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# Clinical study of adebrelimab in combination with apatinib and irinotecan for PD-1 inhibitor-ineffective advanced-stage gastric cancer: study protocol for a single-arm, single-centre, exploratory trial

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## ABSTRACT

**Introduction** Immunotherapy has revolutionised cancer treatment. Immune checkpoint inhibitors have demonstrated significant efficacy across multiple tumour types, including gastric cancer, where several approved programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors show promising antitumour activity. While PD-L1 expression serves as a predictive biomarker for PD-1 inhibitor response, and PD-L1-positive patients generally show better outcomes, therapeutic resistance remains a challenge. Many initial responders eventually develop resistance, and surprisingly, some PD-L1-positive patients fail to achieve expected response rates, indicating emerging resistance mechanisms in potentially responsive populations. Adebrelimab, a PD-L1 inhibitor, demonstrates mechanistic advantages over PD-1 inhibitors, with clinical studies suggesting promising therapeutic potential. When combined with irinotecan, apatinib has shown efficacy in second-line gastric cancer treatment. This study aims to evaluate the efficacy and safety of combining adebrelimab with apatinib and irinotecan for advanced gastric cancer refractory to PD-1 inhibitors.

**Method and analysis** This single-arm, single-centre exploratory trial will be conducted at Renji Hospital, enrolling 32 patients aged 18–75 years. Eligible patients must have initially achieved partial response, complete response or stable disease with progression-free survival (PFS)≥3 months during prior immunotherapy but subsequently progressive disease on imaging. Treatment will continue until meeting discontinuation criteria. The primary endpoint is objective response rate with Clopper-Pearson 95% CI. Secondary endpoints include disease control rate (95% CI), PFS and overall survival (estimated by Kaplan-Meier method), along with safety assessments.

**Ethics and dissemination** All participants will provide informed consent. The protocol has been approved by the Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (LY2023-201-C). The results will be disseminated through peer-reviewed manuscripts, reports and presentations.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ As the first prospective study evaluating adebrelimab rechallenge combined with apatinib/irinotecan for programmed cell death 1 inhibitor-refractory gastric cancer, this trial may provide valuable insights into immune rechallenge strategies for gastric cancer treatment.
⇒ Single-arm design limitation precludes direct comparison with standard therapies.
⇒ The restrictive inclusion criteria and small single-centre sample size may affect the generalisability of findings to broader gastric cancer populations.

**Trial registration number** ChiCTR2300077329.

## BACKGROUND

Gastric cancer remains an important malignancy worldwide, ranking fifth for incidence and fourth for mortality globally.[1] Surgically treated gastric cancer shows high recurrence and poor prognosis, whereas immune checkpoint inhibitors (ICIs) exhibit broad antitumour efficacy. The CheckMate-649 study demonstrated that nivolumab, a programmed cell death 1 (PD-1) inhibitor, combined with chemotherapy, significantly improved overall survival (OS) and progression-free survival (PFS) compared with chemotherapy alone in patients with previously untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinomas.[2] Notably, in the Chinese subgroup analysis, the 5-year OS rate reached 24% with nivolumab plus chemotherapy, compared with only 8% with chemotherapy alone, marking a historic breakthrough in the treatment of advanced gastric cancer and setting a new benchmark

for long-term survival. According to the KEYNOTE-811 study, pembrolizumab combined with trastuzumab and chemotherapy has demonstrated significant clinical benefits in patients with unresectable, human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric or gastro-oesophageal junction cancer. The final analysis confirmed that this combination therapy significantly improved OS, PFS and objective response rate (ORR) compared with placebo plus trastuzumab and chemotherapy, particularly in patients with programmed cell death-ligand 1 combined positive score (PD-L1 CPS)≥1.[3] Immunotherapy has significantly transformed the treatment landscape of gastric cancer, and the search for molecular biomarkers has become a major focus of research. A systematic review and meta-analysis, which included 12 prospective studies and 6488 patients, was conducted to pool and analyse data. Among these, six were phase III randomised controlled trials. The study extracted HRs and 95% CIs for ORR, disease control rate (DCR), PFS and OS at different PD-L1 cut-off values. The results demonstrated that the efficacy and survival benefits of immunotherapy in gastric cancer improved with increasing PD-L1 CPS expression levels.[4] However, some patients who initially benefit will develop resistance to therapy.[5 6] This means that patients who should benefit from PD-1 inhibitors are becoming resistant. So there is a subset of patients who do not benefit from immunotherapy, including progression after immunotherapy, non-response to immunotherapy or the occurrence of intolerable adverse reactions. For this subset of patients, the choice of second-line treatment has become a challenge.

