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Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: Study protocol for a prospective, single-arm, phase II clinical trial

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Abstract

Introduction

Neoadjuvant chemotherapy has been demonstrated to be effective and recommended as the standard treatment option in patients with locally advanced gastric or gastroesophageal junction (G/GEJ) cancer. In this study, we will explore the efficacy and safety of chemotherapy combined with cadonilimab, a PD-1/CTLA-4 bispecific antibody, in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma.

Methods and analysis

This is a prospective, single-arm, open-label, phase 2 trial that will enrol 37 patients in total. Eligible patients will be registered and receive three cycles of SOX regimen in combination with cadonilimab. Radical D2 gastrectomy will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. The primary endpoint is the pathological complete response (pCR) rate. Secondary endpoints include R0 resection rate, major pathological response (MPR), objective response rate (ORR), 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety.

Ethics and dissemination

Written informed consent will be required from and provided by all patients enrolled. The study protocol has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526). This is the first study to explore the efficacy and safety of neoadjuvant anti-PD-1/CTLA-4 bispecific antibody immunotherapy combined with chemotherapy for resectable, locally advanced G/GEJ cancer, the results of which may provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma.

Trial registration

The study is prospectively registered in the Clinical Trials Registry Platform (ClinicalTrials.Gov) with registration number NCT05948449.

Keywords

gastric cancer, neoadjuvant therapy, S-1, oxaliplatin, cadonilimab

Strengths and limitations of this study

- This is the first study to explore the efficacy and safety of neoadjuvant anti-PD-1/CTLA-4 bispecific antibody immunotherapy combined with chemotherapy for resectable, locally advanced G/GEJ cancer.
- Inclusion/exclusion criteria compatible with the study objectives.
- Simon's two-stage Minimax approach will minimize the sample size.
- As a single-arm, open-label, prospective phase II clinical trial, no control group is used in this clinical trial.

Introduction

Gastric or gastroesophageal junction (G/GEJ) cancer is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths. In 2020, over one million new cases and 769,000 deaths of G/GEJ cancer were estimated to occur globally (1). Surgery is still the main curative treatment for G/GEJ cancer; however, most of patients undergoing gastrectomy will experience disease recurrence due to residual tumor or tumor micrometastasis (2).

Neoadjuvant therapy may significantly reduce the tumor burden, increase the R0 resection rate, reduce the postoperative recurrence rate, and evaluate the tumor response to the treatment regimen. Currently, neoadjuvant therapy has been widely applied to the treatment of a series of cancers, such as breast, rectal, esophageal, head and neck, lung, prostate and many other cancer types (3-6). The MAGIC study from the UK established the role of neoadjuvant chemotherapy in gastric cancer, while the PRODIGY study in South Korea and the RESONANCE and RESOLVE studies in China further confirmed that neoadjuvant chemotherapy can improve the R0 resection rate and prognosis of gastric cancer patients without increasing the incidence of severe postoperative complications (7-10). Although studies have demonstrated the clinical benefit of neoadjuvant chemotherapy for G/GEJ cancer, the pathological complete response (pCR) and long-term survival rates are still unsatisfactory.

Immune checkpoint inhibitors (ICIs), which target programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), have shown promising antitumor effects and revolutionized the treatment of malignancies. Recently, the combination of ICIs and chemotherapy has shown prolonged overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone and reduced the risk of death by 20-35% in the first-line setting of

advanced or metastatic G/GEJ cancer patients in the CheckMate 649 and ORIENT-16 studies (11, 12). The inspiring results of these studies give us rational reasons to further investigate the application of this strategy in neoadjuvant therapy of locally advanced G/GEJ cancer patients. In a single arm, phase II clinical study, Jiang et al. evaluated the efficacy of sintilimab combined with XELOX regimen in locally advanced, resectable G/GEJ adenocarcinoma. A total of 36 patients were enrolled, all of whom underwent surgery, with an R0 resection rate of 97.2%. The pCR and major pathological response (MPR) rates were 19.4% (95% CI: 8.8% to 35.7%; 90% CI: 10.7% to 33.1%) and 47.2% (95% CI: 31.6% to 64.3%), respectively. The DFS and OS at one year were 90.3% (95% CI: 80.4% to 100.0%) and 94.1% (95% CI: 86.5% to 100.0%), respectively (13). In another similar study, the combination of tislelizumab and SOX also showed promising efficacy and safety in neoadjuvant treatment for locally advanced, resectable G/GEJ adenocarcinoma. Thirty-two patients were included in the study. Seventeen patients (53.1%) obtained MPR (≤ 10% survival tumor cells), and 8 patients (25%) achieved pathological complete remission. The annual RFS and OS were 90.0% and 91.4%, respectively (14). These results provide new insight and suggest that chemotherapy combined with immunotherapy may represent a promising therapy for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma. Cadonilimab (AK104), a novel tetrameric form of a PD-1/CTLA-4 bispecific antibody, could retain the efficacy benefit derived from the combination of anti-PD-1 and anti-CTLA-4 while conferring superior safety compared to the coadministration of these individual agents. In recent clinical studies, cadonilimab has shown excellent efficacy and safety in various tumors, including cervical, nasopharyngeal, liver, and other cancers. On June 29, 2022, cadonilimab was approved in China for patients with recurrent or metastatic cervical cancer who failed previous platinum-based chemotherapy (15). In addition, the efficacy and safety of cadonilimab combined with chemotherapy as first-line treatment for patients with

advanced or metastatic G/GEJ adenocarcinoma was announced at the 2022 American Society of Clinical Oncology Gastrointestinal Oncology Symposium (ASCO GI). A total of 96 patients were included, and 88 patients (92%) underwent at least one tumor assessment. The objective response rate (ORR) was 65.9% (58/88), with 2 cases (2.3%) of complete response and 56 cases (63.6%) of partial response. The disease control rate (DCR) was 92.0% (81/88). The median PFS was 7.10 months (95% CI, 5.55-10.48), and the median OS was 17.41 months (95% CI, 12.35-NE) (16). The above results confirm that the combination of cadonilimab and chemotherapy is a potential new treatment option in the first-line setting of gastric cancer.

Inspired by these findings, we conduct a single-arm, phase 2 trial to explore the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. Moreover, we will also explore the predictive biomarkers of immunotherapy response, and establish a predictive model to screen out patients who might benefit from the neoadjuvant immunotherapy-chemotherapy regimen.

Methods and analysis

This is a prospective, single-arm, open-label, phase 2 trial designed to assess the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. All subjects should provide written informed consent before enrollment. The study is prospectively registered at ClinicalTrials.Gov (NCT 05948449). Figure 1 shows an overview of the study design.

Endpoints

The primary endpoint is the pCR rate. Secondary endpoints include R0 resection rate, MPR, ORR (defined as the proportion of patients with the best overall response of complete response (CR) or partial

response (PR)) before surgery, 2-year disease-free survival (DFS) rate, 2-year OS rate and safety profile of the neoadjuvant regimen. Exploratory endpoints include predictive biomarkers of immunotherapy response in the tumor tissue/peripheral blood. The primary analyses will be performed in the intention-to-treat population. All AEs will be analyzed in the safety population, defined as patients administered at least one dose of neoadjuvant treatment. Neoadjuvant or adjuvant treatment emergent AEs were reported separately due to the different regimens applied. Surgery-related morbidity and mortality were analyzed in the per-protocol population, defined as patients who were compliant with the study protocol and proceeded to surgery.

Study population and Eligibility criteria

Inclusion Criteria:

1. Age 18-75 years.
2. Histologically or cytologically confirmed diagnosis of locally advanced G/GEJ adenocarcinoma (cT3-T4a, N+, M0) as assessed by exploratory laparoscopic surgery, ultrasonography and/or CT/MRI.
3. Resectable G/GEJ cancer, as judged by experienced surgeons.
4. There was no previous antitumor treatment.
5. The expected survival is more than 3 months.
6. ECOG PS≤1.
7. Adequate organ function including the following:

- Total bilirubin ≤1.5 times the upper limit of normal (ULN);

- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3×ULN;
- Alkaline phosphatase≤2.5×ULN (if the tumor invaded the liver, ≤3×ULN);
- Serum creatinine≤1.5×ULN;
- Serum amylase and lipase≤1.5×ULN;
- International standardized ratio (INR)/partial thromboplastin time (PTT)≤1.5×ULN;
- Platelet count ≥ 75,000 /mm^3;
- Hemoglobin (Hb) ≥ 9 g/dL;
- Absolute neutrophil count (ANC) ≥ 1500/mm^3;

8. Strict contraception.
9. Patients must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

Exclusion Criteria:

1. Unable to comply with the research program or procedures.
2. Undergoing other drug clinical trials or having participated in any drug clinical trials one month before enrollment.
3. Active autoimmune disease or history of refractory autoimmune disease.
4. Receiving corticosteroids (> 10mg/d prednisone or equivalent dose of steroids) or other systematic immunosuppression therapies within 14 days before enrollment, excluding the following therapies:

steroid hormone replacement therapy (≤10mg/d); local steroid therapy; and short-term, prophylactic steroid therapy for preventing allergies or nausea and vomiting.

