2. Two patients developed immune-related hepatitis after three cycles of chemotherapy combined with immunotherapy. Chemotherapy was continued after the condition was controlled by hormones. Since then, PD1 was not administered again, and both patients achieved cCR or pCR in liver metastases.

Table 2
Adverse events in FAS Set.

Treatment Related Adverse Event	All Grade	Grade 3/4
Total	52 (100)	22 (42.3)
Hematological		
White blood cell decreased	33 (63.5)	5 (9.6)
Neutrophil count decreased	41 (78.8)	19 (36.5)
Platelet count decreased	25 (48.1)	2 (3.8)
Anemia	45 (86.5)	2 (3.8)
Non-hematological		
Alanine aminotranferase increased	26 (50.0)	1 (1.9)
Aspartate aminotranferase increased	27 (51.9)	1 (1.9)
Blood bilirubin increased	5 (9.6)	0
Diarrhea	1 (1.9)	0
Mucositis oral	2 (3.8)	0
Anorexia	17 (32.7)	0
Nausea	17 (32.7)	0
Vomitting	17 (32.7)	0
Alopecia	30 (57.7)	0
Fatigue	5 (9.6)	0
Peripheral sensory neuropathy	24 (46.2)	0
Fever	8 (15.4)	0
Febrile neutropenia	/	2 (3.8)
Rash	11 (21.2)	1 (1.9)
Reactive cutaneouscapillary endothelial proliferation	33 (63.5)	0
Immune Related Adverse events		
Immune-related hepatitis	2 (3.9)	0
Hypoadrenal function	1 (1.9)	1 (1.9)
Dermatitis	1 (1.9)	1 (1.9)

Treatment Related Adverse Event	All Grade	Grade 3/4
Immune-related pneumonitis	1 (1.9)	0
Immune-related myocarditis	3 (5.8)	0

Among the 39 patients who underwent surgery, 12 (30.8%) experienced weight loss of more than 10% but not exceeding 20%, 7(17.9%) had body temperatures higher than 38.5 degrees Celsius, 14 (35.8%) had a hemoglobin decrease over 1 g/dL, and one patient had postoperative intra-abdominal infection and recovered quickly after effective antibiotic treatment. No other surgical complications or surgery-related deaths were observed.

Subgroup analysis

Subgroup analysis was performed to analyze the PFS and OS of the eligible patients according to sex, age, histologic grading, pathologic type, liver metastasis, retroperitoneal lymphatic metastasis, metastatic status, HER2 status, MMR/MSI status and PD-L1 combined positive score (CPS). Univariate analysis showed that SRCC or not (Fig. 3A-B) and histologic grade (Fig. 3C-D) are both related to PFS and OS. There was no significant survival difference in other subgroups, which was illustrated in Fig. 3E and Fig. 3F.

[68Ga]Ga-NOTA-GSI PET/CT in evaluating efficacy of anti-PD-1 immunotherapy combined with Nab-POF regimen

[68Ga]Ga-NOTA-GSI PET/CT imaging was performed in a total of 29 patients after 3–4 cycles of Cam combined with Nab-POF regimen. The SUV value of primary tumor lesion was elevated in 21 patients, and the SUV value of metastatic lesion was elevated in 15 patients. Kaplan-Meier curves showed that patients with elevated SUV value of metastatic lesion had significantly longer PFS (P = 0.024; Fig. 4A) and a tendency of longer OS (P = 0.060; Fig. 4B).

Discussion

Based on the FLOT3 study, the FDZL-GC001 trial assessed PD-1 antibody Cam plus Nab-POF chemotherapy in initially unresectable locally advanced or limited metastatic G/GEJ adenocarcinoma. The primary endpoint was met with an R0 resection rate of 75%. ORR was 88.5%, DCR 98.1%, and 3-year PFS and OS were 56.9% and 62.8%, respectively. Safety was favorable with no treatment-related deaths. This was the first study to use PD-1 antibody combined with Nab-POF for conversion therapy in this patient population.