Current research has two strategies to overcome resistance to ICIs treatment.[7] One strategy is to develop new ICIs with improved efficacy, and many novel immune checkpoint modulators have been extensively studied, including lymphocyte-activation gene 3, T-cell immunoglobulin and mucin-domain containing-3, and so on.[8] Another key strategy is to combine ICIs with other therapies, such as chemotherapy and radiation.[9] Vascular endothelial growth factor (VEGF) signalling suppresses immune responses by inhibiting T-cell recruitment, effector T-cell function and dendritic cell (DC) maturation, and by stimulating regulatory T cells and myeloid-derived suppressor cells.[10] So, VEGF receptor inhibitors combined with ICIs may yield synergistic effects theoretically. This strategy had shown good efficacy in the IMbrave150 study and the CARES study in hepatocellular carcinoma.[11 12] Lenvatinib plus pembrolizumab showed promising antitumour activity with an acceptable safety profile in patients with advanced gastric cancer in the EPOC1706 study.[13] A phase II clinical study of camrelizumab combined with capecitabine and oxaliplatin, followed by camrelizumab plus apatinib as first-line therapy for patients with advanced gastric cancer or metastatic gastric/gastro-oesophageal junction adenocarcinoma demonstrated encouraging antitumour activity and manageable toxicity.[14] Therefore, targeting intracellular signalling pathways by VEGF receptor inhibitors in combination with immunotherapy may be a synergistic and effective way to reverse immune resistance.

Adebrelimab is a recombinant humanised immunoglobulin G4 antibody with strong affinity for human and monkey PD-L1 antigens and no significant binding to either B7 DC molecule or B7 homolog 3. Adebrelimab added to chemotherapy significantly increased OS with an acceptable safety profile in patients with extensive-stage small-cell lung cancer, according to a multicentre, randomised, double-blind, placebo-controlled phase III study.[15] Another trial revealed that the safety profile of adebrelimab was manageable.[16] Adebrelimab is approved as a first-line extensive-stage small cell lung cancer, with ongoing clinical trials investigating its use in other malignancies. Antiangiogenic drugs are currently the key strategy for second-line treatment of gastric cancer.[17 18] Patients with advanced gastric cancer who participated in a multicentre, open-label phase II study of second-line apatinib plus irinotecan had good tolerance.[19] As mentioned above, there is no standard treatment regimen for second-line treatment of patients after progression of immunotherapy and non-responders after immunotherapy. Current second-line treatment for gastric cancer continues to be primarily single-agent chemotherapy, which provides inadequate clinical benefits. On the one hand, apatinib combined with irinotecan has shown good efficacy in relevant clinical data. Chemotherapy can increase tumour mutation burden and antigen presentation through DNA damage, thus enhancing immune response and reversing immune resistance. On the other hand, different from PD-1 inhibitors, PD-L1 inhibitors can block the binding ability of PD-L1 to B7.1 on the surface of T cells, which is conducive to the comprehensive activation of T cells. At the same time, DCs are a key target of PD-L1-blocking antibodies. In patients with cancer, PD-L1 is expressed at significantly higher levels than B7.1 on both peripheral and tumour-associated DCs. By blocking PD-L1 on DCs, the cis-sequestration of B7.1 by PD-L1 is relieved, enabling the B7.1/CD28 interaction to promote T-cell priming.[20] Unlike PD-1 inhibitors, PD-L1 monoclonal antibodies specifically block PD-L1/PD-1 interaction while preserving PD-L2 function, thereby reducing adverse events (AEs) such as interstitial lung disease.[21] The adebrelimab–apatinib–irinotecan combination may offer superior clinical benefits over current second-line regimens for immunotherapy-refractory advanced gastric cancer, representing a promising therapeutic option.

In summary, the study is designed to investigate the efficacy and safety of adebrelimab in combination with apatinib and irinotecan for patients with PD-1 inhibitor-resistant advanced-stage gastric cancer.

## METHODS AND ANALYSIS

### Study design

The study is designed as a prospective, single-centre study and will be conducted from November 2023 to December