5. Active or clinically significant cardiac disease:

- Congestive heart failure > New York Heart Association (NYHA) class 2;
- Active coronary artery disease;
- Arrhythmias requiring treatment other than β-blockers or digoxin;
- Unstable angina (with angina symptoms at rest), new angina within 3 months before enrollment, or new myocardial infarction within 6 months before enrollment

6. Evidence or history of bleeding diathesis or coagulopathy.

7. Grade 3 bleeding events 4 weeks before enrollment.

8. Thromboembolism or arteriovenous events, such as cerebrovascular events (including transient ischemic attack), deep vein thrombosis or pulmonary embolism, occurred 6 months before enrollment.

9. Currently taking anticoagulants.

10. Other tumors that have not been treated or exist at the same time, except carcinoma in situ of the cervix, treated basal cell carcinoma or superficial bladder tumor. If the tumor was cured and no evidence of disease was found for more than 3 years, the patient can be enrolled. All other tumors must be treated at least 3 years before enrollment.

11. Patients with pheochromocytoma.

12. Patients with a history of HIV infection or active hepatitis B/C.

13. Ongoing > level 2 infection.
14. Symptomatic brain metastasis or meningioma.
15. Unhealed wounds, ulcers or fractures.
16. Renal failure patients requiring blood or peritoneal dialysis.
17. Dehydration≥ 1 grade.
18. Epileptic that needs medication.
19. Active, symptomatic interstitial pneumonia, pleural or ascites that causes dyspnea (dyspnea ≥ 2 grade).
20. History of organ transplantation (including corneal transplantation).
21. Allergic to research drugs or similar drugs, or suspected allergies.
22. Malabsorption patients.
23. Pregnant or lactating women.
24. The investigator believes that patients who are not suitable for the study.
25. Medical, psychological or social conditions can affect the recruitment of patients and evaluation of study results.
26. Other antitumor therapy (chemotherapy, radiotherapy, surgery, immunotherapy, biotherapy, chemoembolization) other than investigator drugs. Palliative external irradiation for non-target lesions is allowed.
27. Previously used oxaliplatin, S-1 or cadonilimab.

28. Major surgery 4 weeks before recruitment, open biopsy or major trauma surgery (excluding biliary stents, or percutaneous biliary drainage).

29. Treatment with antitumor Chinese herbal medicine.

30. History of allogeneic blood transfusion within 6 months.

Intervention

Laparoscopic exploration should be performed to detect occult peritoneal metastases and inspect the primary lesion, liver, diaphragm, pelvic organs, bowel and omentum. Patients who meet the inclusion criteria will be enrolled and sign the informed consent form. Then, 3 cycles of neoadjuvant therapy will be administered: S-1: 40-60 mg Bid, d1-14, q3w; oxaliplatin: 130 mg/m^2, iv drip, d1, q3w; cadonilimab (AK104): 10 mg/Kg, iv drip, d1, q3w. Radical D2 gastric cancer resection will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. Afterwards, we will recommend the best postoperative adjuvant treatment, and the adjuvant regimen will be determined by the patients themselves. Follow up will be conducted every 3 months (according to RECIST 1.1 standards) until tumor recurrence, death, or 2 years after surgery.

Statistical analysis

The sample size was calculated based on the assumption that the pCR rate of neoadjuvant SOX chemotherapy is 5.6%. A total of 33 patients treated with neoadjuvant cadonilimab in combination with SOX regimen will provide 80% power to detect a pCR rate of 20% at a one-sided 5% alpha level. Considering a 10% discontinuation rate, 37 assessable patients will be enrolled in the study. Descriptive statistics of baseline and clinicopathological characteristics will be performed. The pCR, MPR, ORR and R0 resection rate will be calculated, and the corresponding CIs will be estimated by the Blaker's binomial

exact method. Kaplan-Meier estimates of DFS and OS probabilities will also be determined, with respective 95% CIs.

Ethics and dissemination

Written informed consent will be required for patients enrolled. This study will be conducted under the Declaration of Helsinki, without causing any extra harm or risks to patients. The protocol has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526) and has been prospectively registered in the Clinical Trials Registry Platform (ClinicalTrials.Gov) with registration number NCT05948449. The protocol and the results of the study will be disseminated to be presented at international oncology congresses, and published in peer-reviewed journals.

Discussion

G/GEJ cancer remains one of the most commonly diagnosed malignancies worldwide. Gastrectomy is the main curative treatment for G/GEJ cancer; however, disease recurrence or metastasis will occur in most patients undergoing gastrectomy. In recent decades, a number of studies have investigated the efficacy of adjuvant chemotherapy in patients with resectable gastric cancer. In the ACTS-GC trial, 1059 patients with stage II or III gastric cancer were enrolled and randomly assigned to either the surgery plus S-1 group or the surgery-only group. The 5-year OS rates in the surgery plus S-1 group and surgery-only group were 71.7 and 61.1% respectively, and the 5-year RFS rates were 65.4 and 53.1% respectively (17). In another study conducted in South Korea, mainland China and Taiwan (the CLASSIC trial), 1035 patients with stage II-IIIB gastric cancer who underwent D2 radical gastrectomy were randomly assigned to the adjuvant chemotherapy (XELOX) group or observation alone group. The 5-year DFS rates were 68 and 53%, respectively (18). Based on the results of these two studies, D2 radical gastrectomy with

adjuvant chemotherapy has been recommended as the standard treatment option for patients with G/GEJ cancer in stage II–III. However, adjuvant therapy for gastric cancer has entered a bottleneck stage in recent years. Many patients experience short-term recurrence after surgery, especially in patients with stage III gastric cancer.

Neoadjuvant therapy has been widely applied to the treatment of several cancers. The MAGIC study, PRODIGY study, and the RESONANCE and RESOLVE studies also established the role of neoadjuvant chemotherapy in G/GEJ cancer, and neoadjuvant chemotherapy has been recommended in patients with locally advanced, resectable G/GEJ cancer by the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Chinese Society of Clinical Oncology (CSCO) clinical practice guidelines. Recently, a number of studies have also evaluated the efficacy of chemotherapy plus PD-1 inhibitors in neoadjuvant therapy of locally advanced G/GEJ cancer patients. The addition of PD-1 inhibitors significantly increases the pCR rate, R0 resection rate and long-term survival, indicating that chemotherapy plus PD-1 inhibitors is a promising treatment option for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma (13, 14).

In addition to PD-1 and PD-L1, CTLA-4 is regarded as another key immune checkpoint. CTLA-4 is not expressed on the surface of initial T cells. After T-cell activation, CTLA-4 expressed on the surface of activated T cells can competitively bind to ligand B7 with CD28, thereby reducing T-cell activation levels and inhibiting T-cell proliferation (19). In theory, CTLA-4 monoclonal antibodies and PD-1 monoclonal antibodies can cooperate and coordinate with each other, effectively weakening tumor immune escape and promoting the killing effect of the immune system. Therefore, the combination of CTLA-4 monoclonal antibody and PD-1 monoclonal antibody may provide a strong foundation for dual immune combination therapy in clinical practice. In the CheckMate 067 study, Hodi et al. investigated

the efficacy and safety of nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone in patients with advanced melanoma (20). Patients with previously untreated, unresectable, stage III or stage IV melanoma were randomly assigned 1:1:1 to the nivolumab plus ipilimumab group, the nivolumab group, or the ipilimumab group. At a minimum follow-up of 48 months from the date that the final patient was enrolled and randomized, the median OS was not reached (95% CI 38·2-not reached) in the nivolumab plus ipilimumab group, 36·9 months (28·3-not reached) in the nivolumab group, and 19·9 months (16·9-24·6) in the ipilimumab group. The median PFS was 11·5 months (95% CI 8·7-19·3) in the nivolumab plus ipilimumab group, 6·9 months (5·1-10·2) in the nivolumab group, and 2·9 months (2·8-3·2) in the ipilimumab group. These results suggested that nivolumab plus ipilimumab can significantly prolong OS and PFS compared with nivolumab alone or ipilimumab alone in patients with advanced melanoma. Subsequently, several studies have also investigated the efficacy of double immunotherapy in non-small cell lung cancer, renal cell carcinoma, colorectal cancer, liver cancer, biliary system tumors and so on (21-24). The combination of CTLA-4 and PD-1 blockers was shown to significantly enhance efficacy, and ipilimumab plus nivolumab was approved for the treatment of metastatic melanoma, advanced renal cell carcinoma and metastatic colorectal cancer with MMR/MSI-H aberrations. Although with promising efficacy, the combination of CTLA-4 and PD-1 blockers significantly increased treatment-related grade 3-4 adverse events (AEs). For example, in the CheckMate 067 study, treatment-related grade 3-4 AEs were reported in 22% (70/313) of patients in the nivolumab alone group and 28% (86/311) of patients in the ipilimumab group, while in the nivolumab plus ipilimumab group, treatment-related grade 3-4 AEs were reported in 59% (185/313) of patients.