Retrospective analyses and single-arm clinical trials on conversion therapy for advanced G/GEJ cancer suggested that patients who achieved R0 resection after chemotherapy might obtain a survival benefit[4, 5]. PD-1 antibodies in the first-line treatment of G/GEJ adenocarcinoma[7, 8] improved the ORR and

prolonged the OS time of patients. Also, in the neoadjuvant treatment of locally advanced, resectable G/GEJ cancer, PD-1/PD-L1 antibodies improved the pCR rate[19–21]. These results suggested that PD-1/PD-L1 antibody can help to improve tumor shrinkage and theoretically increase the chance of successful conversion and R0 resection. Therefore, we combined chemotherapy with a PD-1 antibody as conversion therapy in our study. Not only patients with limited metastatic lesions as FLOT3 trial but locally advanced initially unresectable disease was recruited. Compared with FLOT3 trial, the results of patients with limited metastatic G/GEJ disease in our study showed a significantly higher R0 resection rate (80.5% vs 40.8%), a better ORR (85.4% vs 60%) and pCR rate (24.2% vs 16.7%). Thus, we could see our conversion regimen has a higher chance of tumor regression and conversion to resection. In terms of safety, there were no serious postoperative complications in our study, whereas three patients (8.3%) in FLOT3 experienced serious postoperative complications. Patients exhibited good tolerance to preoperative conversion therapy, with all completing the planned 6 cycles. The results showed lower G3/4 leukopenia (9.6% vs 31.4%) and neutropenia (36.5% vs 46.3%) than that of Flot3. The addition of PD-1 antibody has increased irAEs, but they are controllable. Thus, we could see from the above comparison results that our conversion regimen may be more effective and safer than that of FLOT3 study.

Our study achieved favorable outcomes with a six-month PD-1 antibody application period for most surgically treated patients. Current trials typically administer PD-1 antibody for adjuvant therapy or perioperative treatment for one year. In the neoadjuvant treatment of lung cancer, adding only 3 cycles of immunotherapy has significantly increased the pCR rate and improved long-term survival[22, 23]. This suggests that a six-month duration of PD-1 antibody in perioperative treatment may be adequate.

A major innovation of our study is the exploration of chemotherapy regimen. We changed the drugs of FLOT regimen and ultimately established the Nab-POF regimen after dose determination based on the following considerations. Firstly, the triplet regimen achieved better tumor shrinkage[24] and increases the probability of success of conversion therapy than doublet regimen. Triplet regimen may also help better release antigens to stimulate immunity[25]. Secondly, taxane can improve the tumor immune microenvironment potentially through the alteration of cytokine network and the infiltration of T cells[26, 27]. Taxane can also directly activate the killing ability of T-cells, which has a strong therapeutic effect on tumor-derived organoids and mouse models[28]. We also conducted cytological experiments (to be reported separately) and found that the same dose of Nab-PTX and solvent-based paclitaxel had the same ability to kill GC cells, the same activating effect on T cells and a synergistic antitumor effect with the PD1 antibody. Adding Nab-PTX to the 5-Fu/oxaliplatin doublet regimen may enhance synergy with PD1 antibody. In our study, oxaliplatin and 5-Fu doses match the FLOT regimen, while Nab-PTX dose is lower than standard Nab-PTX but higher than solvent-based paclitaxel, maintaining comparable antitumor and T-cell activation effects while reducing toxicity. This approach avoids T-cell suppression from docetaxel-related myelosuppression in FLOT and eliminates immunosuppressive hormonal pretreatment required with traditional taxanes.