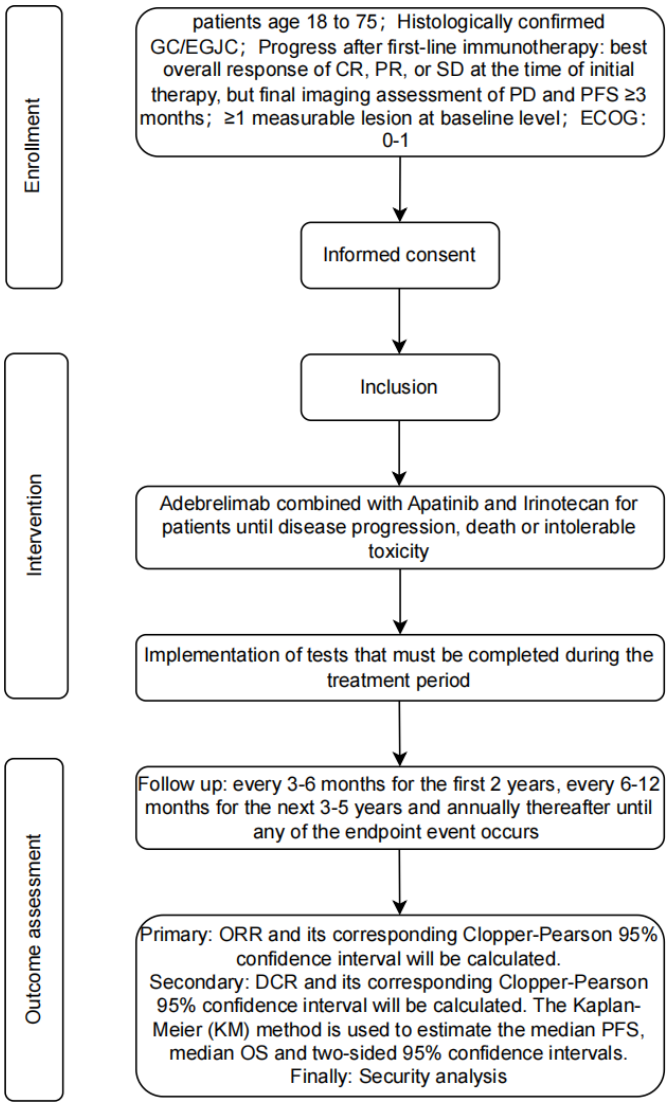


**Figure 1** Flowchart summarising the trial procedure.CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGJC, esophagogastric junction carcinoma; GC, gastric cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

2025 at Renji Hospital, Shanghai Jiao Tong University School of Medicine. The data collection and analysis will be completed to evaluate the efficacy and safety of adebrelimab in combination with apatinib and irinotecan for patients with PD-1 inhibitor-ineffective advanced-stage gastric cancer.

## Study participants

Written informed consent will be provided before starting the trial, and then the participants will be screened by a gastrointestinal surgeon to establish whether they meet the eligibility criteria within 28 days prior to the first dose. Imaging, vital signs, physical examination, laboratory tests and Eastern Cooperative Oncology Group (ECOG) Score assessment should be performed within 7 days prior to the first dose. Eligible subjects will be enrolled in this

**Table 1** Inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | ► All subjects were recruited and signed informed consent on a voluntary basis and were willing and able to comply with scheduled visits, treatment protocols, laboratory tests and other requirements of the study. |
| | ► ≥18 years old, ≤75 years old. |
| | ► Histologically or cytologically confirmed gastric adenocarcinoma, locally advanced and unresectable, local recurrence (local lymph node metastasis) or distant metastasis. |
| | ► ECOG Score: 0–1. |
| | ► Adequate function of major organs, including normal baseline blood routine, hepatic and renal function, as well as cardiac and pulmonary function. |
| | ► HER2 was negative. |
| | ► At least one measurable lesion (based on RECIST V.1.1 criteria). |
| | ► Expected survival time ≥3 months. |
| | ► Progression on or were intolerant to first-line immunochemotherapy:<br>– Patients were also eligible if they progressed during initial chemotherapy, or if patients with postoperative recurrence or metastasis progressed during concurrent chemoradiotherapy.<br>– For neoadjuvant/adjuvant immunotherapy, if patients progress during the treatment or within 6 months after treatment, it is considered as a failure of first-line treatment.<br>– Patients with an adverse immune reaction resulting in discontinuation of the prior anti-PD-1/PD-L1 immunotherapy are also eligible. (Patients must not have experienced any of the following: any grade 3 or more severe immune-related adverse event (irAE); any unresolved grade 2 irAE; or any toxicity condition that resulted in permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy.) |
| | ► Women of childbearing age should consent to take contraception measures during the study period and within 6 months after the study ends. Female subjects must have a negative serum or urine pregnancy test within 7 days before the recruitment. Female subjects must be non-lactating women. Men should consent to contraception during the study period and for 6 months after the end of the study. |