Cadonilimab (AK104) is a novel tetrameric form of a PD-1/CTLA-4 bispecific antibody. In previous studies, cadonilimab has shown promising efficacy and superior safety compared to the coadministration

of these individual agents in gastric, cervical, nasopharyngeal, liver, and other cancers. In this study, we conduct a prospective, single-arm, phase 2 trial to investigate the efficacy and safety of chemotherapy plus cadonilimab as neoadjuvant treatment for locally advanced G/GEJ adenocarcinoma. The primary endpoint in the analysis is the pCR rate, as less time will be required to obtain the primary results. Furthermore, to illustrate the survival benefit, the 2-year DFS rate and 2-year OS rate will also be evaluated. To the best of our knowledge, this is the first study to explore the efficacy of neoadjuvant anti-PD-1/CTLA-4 immunotherapy combined with chemotherapy in G/GEJ cancer. We hope this study will provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma and explore a series of predictive biomarkers of immunotherapy response.

Contributors

JKH, HFG and PFZ participated in the design of the study; PFZ, WHZ, XJL and DH wrote the study protocol. PFZ, KY, HFG and JKH are responsible for conducting and coordination of the trial. All authors reviewed the manuscript draft and approved the final manuscript.

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Competing interests

The authors declare that there is no conflict of interest.

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Figure 1. Study Flow Chart

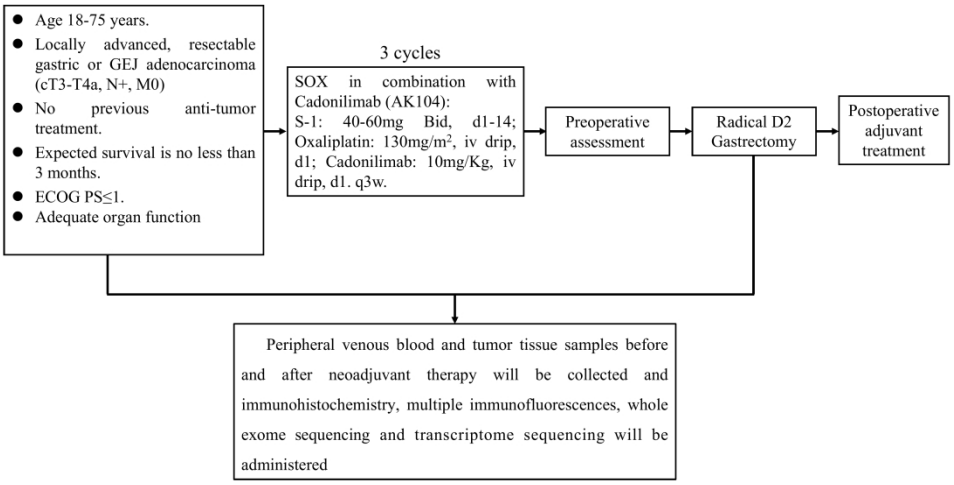

Figure 1. Study Flow Chart

338x190mm (300 x 300 DPI)

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Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: Study protocol for a single-arm, phase II clinical trial

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Abstract

Introduction

Neoadjuvant chemotherapy has been demonstrated to be effective and recommended as the standard treatment option in patients with locally advanced gastric or gastroesophageal junction (G/GEJ) cancer. In this study, we will explore the efficacy and safety of chemotherapy combined with cadonilimab, a PD-1/CTLA-4 bispecific antibody, in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma.

Methods and analysis

This is a single-center, single-arm, open-label, phase 2 trial that will enrol 37 patients in total. Eligible patients will be registered and receive three cycles of SOX regimen in combination with cadonilimab. Radical D2 gastrectomy will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. The primary endpoint is the pathological complete response (pCR) rate. Secondary endpoints include R0 resection rate, major pathological response (MPR), objective response rate (ORR), 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety. The first participant was recruited on September 1, 2023 and the enrollment will be completed in July 2025.

Ethics and dissemination

Written informed consent will be required from and provided by all patients enrolled. The study protocol (version 3.0, April 28, 2023) has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526) and conducted under the Declaration of Helsinki. The results of the study may provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma.

Trial registration

The study is prospectively registered in the Clinical Trials Registry Platform (ClinicalTrials.Gov) with registration number NCT05948449.

Keywords

gastric cancer, neoadjuvant therapy, S-1, oxaliplatin, cadonilimab

Strengths and limitations of this study

- Simon's two-stage optimal approach will allow for early termination due to the absence of treatment efficacy in the first stage.
- Inclusion/exclusion criteria compatible with the study objectives.
- Simon's two-stage Minimax approach will minimize the sample size.
- As a single-arm, open-label, phase II clinical trial, no control group is used in this clinical trial.

Introduction

Gastric or gastroesophageal junction (G/GEJ) cancer is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths. In 2020, over one million new cases and 769,000 deaths of G/GEJ cancer were estimated to occur globally [1]. Surgery is still the main curative treatment for G/GEJ cancer; however, most of patients undergoing gastrectomy will experience disease recurrence due to residual tumor or tumor micrometastasis [2].

Neoadjuvant therapy may significantly reduce the tumor burden, increase the R0 resection rate, reduce the postoperative recurrence rate, and evaluate the tumor response to the treatment regimen. Currently, neoadjuvant therapy has been widely applied to the treatment of a series of cancers, such as breast, rectal, esophageal, head and neck, lung, prostate and many other cancer types [3-6]. The MAGIC study from the UK established the role of neoadjuvant chemotherapy in gastric cancer, while the PRODIGY study in South Korea and the RESONANCE and RESOLVE studies in China further confirmed that neoadjuvant chemotherapy can improve the R0 resection rate and prognosis of gastric cancer patients without increasing the incidence of severe postoperative complications [7-10]. Although studies have demonstrated the clinical benefit of neoadjuvant chemotherapy for G/GEJ cancer, the pathological complete response (pCR) and long-term survival rates are still unsatisfactory.

Immune checkpoint inhibitors (ICIs), which target programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), have shown promising antitumor effects and revolutionized the treatment of malignancies. Recently, the combination of ICIs and chemotherapy has shown prolonged overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone and reduced the risk of death by 20-35% in the first-line setting of

advanced or metastatic G/GEJ cancer patients [11, 12]. The inspiring results of these studies give us rational reasons to further investigate the application of this strategy in neoadjuvant therapy of locally advanced G/GEJ cancer patients. In a single arm, phase II clinical study, Jiang et al. evaluated the efficacy of sintilimab combined with XELOX regimen in locally advanced, resectable G/GEJ adenocarcinoma. A total of 36 patients were enrolled, all of whom underwent surgery, with an R0 resection rate of 97.2%. The pCR and major pathological response (MPR) rates were 19.4% (95% CI: 8.8% to 35.7%; 90% CI: 10.7% to 33.1%) and 47.2% (95% CI: 31.6% to 64.3%), respectively. The DFS and OS at one year were 90.3% (95% CI: 80.4% to 100.0%) and 94.1% (95% CI: 86.5% to 100.0%), respectively [13]. In another similar study, the combination of tislelizumab and SOX also showed promising efficacy and safety in neoadjuvant treatment for locally advanced, resectable G/GEJ adenocarcinoma. Thirty-two patients were included in the study. Seventeen patients (53.1%) obtained MPR (≤ 10% survival tumor cells), and 8 patients (25%) achieved pathological complete remission. The annual RFS and OS were 90.0% and 91.4%, respectively [14]. These results provide new insight and suggest that chemotherapy combined with immunotherapy may represent a promising therapy for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma.