Compared with FLOT4 study (resectable G/GEJ adenocarcinoma), we achieved higher pCR (21.4% vs 16.0%) and similar 3-yr OS (62.4% vs 57%)[14, 29]. Compared with KEYNOTE-585 (pembrolizumab + FLOT), we achieved higher pCR (21.4% vs 17.0%) and similar 3-yr OS (62.4% vs 62%)[21]. Compared with MATTERHORN (durvalumab + FLOT), we achieved similar pCR (21.4% vs 19.2%) and similar 2-yr OS (74.4% vs 75.7%)[20]. Compared with neoadjuvant therapy in our center, we also achieved similar 3-yr OS[30]. These results suggest that compared with neoadjuvant therapy, our study demonstrated a slightly higher pCR rate and similar long-term survival outcomes. It suggested that the combination of PD1 antibody and Nab-POF regimen chemotherapy has strong tumor-shrinking and conversion effects, even in unresectable patients with initially higher tumor burden and more difficulties to achieve pCR compared to patients with initially resectable tumors.

Recently, the only RCT on conversion therapy, AIO-FLOT5 trial reported its negative results at 2024 ASCO meeting[31]. Interruption of chemotherapy after surgery causing early death and failure to exclude chemotherapy-unresponsive cases may contribute to the failure. Besides, high rate of the protocol deviation (30%) and insufficient pre-surgery conversion immunochemotherapy (only four cycles) also are reasons for the failure of the result. Our conversion study partially overcame these existing issues. First, Nab-PTX instead of docetaxel results in lower hematological toxicity. Second, patients received more sufficient pre-surgery conversion immunochemotherapy (a minimum of six cycles). This approach effectively prevented early recurrence and mortality. None of our patients died within one year after surgery, while in the FLOT5 trial, 8% of patients died within 3 months postoperatively. As a result, we obtained better short and long-term outcomes than those of FLOT5 study. Therefore, our treatment regimen is worthy of being studied in a RCT in the future.

A watch-and-wait strategy for patients with rectal cancer who achieve a cCR after neoadjuvant therapy is associated with better quality of life and functional outcome, without an apparent detriment in survival, compared with historical controls treated with chemoradiotherapy and surgery[32, 33]. In our study, three patients had cCR, we adopted the watch-and-wait strategy for patients who wanted to preserve their stomach but did not want surgery. At the last follow-up, the three patients had survived without tumors for 17, 29, and 34 months, respectively, and were still alive.

It is of great importance to search for factors that can predict therapeutic efficacy to help screen out patients who can benefit from conversion therapy. Multivariate analysis showed that good results have been achieved regardless of Her2 status, PD-L1 CPS, whether local or limited, or metastatic site, and MSI status, while only patients with SRCC have poor outcome and are not likely to benefit from conversion therapy. In addition, we have also constructed an exosome liquid biopsy efficacy prediction model. We did a comprehensive analysis of tumor immune microenvironment (TIME), transcriptome dynamics, and gut microbiota in relation to clinical outcomes. The details were illustrated in Supplementary document 1.

Granzyme B, a serine protease, is crucial for the human immune system and functions as an indicator of cellular activation. Theoretically, the isotope-labeled granzyme B PET has the potential to indicate T cell

activation and predict immunotherapy effectiveness. Preclinical studies suggest that granzyme B PET imaging can serve as a quantitatively useful predictive biomarker for efficacious responses to cancer immunotherapy[34, 35]. Our nuclear medicine group conducted the first prospective clinical tria[18] of [68Ga]Ga-NOTA-GSI PET/CT and found that GSI PET/CT is a promising tool for predicting the early response to combined immunotherapy in GC patients. In our study, we discovered that it could predict long-term survival outcomes as metastatic lesions with GSI uptake had a significantly longer PFS. We innovatively adopted the method of GSI PET/CT to detect the activity of T cells, and discovered that it can predict the long-term effects of immunochemotherapy, which is helpful for screening the patients that can benefit from the conversion therapy strategy. Also, the exploratory [68Ga]Ga-NOTA-GSI PET/CT imaging revealed a promising correlation between radiotracer avidity and GZMB expression in the tumor.

Overall, PD-1 antibody Cam combined with Nab-POF regimen chemotherapy safely induced high R0 resection rate with promising long-term effects, providing a new conversion drug treatment option for patients with initially unresectable locally advanced or limited metastatic G/GEJ cancer. The findings warrant further prospective randomize controlled investigations.