Continued

**Table 1** Continued

| | |
|---|---|
| Exclusion criteria | ► Have any active autoimmune disease or a history of autoimmune disease (including but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, pituitaritis, vasculitis, nephritis, hyperthyroidism, etc). |
| | ► Currently receiving immunosuppressors or systemic hormone therapy for immunosuppressor purposes (dose≥10 mg/day, prednisone or other equivalent hormone) and continued use within 2 weeks before recruitment. |
| | ► Patients received treatment with VEGFR inhibitors, such as sorafenib, sunitinib, apatinib, etc. |
| | ► Any of the following conditions that will interfere with oral medications: unable to swallow, having received gastroenterostomy, chronic diarrhoea and intestinal obstruction. |
| | ► Patients with any serious and/or uncontrollable medical condition, including:<br>– Poor blood pressure control (systolic pressure≥150 mm Hg or diastolic pressure≥100 mm Hg).<br>– Having myocardial ischaemia or myocardial infarction and arrhythmia of grade 1 and above (including QT interval≥480 ms) and cardiac insufficiency of grade 1.<br>– Active or uncontrolled severe infection; liver diseases, such as decompensated liver failure, active hepatitis B (HBV-DNA≥$10^4$ copy number/mL or 2000 IU/mL) or hepatitis C (positive anti-HCV antibody, HCV-RNA above the lower limit of detection by assay).<br>– Urine routine examination indicated urinary protein ≥ ++ and confirmed 24-hour urinary protein quantification>1.0 g. |
| | ► Wounds or fractures that have not healed for a long time. |
| | ► Has a tendency to bleed (eg, active peptic ulcer) or is currently receiving thrombolytic or anticoagulant therapy such as warfarin, heparin or its analogues. |
| | ► Patients who have had an arterial/venous thrombotic event within 6 months, such as cerebrovascular accident (including transient ischaemic attack), deep vein thrombosis and pulmonary embolism. |
| | ► The probability of tumour invasion of important blood vessels is high based on radiological examination, which may lead to fatal bleeding during future study. |
| | ► Pregnant or breastfeeding. |
| | ► Patients with a history of other malignant tumours in the past 5 years (except cured basal cell carcinoma and cervical carcinoma in situ). |
| | ► Patients with a history of psychotropic drug abuse and addiction or mental disorders. |
| | ► Patients who have participated in clinical trials of other drugs in the past 4 weeks. |
| | ► A concomitant disease determined by the investigator to seriously compromise the patient's safety or prevent the patient from completing the study; other patients deemed unsuitable for participation. |
| | ► Other patients who are considered inappropriate for participation by the investigator. |

ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; VEGFR, vascular endothelial growth factor receptor.

study to receive immune rechallenge therapy. During the treatment periods, patients will receive medication until disease progression, death or intolerable toxicity occurs. In this study, every 3 weeks is a treatment course, and imaging evaluation will be required to determine the efficacy of treatment after completing every two treatment courses. During the follow-up period, follow-up visits will be made every 3–6 months for the first 2 years, then every 6–12 months for the next 3–5 years and annually thereafter. Figure 1 summarises the flow of participants.

### Inclusion and exclusion criteria

Complete inclusion/exclusion criteria are detailed in table 1.

### Intervention

Eligible participants will receive adebrelimab (Suzhou Shengdiya Biopharmaceutical, 20 mg/kg, every 3 weeks, on the first day), apatinib (Jiangsu Hengrui Pharmaceuticals, 250 mg, once daily) and irinotecan (manufacturer not specified, 180 mg/$m^2$, every 3 weeks, on the first day) every 3 weeks as a course until disease progression, intolerable toxicity, initiation of new antitumour therapy, withdrawal of informed consent or termination by the judgement of the investigator, whichever occurs first. Dose increases or decreases are not recommended for adebrelimab. Depending on the patient's safety and tolerability, adebrelimab may require a suspension of dosing or permanent discontinuation. For apatinib, when a patient develops a grade 3/4 haematologic or non-haematologic adverse reaction, it is recommended that the drug be suspended until symptoms resolve or disappear and the dose be reduced. Dose reduction or temporary discontinuation of apatinib may be considered using the following

two approaches: (1) first dose adjustment: 250 mg, taken for 5 days followed by a 2-day break; (2) second dose adjustment: 250 mg, taken every other day. In this study, the initial dose of irinotecan hydrochloride injection is standardised for all patients to ensure consistency. While the manufacturer of the drug is not restricted, the dosing adjustment guidelines and discontinuation criteria will be uniformly based on the prescribing information provided by the selected manufacturer. This ensures that, although the drug may be produced by different manufacturers, the principles for dose adjustment and drug administration remain consistent across all patients.

A maximum of no more than 4 weeks of drug suspension and up to two dose downward adjustments will be allowed during the study period. Only metered dose downward adjustments, not dose rollbacks, are allowed during the study period.