Cadonilimab (AK104), a novel tetrameric form of a PD-1/CTLA-4 bispecific antibody, could retain the efficacy benefit derived from the combination of anti-PD-1 and anti-CTLA-4 while conferring superior safety compared to the coadministration of these individual agents. In recent clinical studies, cadonilimab has shown excellent efficacy and safety in various tumors, including cervical, nasopharyngeal, liver, and other cancers. On June 29, 2022, cadonilimab was approved in China for patients with recurrent or metastatic cervical cancer who failed previous platinum-based chemotherapy [15]. In addition, the efficacy and safety of cadonilimab combined with chemotherapy as first-line treatment for patients with advanced

or metastatic G/GEJ adenocarcinoma was announced at the 2022 American Society of Clinical Oncology Gastrointestinal Oncology Symposium (ASCO GI). A total of 96 patients were included, and 88 patients (92%) underwent at least one tumor assessment. The objective response rate (ORR) was 65.9% (58/88), with 2 cases (2.3%) of complete response and 56 cases (63.6%) of partial response. The disease control rate (DCR) was 92.0% (81/88). The median PFS was 7.10 months (95% CI, 5.55-10.48), and the median OS was 17.41 months (95% CI, 12.35-NE) [16]. The above results confirm that the combination of cadonilimab and chemotherapy is a potential new treatment option in the first-line setting of gastric cancer.

Inspired by these findings, we conduct a single-arm, phase 2 trial to explore the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. Moreover, we will also explore the predictive biomarkers of immunotherapy response, and establish a predictive model to screen out patients who might benefit from the neoadjuvant immunotherapy-chemotherapy regimen.

Methods and analysis

This is a single-center, single-arm, open-label, phase 2 trial designed to assess the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. Participants will be enrolled from West China Hospital, Sichuan University, Chengdu, China. All subjects should provide written informed consent before enrollment. The study is prospectively registered at ClinicalTrials.Gov (NCT 05948449). The first participant was recruited on September 1, 2023 and the enrollment will be completed in July 2025. Figure 1 shows an overview of the study design.

Endpoints

The primary endpoint is the pCR rate. Secondary endpoints include R0 resection rate, MPR, ORR (defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR)) before surgery, 2-year disease-free survival (DFS) rate, 2-year OS rate and safety profile. Exploratory endpoints include predictive biomarkers of immunotherapy response. The primary analyses will be performed in the intention-to-treat (ITT) population. All AEs will be analyzed in the safety population, defined as patients administered at least one dose of neoadjuvant treatment. Neoadjuvant or adjuvant treatment emergent AEs were reported separately due to the different regimens applied. Surgery-related morbidity and mortality were analyzed in the per-protocol population, defined as patients who were compliant with the study protocol and proceeded to surgery. To determine whether high pCR rates can translate into longer survival, follow-up of these participant will last for at least 2 years.

Study population and Eligibility criteria

Inclusion Criteria:

1. Age 18-75 years.
2. Histologically or cytologically confirmed diagnosis of locally advanced G/GEJ adenocarcinoma (cT3-T4a, N+, M0) as assessed by exploratory laparoscopic surgery, ultrasonography and/or CT/MRI.
3. Resectable G/GEJ cancer, as judged by experienced surgeons.
4. There was no previous antitumor treatment.
5. The expected survival is more than 3 months.
6. ECOG PS≤1.
7. Adequate organ function including the following:

- Total bilirubin ≤1.5 times the upper limit of normal (ULN);
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3×ULN;
- Alkaline phosphatase≤2.5×ULN (if the tumor invaded the liver, ≤3×ULN);
- Serum creatinine≤1.5×ULN;
- Serum amylase and lipase≤1.5×ULN;
- International standardized ratio (INR)/partial thromboplastin time (PTT)≤1.5×ULN;
- Platelet count ≥ 75,000 /mm^3;
- Hemoglobin (Hb) ≥ 9 g/dL;
- Absolute neutrophil count (ANC) ≥ 1500/mm^3;

8. Strict contraception.
9. Patients must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

Exclusion Criteria:

1. Unable to comply with the research program or procedures.
2. Undergoing other drug clinical trials or having participated in any drug clinical trials one month before enrollment.
3. Active autoimmune disease or history of refractory autoimmune disease.
4. Receiving corticosteroids (> 10mg/d prednisone or equivalent dose of steroids) or other systematic immunosuppression therapies within 14 days before enrollment, excluding the following therapies:

steroid hormone replacement therapy (≤10mg/d); local steroid therapy; and short-term, prophylactic steroid therapy for preventing allergies or nausea and vomiting.

5. Active or clinically significant cardiac disease:

- Congestive heart failure > New York Heart Association (NYHA) class 2;
- Active coronary artery disease;
- Arrhythmias requiring treatment other than β-blockers or digoxin;
- Unstable angina (with angina symptoms at rest), new angina within 3 months before enrollment, or new myocardial infarction within 6 months before enrollment

6. Evidence or history of bleeding diathesis or coagulopathy.

7. Grade 3 bleeding events 4 weeks before enrollment.

8. Thromboembolism or arteriovenous events, such as cerebrovascular events (including transient ischemic attack), deep vein thrombosis or pulmonary embolism, occurred 6 months before enrollment.

9. Currently taking anticoagulants.

10. Other tumors that have not been treated or exist at the same time, except carcinoma in situ of the cervix, treated basal cell carcinoma or superficial bladder tumor. If the tumor was cured and no evidence of disease was found for more than 3 years, the patient can be enrolled. All other tumors must be treated at least 3 years before enrollment.

11. Patients with pheochromocytoma.

12. Patients with a history of HIV infection or active hepatitis B/C.

13. Ongoing > level 2 infection.

14. Symptomatic brain metastasis or meningioma.

15. Unhealed wounds, ulcers or fractures.

16. Renal failure patients requiring blood or peritoneal dialysis.

17. Dehydration≥ 1 grade.

18. Epileptic that needs medication.

19. Active, symptomatic interstitial pneumonia, pleural or ascites that causes dyspnea (dyspnea ≥ 2 grade).

20. History of organ transplantation (including corneal transplantation).

21. Allergic to research drugs or similar drugs, or suspected allergies.

22. Malabsorption patients.

23. Pregnant or lactating women.

24. The investigator believes that patients who are not suitable for the study.

25. Medical, psychological or social conditions can affect the recruitment of patients and evaluation of study results.

26. Other antitumor therapy (chemotherapy, radiotherapy, surgery, immunotherapy, biotherapy, chemoembolization) other than investigator drugs. Palliative external irradiation for non-target lesions is allowed.

27. Previously used oxaliplatin, S-1 or cadonilimab.

28. Major surgery 4 weeks before recruitment, open biopsy or major trauma surgery (excluding biliary stents, or percutaneous biliary drainage).

29. Treatment with antitumor Chinese herbal medicine.

30. History of allogeneic blood transfusion within 6 months.

Intervention

Laparoscopic exploration should be performed to detect occult peritoneal metastases and inspect the primary lesion, liver, diaphragm, pelvic organs, bowel and omentum. Patients who meet the inclusion criteria will be enrolled and sign the informed consent form. Then, 3 cycles of neoadjuvant therapy will be administered: S-1: 40-60 mg Bid, d1-14, q3w; oxaliplatin: 130 mg/m^2, iv drip, d1, q3w; cadonilimab (AK104): 10 mg/Kg, iv drip, d1, q3w. Antiemetic, acid suppressing, and anti-allergic treatments are allowed. Radical D2 gastric cancer resection will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. Afterwards, we will recommend the best postoperative adjuvant treatment, and the adjuvant regimen will be determined by the patients themselves. Follow up will be conducted every 3 months (according to RECIST 1.1 standards) until tumor recurrence, death, or 2 years after surgery.

Statistical analysis

The sample size was calculated based on the assumption that the pCR rate of neoadjuvant SOX chemotherapy is 5.6% [10]. A total of 33 patients treated with neoadjuvant cadonilimab in combination with SOX regimen will provide 80% power to detect a pCR rate of 20% at a one-sided 5% alpha level. Considering a 10% discontinuation rate, 37 assessable patients will be enrolled in the study. Descriptive statistics of baseline and clinicopathological characteristics will be performed. The pCR, MPR, ORR and

R0 resection rate will be calculated, and the corresponding CIs will be estimated by the Blaker's binomial exact method. Kaplan-Meier estimates of DFS and OS probabilities will also be determined, with respective 95% CIs. All efficacy analyses will be performed in the ITT population and all AEs will be analyzed in the safety population, defined as patients administered at least one dose of neoadjuvant treatment.