Declarations

Aknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

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Disclosure

The authors have declared no conflicts of interest.

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Figures

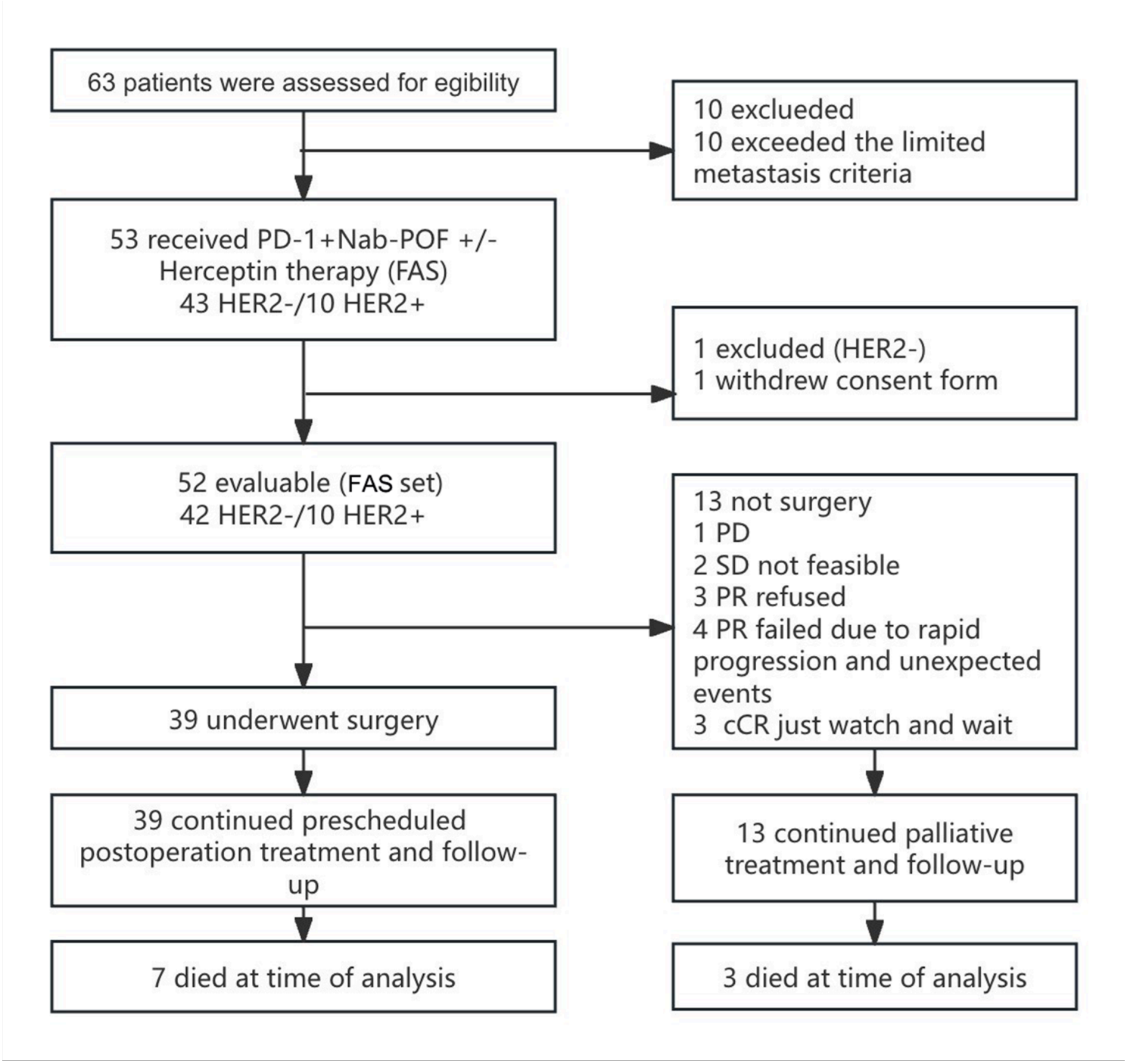


Figure 1

Trial profile. FAS, full analysis set; Nab-POF, nanoparticle albumin-bound paclitaxel, oxaliplatin, 5-FU; PD-1, Programmed Cell Death 1; HER2, Human Epidermal Growth Factor Receptor 2; PD, Progressive Disease; SD, Stable Disease; PR, Partial Response.