## Definition of tumour progression

### Imaging assessment (RECIST V.1.1)

Tumour progression is confirmed by enhanced CT or MRI scans of the chest, abdomen, pelvis or lesion sites (mandatory for all participants at each evaluation timepoint).

### Clinical symptom evaluation

Development or worsening of tumour-related symptoms (eg, pain, obstruction) supported by imaging or laboratory findings indicates progression (mandatory for all participants at each evaluation timepoint).

### Tumour marker elevation

A significant and sustained increase in tumour markers (eg, Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA19-9)) alongside imaging or clinical evidence supports progression (mandatory for all participants at each evaluation timepoint).

### Exploratory laparoscopy or biopsy (if needed)

All enrolled patients will undergo mandatory multidisciplinary team evaluation at each assessment, including standard imaging (RECIST V.1.1), clinical symptom monitoring and tumour marker analysis. For equivocal lesions with indeterminate imaging features, exploratory laparoscopy or biopsy will be performed. During the laparoscopic exploration, ascitic fluid can be obtained when suspicious peritoneal metastasis and cancerous ascites are present. These invasive procedures will be reserved for cases where conventional assessments remain inconclusive.

## Outcome measures

### Primary outcome

To calculate the ORR in patients with PD-1 inhibitor-ineffective advanced-stage gastric cancer.

### Secondary outcomes

- To evaluate the DCR, PFS and OS in patients with PD-1 inhibitor-ineffective advanced-stage gastric cancer.
- To observe the safety and AEs in patients with PD-1 inhibitor-ineffective advanced-stage gastric cancer.

## Sample size calculation

According to the 2022 Chinese Society of Clinical Oncology guidelines for the diagnosis and treatment of gastric cancer, the second-line recommended treatment regimen for advanced gastric cancer is paclitaxel/docetaxel/irinotecan monotherapy and the ORR of second-line treatment of gastric cancer with irinotecan/docetaxel monotherapy in the study of WJOG4007 is 13.6%–20.9%.[22] There is no standard regimen for the backline treatment of patients after progression of immunotherapy and non-responders after immunotherapy. Therefore, this study adopts the Simon two-stage design, comparing the ORR of 15% in previous studies and setting the expected 35%, with a one-sided type I error rate of 0.05 and 80% power. The study will enrol 15 patients in the first stage. If ≥3 patients achieve an objective response, the study will proceed to patient recruitment for the second stage; otherwise, it will be terminated early for futility. If the study enters the second stage, an additional 13 patients will be enrolled (cumulative total of 28). If ≥7 patients achieve a response across both stages, the regimen will be considered worthy of further investigation. Accounting for a 10% dropout rate, the final planned sample size is 32 patients. All statistical calculations were performed using PASS 15 software (V.15.0.5).

## Statistical analysis

The statistical analysis will be based on the full analysis set and the safety set. Measurement data will be summarised by using means, SD, medians, maximums and minimums; count data are summarised by using frequencies and percentages. The evaluation data will be based on the following response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease and not evaluable. ORR is defined as the proportion of patients who achieve the CR or PR within a specified time frame, as assessed by the investigator according to the RECIST V.1.1 criteria. DCR is defined as the proportion of patients who achieve CR, PR or SD within a specified time frame, as also assessed by the investigator according to the RECIST V.1.1 criteria. PFS is defined as the time from the first administration of the study drug to disease progression (based on radiological assessment) or death from any cause, whichever occurs first. OS is defined as the time from the first administration of the study drug to death from any cause. ORR and DCR will be calculated, along with their corresponding Clopper-Pearson 95% CIs. The Kaplan-Meier method will be used to analyse PFS and OS. All statistical data will be analysed by SPSS software 20.

## Data collection and monitoring

Demographic data, tumour diagnosis and treatment history (surgical history, systemic treatment history, radiotherapy history), comorbidities and imaging