Patient and public involvement

Patients were not involved in the protocol development and study design. The results will be disseminated to the public through seminars, public talks and peer-reviewed journals.

Ethics and dissemination

Written informed consent will be required for patients enrolled. This study will be conducted under the Declaration of Helsinki, without causing any extra harm or risks to patients. The protocol (version 3.0, April 28, 2023) has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526) and has been prospectively registered in the Clinical Trials Registry Platform (ClinicalTrials.Gov) with registration number NCT05948449. The results of the study will be presented at international oncology congresses and published in peer-reviewed journals.

Discussion

G/GEJ cancer remains one of the most commonly diagnosed malignancies worldwide. Gastrectomy is the main curative treatment for G/GEJ cancer; however, disease recurrence or metastasis will occur in most patients undergoing gastrectomy. In recent decades, a number of studies have investigated the efficacy of adjuvant chemotherapy in patients with resectable gastric cancer. In the ACTS-GC trial, 1059 patients with stage II or III gastric cancer were enrolled and randomly assigned to either the surgery plus S-1 group or the surgery-only group. The 5-year OS rates in the surgery plus S-1 group and surgery-only

group were 71.7 and 61.1% respectively, and the 5-year RFS rates were 65.4 and 53.1% respectively [17]. In another study conducted in South Korea, mainland China and Taiwan (the CLASSIC trial), 1035 patients with stage II-IIIB gastric cancer who underwent D2 radical gastrectomy were randomly assigned to the adjuvant chemotherapy (XELOX) group or observation alone group. The 5-year DFS rates were 68 and 53%, respectively [18]. Based on the results of these two studies, D2 radical gastrectomy with adjuvant chemotherapy has been recommended as the standard treatment option for patients with G/GEJ cancer in stage II–III. However, adjuvant therapy for gastric cancer has entered a bottleneck stage in recent years. Many patients experience short-term recurrence after surgery, especially in patients with stage III gastric cancer.

Neoadjuvant therapy has been widely applied to the treatment of several cancers. The MAGIC study, PRODIGY study, and the RESONANCE and RESOLVE studies also established the role of neoadjuvant chemotherapy in G/GEJ cancer, and neoadjuvant chemotherapy has been recommended in patients with locally advanced, resectable G/GEJ cancer by the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Chinese Society of Clinical Oncology (CSCO) clinical practice guidelines. Recently, a number of studies have also evaluated the efficacy of chemotherapy plus PD-1 inhibitors in neoadjuvant therapy of locally advanced G/GEJ cancer patients. The addition of PD-1 inhibitors significantly increases the pCR rate, R0 resection rate and long-term survival, indicating that chemotherapy plus PD-1 inhibitors is a promising treatment option for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma [13, 14].

In addition to PD-1 and PD-L1, CTLA-4 is regarded as another key immune checkpoint. CTLA-4 is not expressed on the surface of initial T cells. After T-cell activation, CTLA-4 expressed on the surface of activated T cells can competitively bind to ligand B7 with CD28, thereby reducing T-cell activation

levels and inhibiting T-cell proliferation [19]. In theory, CTLA-4 monoclonal antibodies and PD-1 monoclonal antibodies can cooperate and coordinate with each other, effectively weakening tumor immune escape and promoting the killing effect of the immune system. Therefore, the combination of CTLA-4 monoclonal antibody and PD-1 monoclonal antibody may provide a strong foundation for dual immune combination therapy in clinical practice. In the CheckMate 067 study, Hodi et al. investigated the efficacy and safety of nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone in patients with advanced melanoma [20]. Patients with previously untreated, unresectable, stage III or stage IV melanoma were randomly assigned 1:1:1 to the nivolumab plus ipilimumab group, the nivolumab group, or the ipilimumab group. At a minimum follow-up of 48 months from the date that the final patient was enrolled and randomized, the median OS was not reached (95% CI 38·2-not reached) in the nivolumab plus ipilimumab group, 36·9 months (28·3-not reached) in the nivolumab group, and 19·9 months (16·9-24·6) in the ipilimumab group. The median PFS was 11·5 months (95% CI 8·7-19·3) in the nivolumab plus ipilimumab group, 6·9 months (5·1-10·2) in the nivolumab group, and 2·9 months (2·8-3·2) in the ipilimumab group. These results suggested that nivolumab plus ipilimumab can significantly prolong OS and PFS compared with nivolumab alone or ipilimumab alone in patients with advanced melanoma. Subsequently, several studies have also investigated the efficacy of double immunotherapy in non-small cell lung cancer, renal cell carcinoma, colorectal cancer, liver cancer, biliary system tumors and so on [21-24]. The combination of CTLA-4 and PD-1 blockers was shown to significantly enhance efficacy, and ipilimumab plus nivolumab was approved for the treatment of metastatic melanoma, advanced renal cell carcinoma and metastatic colorectal cancer with MMR/MSI-H aberrations. Although with promising efficacy, the combination of CTLA-4 and PD-1 blockers significantly increased treatment-related grade 3-4 adverse events (AEs). For example, in the CheckMate

067 study, treatment-related grade 3-4 AEs were reported in 22% (70/313) of patients in the nivolumab alone group and 28% (86/311) of patients in the ipilimumab group, while in the nivolumab plus ipilimumab group, treatment-related grade 3-4 AEs were reported in 59% (185/313) of patients.

Cadonilimab (AK104) is a novel tetrameric form of a PD-1/CTLA-4 bispecific antibody. In previous studies, cadonilimab has shown promising efficacy and superior safety compared to the coadministration of these individual agents in gastric, cervical, nasopharyngeal, liver, and other cancers. In this study, we conduct a single-arm, phase 2 trial to investigate the efficacy and safety of chemotherapy plus cadonilimab as neoadjuvant treatment for locally advanced G/GEJ adenocarcinoma. To the best of our knowledge, this is the first study to explore the efficacy of neoadjuvant anti-PD-1/CTLA-4 immunotherapy combined with chemotherapy in G/GEJ cancer. However, the limitations of our study should also be addressed. First, this is a single-center, single-arm, small sample phase II study, large-cohort, randomized, phase III studies are required to further compare the efficacy and safety of neoadjuvant chemotherapy combined with cadonilimab versus standard chemotherapy in advanced/metastatic GC in the future. Second, the primary endpoint in the study was pCR rate, as less time will be required to obtain the primary results. Whether the high response rate of neoadjuvant therapy can translate into long-term survival benefits remain a focus of interest. Thus, the 2-year DFS rate and 2-year OS rate will also be evaluated to illustrate the survival benefit in the study. We hope this study will provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma and explore a series of predictive biomarkers of immunotherapy response.

Contributors

JKH, HFG and PFZ participated in the design of the study; PFZ, WHZ, XJL and DH wrote the study

protocol. PFZ, KY, HFG and JKH are responsible for conducting and coordination of the trial. All authors reviewed the manuscript draft and approved the final manuscript. JKH and HFG are the guarantor.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data generated in the current study are available from the corresponding author upon reasonable request.

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Figure 1. Study Flow Chart

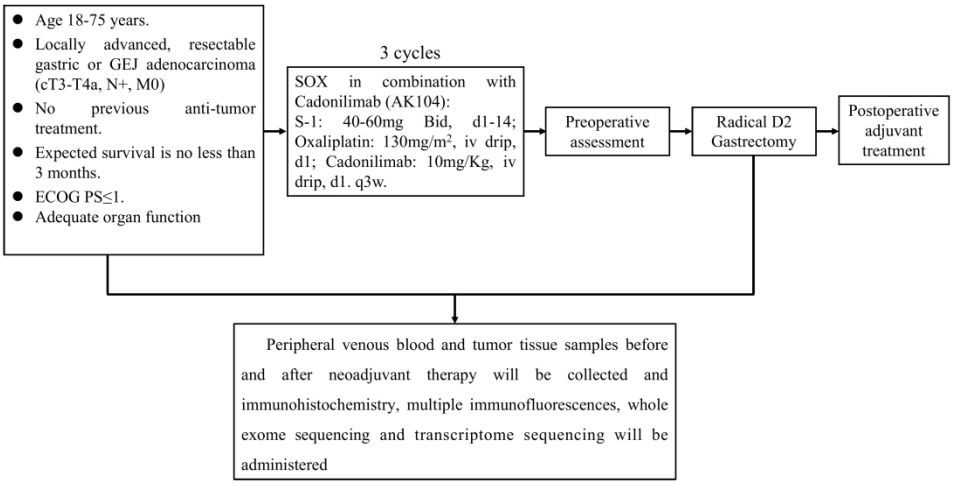

Figure 1. Study Flow Chart

338x190mm (300 x 300 DPI)

Informed Consent Form · Consent Signature Page

Name of study: Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: a single-arm, phase II clinical trial

Sponsor: West China Hospital, Sichuan University

Statement of Investigators: I have informed the participant of the research background, purpose, implementation process, risks, and benefits of a single arm, phase II clinical study evaluating the efficacy and safety of chemotherapy combined with cadonilimab (AK104) in neoadjuvant therapy for locally advanced gastric cancer/gastroesophageal junction adenocarcinoma. We give him/her sufficient time to read the informed consent form, discuss with others, and answer their research questions; I have informed the subject that they can contact the research doctor at any time when encountering research related issues, and can contact the Biomedical Ethics Review Committee of West China Hospital of Sichuan University at any time when encountering issues related to their own rights/interests, and have provided accurate contact information; I have informed the subject that he/she can withdraw from this study without any reason; I have informed the subject that he/she will receive a copy of this informed consent form, which includes my and his/her signatures.