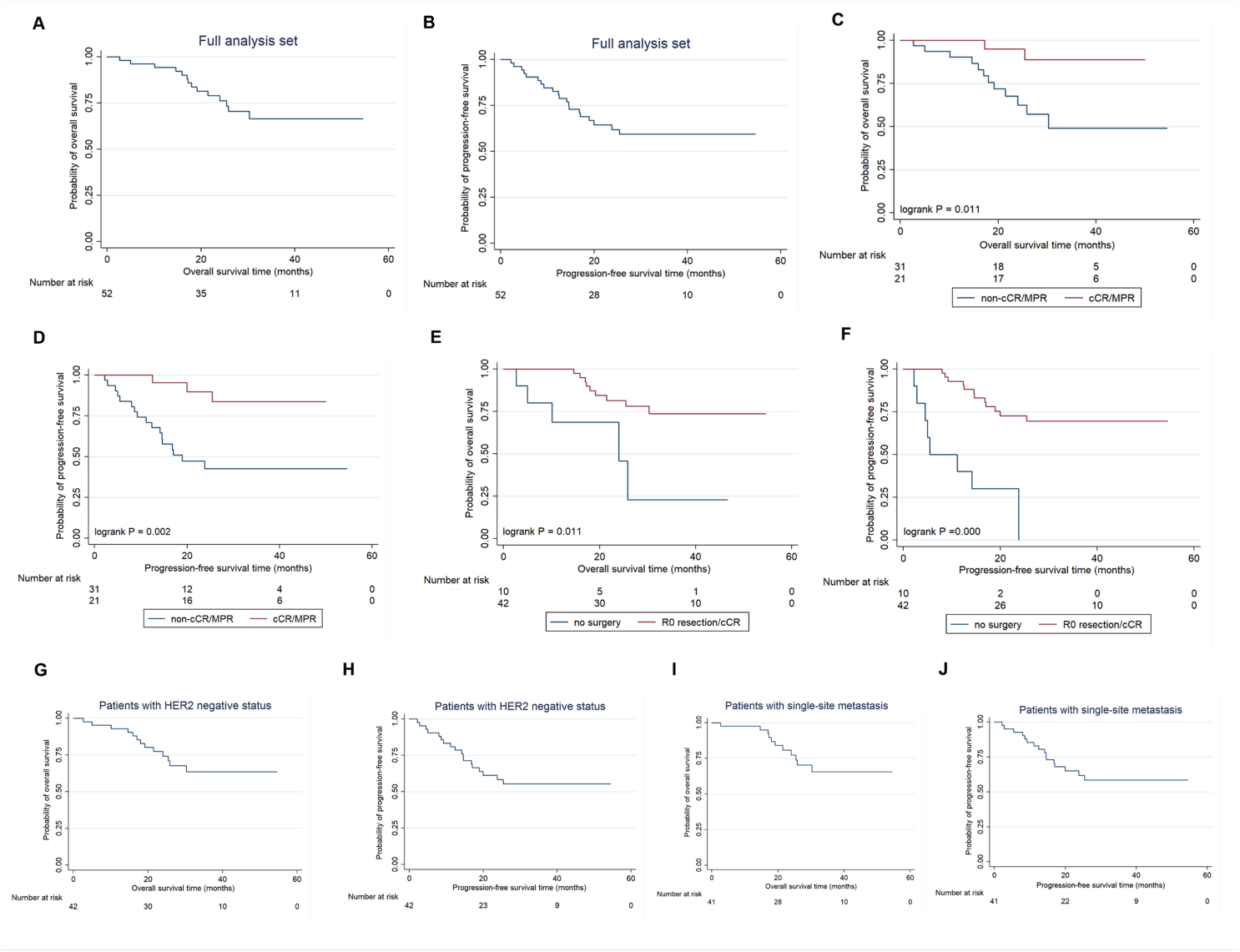


Figure 2

Kaplan-Meier estimates of survival for patients with G/GEJ cancer. (A) OS curves of patients in the FAS set. (B) PFS curves of patients in the FAS set. Patients with cCR or MPR had a less favorable OS (C) and significantly longer PFS (D) than others. Patients who achieved cCR or R0 resection had a tendency of longer OS (E) and significantly longer PFS (F) than those who did not achieve cCR or the criteria of resection. (G) OS curves of patients with HER2 negative status. (H) PFS curves of patients with HER2 negative status. (I) OS curves of patients with single-site metastasis. (J) PFS curves of patients with single-site metastasis. Abbreviations: PFS, progression-free; OS, overall survival.