examinations (enhanced CT scan of the chest, abdomen, pelvis and lesion sites, MRI of the brain, or enhanced CT scan) should be registered completely 28 days prior to the first dose. The patient demographic data (including identity card number, sex, date of birth, age at diagnosis, disease duration, nationality, height and weight) will be retrospectively extracted from our institutional electronic medical record system. If patients are allergic to the enhanced CT contrast agent, a plain scan can be performed. Bone scans will be performed only when clinically indicated. ECOG Score, vital signs, height and weight (the medication dosage will be recalculated if subjects lose at least 10% of their body weight during treatment), physical examination (general condition, head and face, skin, lymph nodes, eyes, ear, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, mental state, etc), laboratory tests (blood routine, urine routine, blood biochemistry, stool routine, coagulation function, thyroid function test, ECG) need to be completed within 7 days of the first dose, before each cycle of treatment and at the end of treatment/withdrawal from the study. Pituitary–adrenal axis and echocardiography will be examined within 7 days prior to the initial medication. After that, it is up to the doctor's discretion to decide whether or not to review. Virological indicators will be examined within 14 days before the first dose. Imaging examinations should be conducted every two cycles during the treatment period. If new lesions are suspected, they can be checked promptly. When subjects are out of the group for any reason, imaging examinations should be performed in time (±6 weeks). The first PR/CR should be confirmed in time (4 weeks±10 days). If the disease first progresses, it needs to be confirmed by imaging after 4–6 weeks. At the end of the study or withdrawal from the study, if the patient has not been examined within 14 days prior to the end of the study, ECOG Score, vital signs, physical examination, blood routine, urine routine, blood biochemistry, stool routine, thyroid function test, pregnancy test and assessment of AEs should be performed. If an imaging examination was not performed within 6 weeks prior to the end of treatment, an imaging examination should be performed at the end of the study to evaluate efficacy. For patients with non-radiographic evidence of progression (intolerance or other conditions), tumour evaluation will be performed every 3 months after the end of treatment until disease progression, death or the initiation of other antitumour therapy. During follow-up, assessments will occur every 3–6 months (years 0–2), every 6–12 months (years 3–5) and annually thereafter until: radiographic progression, new antitumour therapy, consent withdrawal, loss to follow-up or death. Subjects with no imaging progress should still be evaluated according to the diagnosis and treatment norms for gastric cancer (table 2).

### Safety and AE monitoring

An AE refers to any unfavourable clinical occurrence in a study participant, regardless of causal association with treatment, encompassing unintended symptoms, signs, laboratory anomalies or disease manifestations. For example: (1) The original medical condition/disease is aggravated prior to entry into the clinical trial. (2) Any new adverse medical condition (including symptoms, signs, or recently diagnosed disease). (3) Abnormal laboratory results with clinical significance. Serious AE refers to a medical event occurring during a clinical trial that requires hospitalisation or prolongs the current hospitalisation, causes persistent or significant disability, affects working capacity, endangers life or results in congenital malformation/birth defects and other medical events.

AEs will be graded according to the standardised criteria of National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.[23] Investigators must thoroughly document all AEs, including the specific AE term, detailed symptom description, onset/offset timing, severity grade (per CTCAE criteria), duration, relationship to investigational product (assessed using standardised causality criteria), any study drug modifications (dose adjustments/interruptions) and final outcome (resolution status).

### Ethics and dissemination

The study has been approved by Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (LY2023-201-C) and registered in the Chinese Clinical Trial Registry (ChiCTR2300077329). The trial will be conducted according to the principles of the Declaration of Helsinki and in accordance with Good Clinical Practice standards. Informed consent will be obtained from the coordinators or researchers associated with this protocol. It details drug use, study procedures and the risks of the study. Informed consent must be obtained from the patient before the study is conducted. Participants may withdraw their consent at any time throughout the clinical study. All personal information about the subject will be kept strictly confidential.

The results will be published in open-access, peer-reviewed medical literature and submitted for presentation at national and international conferences.

## DISCUSSION

The efficacy and safety of immunotherapy in advanced gastric cancer have provided promising prospects for clinical treatment options. Although it has been approved for first-line treatment indications, not all patients benefit from or sustain benefits from immunotherapy. The majority of patients inevitably experience disease progression. Consequently, determining the optimal subsequent treatment strategies following progression on immunotherapy has emerged as a new challenge in clinical practice. Whether ICIs can continue to be used across lines remains controversial, and more clinical exploration is

**Table 2** Check and visit schedule

| Check/visit | Screening | | Treatment period | | End of treatment/ withdrawal | Follow-up period* |
|---|---|---|---|---|---|---|
| | d−28 to d−8 | d−7 to d−1 | First cycle (21 d) C1/D1 | Second cycle (21 d) C2/D1 (±3 days) | | |
| Sign informed consent form | √ | | | | | |
| Demographic data | √ | | | | | |
| Tumour history | √ | | | | | |
| Combined disease and treatment history | √ | | | | | |
| Enrolment verification criteria | | √ | | | | |
| ECOG Score† | | √ | | √ | √ | |
| Physical examination‡ | | √ | | √ | √ | |
| Vital signs§ | | √ | | √ | √ | |
| Height and weight¶ | | √ | | √ | √ | |
| Blood routine** | | √ | | √ | √ | |
| Urine routine†† | | √ | | √ | √ | |
| Blood biochemical‡‡ | | √ | | √ | √ | |
| Stool routine§§ | | √ | | √ | √ | |
| Coagulation test¶¶ | | √ | | √ | √ | |
| Thyroid function test*** | √ | | | | √ | |
| Pituitary–adrenal test††† | √ | | Check if necessary | | | |
| Examination of virological indicators‡‡‡ | √ | | | | | |
| Echocardiography§§§ | | √ | Check if necessary | | | |
| ECG¶¶¶ | | √ | | √ | | |
| Imaging evaluation**** | √ | | Check once every two cycles | | √ | |
| Pregnancy test†††† | | √ | | | √ | |
| Investigational drug‡‡‡‡ | | | √ | √ | | |