Statement of Participants: I have read the above introduction about this study, and my researchers have fully explained and explained to me the purpose, operation process, potential risks and benefits of participating in this study, and answered all my relevant questions. I voluntarily participate in this study.

Name of participant：

Signature of participant： Date：_ _ YEAR _ _ MONTH _ _ DAY

Email：　　Phone：

Name of legal representative：　　（ if applicable ）

Relationship with participant：

Signature of legal representative：　　Date: _　_ YEAR _　_ MONTH _　_ DAY

Reason for requiring legal representative to sign:

Signature of investigator：　　Date:　_　_ YEAR _　_ MONTH _　_ DAY

Phone：

Biomedical Ethics Review Committee of West China Hospital, Sichuan University　Phone：028-85422654，028-85423237

Version 3.0 Date：2023/05/21

BMJ Open

Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: study protocol for a single-arm, phase 2 clinical trial

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Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: study protocol for a single-arm, phase 2 clinical trial

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Abstract

Introduction

Neoadjuvant chemotherapy has been demonstrated to be effective and recommended as the standard treatment option in patients with locally advanced gastric or gastroesophageal junction (G/GEJ) cancer. In this study, we will explore the efficacy and safety of chemotherapy combined with cadonilimab, a PD-1/CTLA-4 bispecific antibody, in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma.

Methods and analysis

This is a single-centre, single-arm, open-label, phase 2 trial that will enrol 37 patients in total. Eligible patients will be registered and receive three cycles of SOX regimen in combination with cadonilimab. Radical D2 gastrectomy will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. The primary endpoint is the pathological complete response (pCR) rate. Secondary endpoints are R0 resection rate, major pathological response (MPR), 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety. The first participant was recruited on September 1, 2023 and the enrolment will be completed in July 2025.

Ethics and dissemination

Written informed consent will be required from and provided by all patients enrolled. The study protocol (version 3.0, April 28, 2023) has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526) and conducted under the Declaration of Helsinki. The results of the study may provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma.

Trial registration

ClinicalTrials.gov, NCT05948449.

Keywords

gastric cancer, neoadjuvant therapy, S-1, oxaliplatin, cadonilimab

Strengths and limitations of this study

- Inclusion/exclusion criteria compatible with the study objectives.
- Simon's two-stage Minimax approach will minimize the sample size.
- Simon's two-stage optimal approach will allow for early termination due to the absence of treatment efficacy in the first stage.
- The study is a single-arm, open-label, phase 2 clinical trial with no control group.

INTRODUCTION

Gastric or gastroesophageal junction (G/GEJ) cancer is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths. In 2020, over one million new cases and 769,000 deaths of G/GEJ cancer were estimated to occur globally [1]. Surgery is still the main curative treatment for G/GEJ cancer; however, most of patients undergoing gastrectomy will experience disease recurrence due to residual tumour or tumour micrometastasis [2].

Neoadjuvant therapy may significantly reduce the tumour burden, increase the R0 resection rate, reduce the postoperative recurrence rate, and evaluate the tumour response to the treatment regimen. Currently, neoadjuvant therapy has been widely applied to the treatment of a series of cancers, such as breast, rectal, oesophageal, head and neck, lung, prostate and many other cancer types [3-6]. The MAGIC study from the UK established the role of neoadjuvant chemotherapy in gastric cancer, while the PRODIGY study in South Korea, the RESONANCE study and the RESOLVE study in China further confirmed that neoadjuvant chemotherapy can improve the R0 resection rate and prognosis of gastric cancer patients without increasing the incidence of severe postoperative complications [7-10]. Although studies have demonstrated the clinical benefit of neoadjuvant chemotherapy for G/GEJ cancer, the pathological complete response (pCR) and long-term survival rates are still unsatisfactory.

Immune checkpoint inhibitors (ICIs), which target programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), have shown promising antitumor effects and revolutionized the treatment of malignancies. Recently, the combination of ICIs and chemotherapy has shown prolonged overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone and reduced the risk of death by 20-35% in the first-line setting of advanced or metastatic G/GEJ cancer patients [11, 12]. The inspiring results of these studies give us rational

reasons to further investigate the application of this strategy in neoadjuvant therapy of locally advanced G/GEJ cancer patients. In a single arm, phase 2 clinical study, Jiang et al. evaluated the efficacy of sintilimab combined with XELOX regimen in locally advanced, resectable G/GEJ adenocarcinoma. A total of 36 patients were enrolled, all of whom underwent surgery, with an R0 resection rate of 97.2%. The pCR and major pathological response (MPR) rates were 19.4% (95% CI: 8.8% to 35.7%; 90% CI: 10.7% to 33.1%) and 47.2% (95% CI: 31.6% to 64.3%), respectively. The disease-free survival (DFS) and OS at one year were 90.3% (95% CI: 80.4% to 100.0%) and 94.1% (95% CI: 86.5% to 100.0%), respectively [13]. In another similar study, the combination of tislelizumab and SOX also showed promising efficacy and safety in neoadjuvant treatment for locally advanced, resectable G/GEJ adenocarcinoma. Thirty-two patients were included in the study. Seventeen patients (53.1%) obtained MPR (≤ 10% survival tumour cells), and 8 patients (25%) achieved pCR. The annual relapse-free survival (RFS) and OS were 90.0% and 91.4%, respectively [14]. These results provide new insight and suggest that chemotherapy combined with immunotherapy may represent a promising therapy for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma.

Cadonilimab (AK104), a novel tetrameric form of PD-1/CTLA-4 bispecific antibody, could retain the efficacy benefit derived from the combination of anti-PD-1 and anti-CTLA-4 while conferring superior safety compared to the coadministration of these individual agents. In recent studies, cadonilimab has shown excellent efficacy and safety in various tumours, including cervical, nasopharyngeal, liver, and other cancers. On June 29, 2022, cadonilimab was approved in China for patients with recurrent or metastatic cervical cancer who failed previous platinum-based chemotherapy [15]. In addition, the efficacy and safety of cadonilimab combined with chemotherapy as first-line treatment for patients with advanced or metastatic G/GEJ adenocarcinoma was announced at the 2022 American Society of Clinical Oncology

Gastrointestinal Oncology Symposium (ASCO GI). A total of 96 patients were included, and 88 patients (92%) underwent at least one tumour assessment. The objective response rate (ORR) was 65.9% (58/88), with 2 cases (2.3%) of complete response and 56 cases (63.6%) of partial response. The disease control rate (DCR) was 92.0% (81/88). The median PFS was 7.10 months (95% CI, 5.55-10.48), and the median OS was 17.41 months (95% CI, 12.35-NE) [16]. The above results confirm that the combination of cadonilimab and chemotherapy is a potential new treatment option in the first-line setting of gastric cancer.

Inspired by these findings, we conduct a single-arm, phase 2 trial to explore the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. Moreover, we will also explore the predictive biomarkers of immunotherapy response, and establish a predictive model to screen out patients who might benefit from the neoadjuvant immunotherapy-chemotherapy regimen.

METHODS AND ANALYSIS

This is a single-centre, single-arm, open-label, phase 2 trial designed to assess the efficacy and safety of chemotherapy combined with cadonilimab in neoadjuvant therapy for locally advanced G/GEJ adenocarcinoma. Participants will be enrolled from West China Hospital, Sichuan University, Chengdu, China. All participants are required to provide written informed consent before enrolment (Supplemental Material). The study has been prospectively registered at ClinicalTrials.gov (NCT05948449). The first participant was recruited on September 1, 2023, and enrolment should be completed in July 2025. Figure 1 shows an overview of the study design.