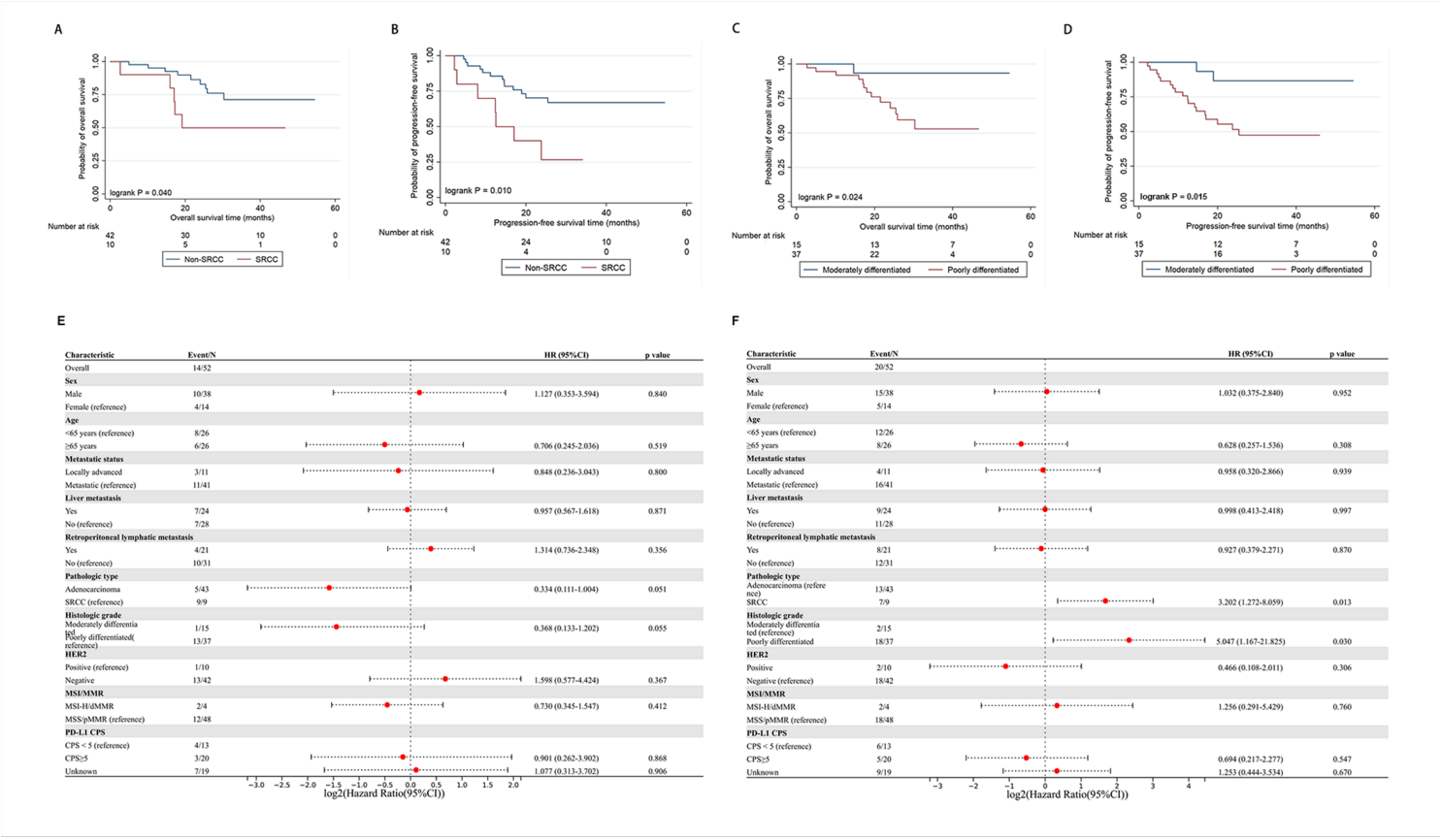


Figure 3

Subgroup analysis of PFS and OS. Patients with SRCC had significantly shorter OS (A) and PFS (B) than those with non-SRCC. Patients with moderately differentiated histologic grade had significantly longer PFS (C) and OS (D) than those with poorly differentiated histologic grade. The forest plot with difference for PFS (E) and OS (F) in subgroups. Abbreviations: PFS, progression-free; OS, overall survival; SRCC, signet ring cell carcinoma.

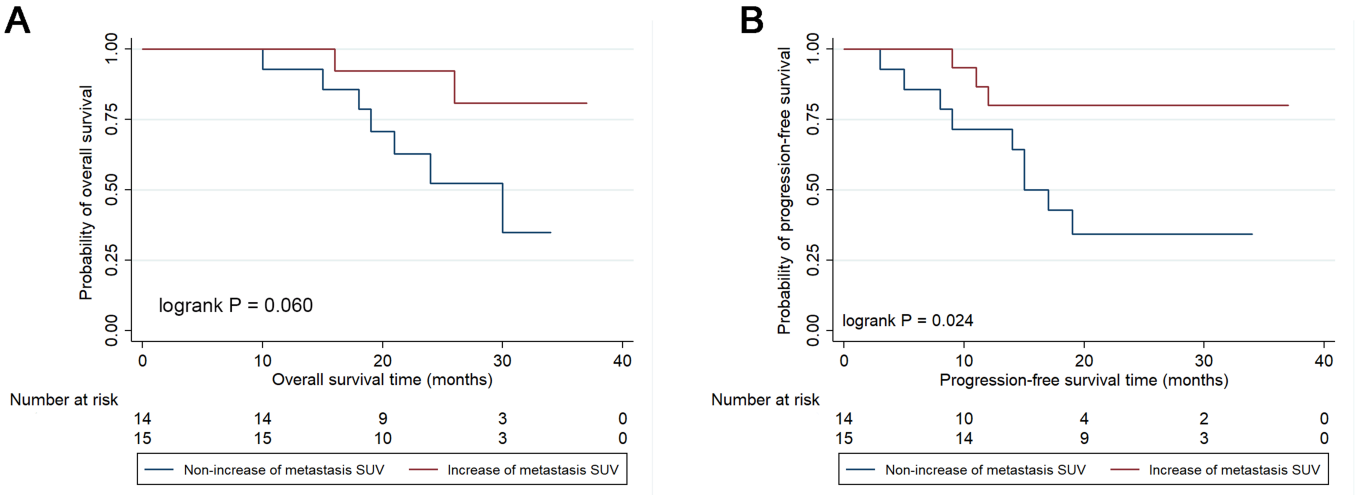


Figure 4

[68Ga]Ga-NOTA-GSI PET/CT in efficacy evaluation. (A) Patients with increase of metastasis SUV had significantly longer PFS time. (B) Patients with increase of metastasis SUV had a tendency of longer OS time.

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