Continued

**Table 2** Continued

| Check/visit | Screening | | Treatment period | | | |
|---|---|---|---|---|---|---|
| | d−28 to d−8 | d−7 to d−1 | First cycle (21 d) C1/D1 | Second cycle (21 d) C2/D1 (±3 days) | End of treatment/ withdrawal | Follow-up period* |
| Concurrent therapy | √ | √ | √ | √ | √ | √ |
| Adverse events§§§§ | √ | √ | √ | √ | √ | √ |

*Follow-up period: at the end of treatment or withdrawal from the study, participants enter survival follow-up until death, loss of follow-up, withdrawal of informed consent or study termination.
†ECOG Score is recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
‡A physical examination is recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study (general condition, head and face, skin, lymph nodes, eyes, ear, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, mental state, etc).
§Vital signs, including pulse, respiratory rate, body temperature and blood pressure, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
¶Height and weight should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study. If the subject loses at least 10% of his or her body weight during treatment, a recalculation of the drug dosage is required.
**Blood routine, including RBC, HGB, PLT, WBC, NEUT, lymphocyte count, etc, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
††Urine routine, including urine white blood cells, urine red blood cells, urine protein, urine sugar, etc, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
‡‡Blood biochemical, including ALT, AST, γ-GT, TBIL, DBIL, AKP, BUN, TP, ALB, Cr, GLU, $K^+$, $Na^+$, $Ca^{2+}$, $Mg^{2+}$, $Cl^-$, etc, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
§§Stool routine should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
¶¶Coagulation test, including APTT, PT, TT, FIB and INR, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study.
***Thyroid function test, including TSH, FT3 and FT4, should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study. If FT3 and FT4 are unavailable, T3 and T4 can be used.
†††Pituitary–adrenal test, including adrenocorticotropic hormone, cortisol and serum cortisol, should be completed within 7 days before the first dose and then the researcher will decide whether it needs to be performed.
‡‡‡Examination of virological indicators, including HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab, HIV-Ag/Ab, should be completed within 14 days before the first dose and then examinations are performed according to the actual situation during the study.
§§§Echocardiography should be completed within 7 days before the first dose and then examinations are performed according to the actual situation during the study.
¶¶¶ECG should be recorded within 7 days before the first dose, before each cycle of treatment and at the end of treatment or withdrawal from the study. Attention should be paid to QT, QTc and P–R intervals. If the patient has chest pain, heart palpitations or other cardiac symptoms, an ECG can be added at any time. The abnormal ECG with significant clinical significance should be supplemented by cardiac colour ultrasound. If symptoms such as pain and palpitation occur in the precardiac area, the myocardial enzyme profile should be tested immediately.
****Imaging evaluation should be completed within 28 days before the first dose and should be completed once every two cycles of the treatment period. If new lesions are suspected, they can be checked promptly. When subjects are out of the group for any reason, imaging examinations should be performed in time (±6 weeks). The first PR/CR should be confirmed in time (4 weeks±10 days). If the disease first progresses, it needs to be confirmed by imaging after 4–6 weeks. Subjects with no radiographic progression during follow-up should continue to be evaluated according to gastric cancer diagnosis and treatment guidelines until disease progression or other antitumour therapy is initiated. In addition to disease progression confirmed by imaging, subjects who end treatment for other reasons should also be imaged as often as possible at the frequency specified by the protocol until documented confirmation of disease progression, initiation of new antitumour therapy or death.
††††Pregnancy test is suitable for women of childbearing age. Serum pregnancy test is used during the screening period, and urine pregnancy test can be used at other timepoints.
‡‡‡‡Investigational drug includes adebrelimab in combination with apatinib and irinotecan.
§§§§Adverse events: the recording period is from the signing of the informed consent to 90 days after the last dose. Adverse events should be followed until they disappear, return to baseline level or ≤grade 1, reach a stable state or are reasonably explained (eg, loss of visit, death).
AKP, alkaline phosphatase; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C1, cycle 1; C2, cycle 2; Cr, creatinine; CR, complete response; d, day; D1, day 1; DBIL, direct bilirubin; ECOG, Eastern Cooperative Oncology Group; FIB, fibrinogen; FT3, free triiodothyronine; FT4, free thyroxine; GLU, glucose; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HGB, haemoglobin; INR, international normalised ratio; NEUT, neutrophil count; PLT, platelet count; PR, partial response; P-R, PR interval; PT, prothrombin time; QT, QT interval; QTc, corrected QT interval; RBC, red blood cell count; TBIL, total bilirubin; TP, total protein; TSH, thyroid stimulating hormone; TT, thrombin time; WBC, white blood cell count; γ-GT, gamma-glutamyl transferase.