Endpoints

The primary endpoint is the pCR rate. Secondary endpoints are R0 resection rate, MPR, 2-year disease-

free survival (DFS) rate, 2-year OS rate and safety profile. Exploratory endpoints are predictive biomarkers of immunotherapy response. The primary analyses will be performed in the intention-to-treat (ITT) population. All AEs will be analysed in the safety population, defined as patients administered at least one dose of neoadjuvant treatment. Neoadjuvant or adjuvant treatment emergent AEs will be reported separately due to the different regimens applied. Surgery-related morbidity and mortality will be analysed in the per-protocol population, defined as patients who were compliant with the study protocol and proceeded to surgery. To determine whether high pCR rates can translate into longer survival, follow-up of these participant will last for at least 2 years.

Study population and eligibility criteria

Inclusion criteria:

1. Age 18-75 years.
2. Histologically or cytologically confirmed diagnosis of locally advanced G/GEJ adenocarcinoma (cT3-T4a, N+, M0) as assessed by exploratory laparoscopic surgery, ultrasonography and/or CT/MRI.
3. Resectable G/GEJ cancer, as judged by experienced surgeons.
4. There was no previous antitumor treatment.
5. The expected survival is more than 3 months.
6. ECOG PS≤1.
7. Adequate organ function including the following:

- Total bilirubin ≤1.5 times the upper limit of normal (ULN);

- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3×ULN;
- Alkaline phosphatase≤2.5×ULN (if the tumour invaded the liver, ≤3×ULN);
- Serum creatinine≤1.5×ULN;
- Serum amylase and lipase≤1.5×ULN;
- International standardized ratio (INR)/partial thromboplastin time (PTT)≤1.5×ULN;
- Platelet count ≥ 75,000 /mm^3;
- Haemoglobin (Hb) ≥ 9 g/dL;
- Absolute neutrophil count (ANC) ≥ 1500/mm^3;

8. Strict contraception.

9. Patients must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

Exclusion criteria:

1. Unable to comply with the research program or procedures.

2. Undergoing other drug clinical trials or having participated in any drug clinical trials one month before enrollment.

3. Active autoimmune disease or history of refractory autoimmune disease.

4. Receiving corticosteroids (> 10mg/d prednisone or equivalent dose of steroids) or other systematic immunosuppression therapies within 14 days before enrolment, excluding the following therapies:

steroid hormone replacement therapy (≤10mg/d); local steroid therapy; and short-term, prophylactic steroid therapy for preventing allergies or nausea and vomiting.

5. Active or clinically significant cardiac disease:

- Congestive heart failure > New York Heart Association (NYHA) class 2;
- Active coronary artery disease;
- Arrhythmias requiring treatment other than β-blockers or digoxin;
- Unstable angina (with angina symptoms at rest), new angina within 3 months before enrolment, or new myocardial infarction within 6 months before enrolment

6. Evidence or history of bleeding diathesis or coagulopathy.

7. Grade 3 bleeding events 4 weeks before enrolment.

8. Thromboembolism or arteriovenous events, such as cerebrovascular events (including transient ischemic attack), deep vein thrombosis or pulmonary embolism, occurred 6 months before enrolment.

9. Currently taking anticoagulants.

10. Other tumours that have not been treated or exist at the same time, except carcinoma in situ of the cervix, treated basal cell carcinoma or superficial bladder tumour. If the tumour was cured and no evidence of disease was found for more than 3 years, the patient can be enrolled. All other tumours must be treated at least 3 years before enrolment.

11. Patients with pheochromocytoma.

12. Patients with a history of HIV infection or active hepatitis B/C.

13. Ongoing > level 2 infection.

14. Symptomatic brain metastasis or meningioma.

15. Unhealed wounds, ulcers or fractures.

16. Renal failure patients requiring blood or peritoneal dialysis.

17. Dehydration≥ 1 grade.

18. Epileptic that needs medication.

19. Active, symptomatic interstitial pneumonia, pleural or ascites that causes dyspnoea (dyspnoea ≥ 2 grade).

20. History of organ transplantation (including corneal transplantation).

21. Allergic to research drugs or similar drugs, or suspected allergies.

22. Malabsorption patients.

23. Pregnant or lactating women.

24. The investigator believes that patients who are not suitable for the study.

25. Medical, psychological or social conditions can affect the recruitment of patients and evaluation of study results.

26. Other antitumor therapy (chemotherapy, radiotherapy, surgery, immunotherapy, biotherapy, chemoembolization) other than investigator drugs. Palliative external irradiation for non-target lesions is allowed.

27. Previously used oxaliplatin, S-1 or cadonilimab.

28. Major surgery 4 weeks before recruitment, open biopsy or major trauma surgery (excluding biliary stents, or percutaneous biliary drainage).

29. Treatment with antitumor Chinese herbal medicine.

30. History of allogeneic blood transfusion within 6 months.

Intervention

Laparoscopic exploration should be performed to detect occult peritoneal metastases and inspect the primary lesion, liver, diaphragm, pelvic organs, bowel and omentum. Patients who meet the inclusion criteria will be enrolled and sign the informed consent form. Then, 3 cycles of neoadjuvant therapy will be administered: S-1: 40-60 mg Bid, d1-14, q3w; oxaliplatin: 130 mg/m^2, iv drip, d1, q3w; cadonilimab (AK104): 10 mg/Kg, iv drip, d1, q3w. Antiemetic, acid suppressing, and anti-allergic treatments are allowed. Radical D2 gastric cancer resection will be performed within 4 weeks after the last administration of chemotherapy plus cadonilimab. Afterwards, we will recommend the best postoperative adjuvant treatment, and the adjuvant regimen will be determined by the patients themselves. Follow up will be conducted every 3 months (according to RECIST 1.1 standards) until tumour recurrence, death, or 2 years after surgery.

Statistical analysis

The sample size was calculated based on the assumption that the pCR rate of neoadjuvant SOX chemotherapy is 5.6% [10]. A total of 33 patients treated with neoadjuvant cadonilimab in combination with SOX regimen will provide 80% power to detect a pCR rate of 20% at a one-sided 5% alpha level. Considering a 10% discontinuation rate, 37 assessable patients will be enrolled in the study. Descriptive statistics of baseline and clinicopathological characteristics will be performed. The pCR, MPR, and R0

resection rate will be calculated, and the corresponding CIs will be estimated by the Blaker's binomial exact method. Kaplan-Meier estimates of DFS and OS probabilities will also be determined, with respective 95% CIs. All efficacy analyses will be performed in the ITT population and all AEs will be analyzed in the safety population, defined as patients administered at least one dose of neoadjuvant treatment.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Written informed consent will be required for patients enrolled. This study will be conducted under the Declaration of Helsinki, without causing any extra harm or risks to patients. The protocol (version 3.0, April 28, 2023) has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2023526) and has been prospectively registered on ClinicalTrials.gov with registration number NCT05948449. The results of the study will be presented at international oncology congresses and published in peer-reviewed journals.

DISCUSSION

G/GEJ cancer remains one of the most commonly diagnosed malignancies worldwide. Gastrectomy is the main curative treatment for G/GEJ cancer; however, disease recurrence or metastasis will occur in most patients undergoing gastrectomy. In recent decades, a number of studies have investigated the efficacy of adjuvant chemotherapy in patients with resectable gastric cancer. In the ACTS-GC trial, 1059 patients with stage II or III gastric cancer were enrolled and randomly assigned to either the surgery plus S-1 group or the surgery-only group. The 5-year OS rates in the surgery plus S-1 group and surgery-only group were 71.7 and 61.1% respectively, and the 5-year RFS rates were 65.4 and 53.1% respectively [17].

In another study conducted in South Korea, mainland China and Taiwan (the CLASSIC trial), 1035 patients with stage II-IIIB gastric cancer who underwent D2 radical gastrectomy were randomly assigned to the adjuvant chemotherapy (XELOX) group or observation alone group. The 5-year DFS rates were 68 and 53%, respectively [18]. Based on the results of these two studies, D2 radical gastrectomy with adjuvant chemotherapy has been recommended as the standard treatment option for patients with G/GEJ cancer in stage II–III. However, adjuvant therapy for gastric cancer has entered a bottleneck stage in recent years. Many patients experience short-term recurrence after surgery, especially in patients with stage III gastric cancer.