needed. Clinical explorations of immune rechallenge or retreatment are currently available in several tumour types. A meta-analysis of 60 studies of advanced solid tumours eligible for ICIs rechallenge in melanoma, lung cancer, renal cell carcinoma, hepatocellular carcinoma, uroepithelial carcinoma, gastric cancer and cervical cancer[24] showed an ORR of 21.6% and a DCR of 55.8%, with an overall incidence of grade≥3 immune-related adverse events (irAE) of 16.7%. This suggests that patients with advanced solid tumours that have relapsed or progressed after treatment with ICIs may benefit from rechallenge with ICIs, without increasing the incidence of irAE. A real-world study[25] evaluated the efficacy and safety of continuing ICIs therapy in the second-line setting for patients with advanced gastric cancerfollowing progression on first-line immunotherapy. Among the second-line treatment regimens, 87 patients (40.1%) received ICIs combined with chemotherapy (I+C), while 130 patients (59.9%) received I+C and antiangiogenic agents (I+C+A). The median OS was 9.3 months (95% CI 8.5 to 10.1) and 11.5 months (95% CI 9.3 to 13.7), respectively (p=0.032), and the median PFS was 4.2 months (95% CI 3.1 to 5.3) and 5.2 months (95% CI 4.3 to 6.1), respectively (p=0.082). Cox regression analysis identified ECOG 0–1, first-line PFS≥6 months, second-line regimen (I+C+A) and second-line treatment duration>3 cycles as independent prognostic factors for OS in the second-line setting. The incidence of grade≥3 treatment-related AEs was 20.7%, and irAEs occurred in 6.5% of patients. No treatment-related deaths were reported.

Adebrelimab has been shown to be effective and safe in advanced esophageal squamous cell carcinoma, extensive-stage small cell lung cancer, and resectable non-small cell lung cancer.[26] No prior studies have evaluated adebrelimab rechallenge in PD-1 inhibitor-refractory advanced gastric cancer, making this investigation novel. Apatinib reshapes the immunosuppressive tumour ecosystem in gastric cancer and enhances the effect of anti-PD-1 immunotherapy.[27] There is a continuing debate on the best second-line chemotherapy treatment for individuals with advanced gastric cancer. Anti-VEGF targeted therapy has established efficacy in both second-line and third-line gastric cancer treatment. It has been shown that apatinib, a highly selective VEGF receptor 2 inhibitor, is an effective and well-tolerated third-line therapy for gastric cancer. Moreover, the efficacy and safety of combining apatinib with irinotecan as a second-line chemotherapy in advanced gastric cancer have been confirmed.[19] We are here to investigate the efficacy and safety of adebrelimab in combination with apatinib and irinotecan for patients with PD-1 inhibitor-resistant advanced-stage gastric cancer.

However, the single-centre, small-sample prospective clinical studies have certain limitations. First, as the study is conducted at a single centre, the geographical and representational scope of the patient population may be limited, potentially affecting the generalisability of the results and making it difficult to comprehensively reflect the treatment efficacy in a broader population. Second, the small sample size may result in insufficient statistical power, making it challenging to detect smaller clinical differences or rare AEs, while also increasing the risk of random errors in the results. Additionally, the lack of a control group means the study cannot directly compare the intervention with standard treatment or placebo, which may impact the reliability of the conclusions.

It is particularly noteworthy that this study focuses on the field of immunotherapy rechallenge, where current research is relatively scarce and there is a lack of mature findings for reference. The mechanisms of immunotherapy rechallenge are complex, and patient responses to treatment may exhibit significant heterogeneity. Therefore, conclusions drawn from small-sample studies need to be interpreted with caution. Future multicentre, large-sample randomised controlled trials, combined with longer-term follow-up data, are needed to further validate and generalise these preliminary findings and provide more reliable evidence-based support for immunotherapy rechallenge.

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