Neoadjuvant therapy has been widely applied to the treatment of several cancers. The MAGIC study, PRODIGY study, and the RESONANCE and RESOLVE studies also established the role of neoadjuvant chemotherapy in G/GEJ cancer, and neoadjuvant chemotherapy has been recommended in patients with locally advanced, resectable G/GEJ cancer by the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Chinese Society of Clinical Oncology (CSCO) clinical practice guidelines. Recently, a number of studies have also evaluated the efficacy of chemotherapy plus PD-1 inhibitors in neoadjuvant therapy of locally advanced G/GEJ cancer patients. The addition of PD-1 inhibitors significantly increases the pCR rate, R0 resection rate and long-term survival, indicating that chemotherapy plus PD-1 inhibitors is a promising treatment option for the neoadjuvant treatment of locally advanced, resectable G/GEJ adenocarcinoma [13, 14].

In addition to PD-1 and PD-L1, CTLA-4 is regarded as another key immune checkpoint. CTLA-4 is not expressed on the surface of initial T cells. After T-cell activation, CTLA-4 expressed on the surface of activated T cells can competitively bind to ligand B7 with CD28, thereby reducing T-cell activation levels and inhibiting T-cell proliferation [19]. In theory, CTLA-4 monoclonal antibodies and PD-1

monoclonal antibodies can cooperate and coordinate with each other, effectively weakening tumour immune escape and promoting the killing effect of the immune system. Therefore, the combination of CTLA-4 monoclonal antibody and PD-1 monoclonal antibody may provide a strong foundation for dual immune combination therapy in clinical practice. In the CheckMate 067 study, Hodi et al. investigated the efficacy and safety of nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone in patients with advanced melanoma [20]. Patients with previously untreated, unresectable, stage III or stage IV melanoma were randomly assigned 1:1:1 to the nivolumab plus ipilimumab group, the nivolumab group, or the ipilimumab group. At a minimum follow-up of 48 months from the date that the final patient was enrolled and randomized, the median OS was not reached (95% CI 38·2-not reached) in the nivolumab plus ipilimumab group, 36·9 months (28·3-not reached) in the nivolumab group, and 19·9 months (16·9-24·6) in the ipilimumab group. The median PFS was 11·5 months (95% CI 8·7-19·3) in the nivolumab plus ipilimumab group, 6·9 months (5·1-10·2) in the nivolumab group, and 2·9 months (2·8-3·2) in the ipilimumab group. These results suggested that nivolumab plus ipilimumab can significantly prolong OS and PFS compared with nivolumab alone or ipilimumab alone in patients with advanced melanoma. Subsequently, several studies have also investigated the efficacy of double immunotherapy in non-small cell lung cancer, renal cell carcinoma, colorectal cancer, liver cancer, biliary system tumours and so on [21-24]. The combination of CTLA-4 and PD-1 blockers was shown to significantly enhance efficacy, and ipilimumab plus nivolumab was approved for the treatment of metastatic melanoma, advanced renal cell carcinoma and metastatic colorectal cancer with MMR/MSI-H aberrations. Although with promising efficacy, the combination of CTLA-4 and PD-1 blockers significantly increased treatment-related grade 3-4 adverse events (AEs). For example, in the CheckMate 067 study, treatment-related grade 3-4 AEs were reported in 22% (70/313) of patients in the nivolumab

alone group and 28% (86/311) of patients in the ipilimumab group, while in the nivolumab plus ipilimumab group, treatment-related grade 3-4 AEs were reported in 59% (185/313) of patients.

Cadonilimab (AK104) is a novel tetrameric form of PD-1/CTLA-4 bispecific antibody. In previous studies, cadonilimab has shown promising efficacy and superior safety compared to the coadministration of these individual agents in gastric, cervical, nasopharyngeal, liver, and other cancers. In this study, we conduct a single-arm, phase 2 trial to investigate the efficacy and safety of chemotherapy plus cadonilimab as neoadjuvant treatment for locally advanced G/GEJ adenocarcinoma. To the best of our knowledge, this is the first study to explore the efficacy of neoadjuvant anti-PD-1/CTLA-4 immunotherapy combined with chemotherapy in G/GEJ cancer. However, the limitations of our study should also be addressed. First, this is a single-centre, single-arm, small sample phase 2 study, large-cohort, randomized, phase 3 studies are required to further compare the efficacy and safety of neoadjuvant chemotherapy combined with cadonilimab versus standard chemotherapy in advanced/metastatic GC in the future. Second, the primary endpoint in the study is pCR rate, as less time will be required to obtain the primary results. Whether the high response rate of neoadjuvant therapy can translate into long-term survival benefits remain a focus of interest. Thus, the 2-year DFS rate and 2-year OS rate will also be evaluated to illustrate the survival benefit in the study. We hope this study will provide more evidence for neoadjuvant immunotherapy combined with chemotherapy in locally advanced G/GEJ adenocarcinoma and explore a series of predictive biomarkers of immunotherapy response.

Contributors

JKH, HFG and PFZ participated in the design of the study; PFZ, WHZ, XJL and DH wrote the study protocol. PFZ, KY, HFG and JKH are responsible for conducting and coordination of the trial. All authors reviewed the manuscript draft and approved the final manuscript. JKH and HFG are the guarantor.

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Competing interests

The authors declare that there is no competing interests.

Data availability statement

The data generated in the current study will be available from the corresponding author upon reasonable request after the study has been completed.

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FIGURE TITLE

Figure 1. Study flowchart

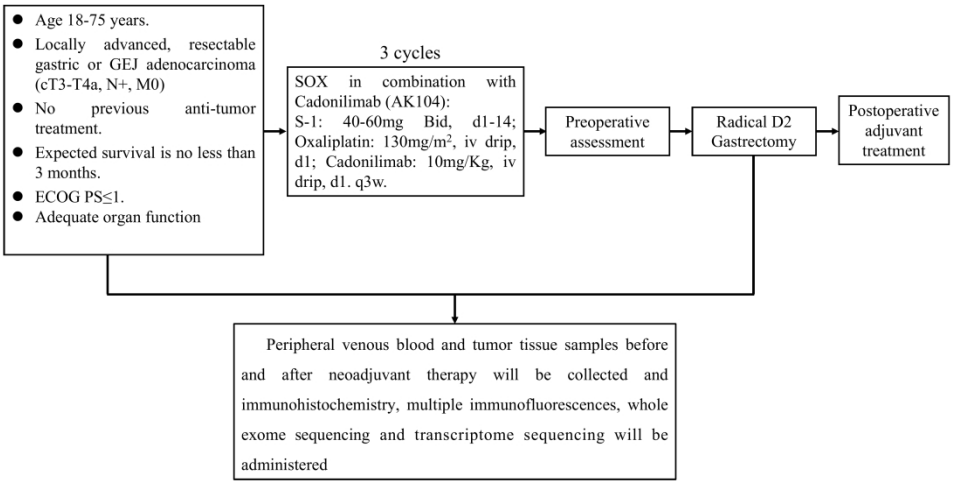

Figure 1. Study Flow Chart

338x190mm (300 x 300 DPI)

Version 3.0 Date：2023/05/21

Informed Consent Form · Consent Signature Page

Name of study: Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastroesophageal junction adenocarcinoma: a single-arm, phase II clinical trial

Sponsor: West China Hospital, Sichuan University

Statement of Investigators: I have informed the participant of the research background, purpose, implementation process, risks, and benefits of a single arm, phase II clinical study evaluating the efficacy and safety of chemotherapy combined with cadonilimab (AK104) in neoadjuvant therapy for locally advanced gastric cancer/gastroesophageal junction adenocarcinoma. We give him/her sufficient time to read the informed consent form, discuss with others, and answer their research questions; I have informed the subject that they can contact the research doctor at any time when encountering research related issues, and can contact the Biomedical Ethics Review Committee of West China Hospital of Sichuan University at any time when encountering issues related to their own rights/interests, and have provided accurate contact information; I have informed the subject that he/she can withdraw from this study without any reason; I have informed the subject that he/she will receive a copy of this informed consent form, which includes my and his/her signatures.

Statement of Participants: I have read the above introduction about this study, and my researchers have fully explained and explained to me the purpose, operation process, potential risks and benefits of participating in this study, and answered all my relevant questions. I voluntarily participate in this study.

Name of participant：

Signature of participant： Date：_ _ YEAR _ _ MONTH _ _ DAY

Email： Phone：

Name of legal representative： （if applicable）

Relationship with participant：

Signature of legal representative： Date: _ _ YEAR _ _ MONTH _ _ DAY

Reason for requiring legal representative to sign:

Signature of investigator： Date: _ _ YEAR _ _ MONTH _ _ DAY

Phone：

Biomedical Ethics Review Committee of West China Hospital, Sichuan University Phone：028-85422654，028-85423237

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