






BMJ Open Long-course chemoradiation plus concurrent/sequential PD-1 blockade as neoadjuvant treatment for MMR-status-unscreened locally advanced rectal cancer: protocol of a multicentre, phase 2, randomised controlled trial (the POLAR-STAR trial)

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ABSTRACT

Introduction Recent preclinical studies have discovered unique synergism between radiotherapy and immune checkpoint inhibitors, which has already brought significant survival benefit in lung cancer. In locally advanced rectal cancer (LARC), neoadjuvant radiotherapy plus immune checkpoint inhibitors have also achieved surprisingly high pathological complete response (pCR) rates even in proficient mismatch-repair patients. As existing researches are all phase 2, single-cohort trials, we aim to conduct a randomised, controlled trial to further clarify the efficacy and safety of this novel combination therapy.

Methods and analysis Eligible patients with LARC are randomised to three arms (two experiment arms, one control arm). Patients in all arms receive long-course radiotherapy plus concurrent capecitabine as neoadjuvant therapy, as well as radical surgery. Distinguishingly, patients in arm 1 also receive anti-PD-1 (Programmed Death 1) treatment starting at Day 8 of radiation (concurrent plan), and patients in arm 2 receive anti-PD-1 treatment starting 2 weeks after completion of radiation (sequential plan). Tislelizumab (anti-PD-1) is scheduled to be administered at 200 mg each time for three consecutive times, with 3-week intervals. Randomisation is stratified by different participating centres, with a block size of 6. The primary endpoint is pCR rate, and secondary endpoints include neoadjuvant-treatment-related adverse event rate, as well as disease-free and overall survival rates at 2, 3 and 5 years postoperation. Data will be analysed with an intention-to-treat approach.

Ethics and dissemination This protocol has been approved by the institutional ethical committee of Beijing Friendship Hospital (the primary centre) with an identifying

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ As a phase 2 clinical trial, this study integrated meticulous power and sample size calculation to compare the pathological complete response (pCR) rates between the two experiment arms (radiation plus Programmed Death-1 blockade followed by radical surgery) with the control arm (radiation followed by radical surgery), respectively.
- ⇒ Each patient to be included has a chance of 2/3 to enter the experiment arms.
- ⇒ The primary endpoint of this study is pCR rate, therefore long-term survival results will not be reported in the initial paper.

serial number of 2022-P2-050-01. Before publication to peer-reviewed journals, data of this research will be stored in a specially developed clinical trial database.

Trial registration number NCT05245474.

BACKGROUND

Among all newly diagnosed rectal cancer cases in China, 64.7% are locally advanced (clinically staged II/III).¹ For these patients, the application of neoadjuvant chemoradiation before TME (total mesorectal excision) surgery cannot only increase sphincter-preserving rate and R0 resection rate, but also reduce local recurrence rate.² However, current pathological complete response (pCR) rate, 5-year OS (overall survival) rate and 10-year OS rate of neoadjuvant

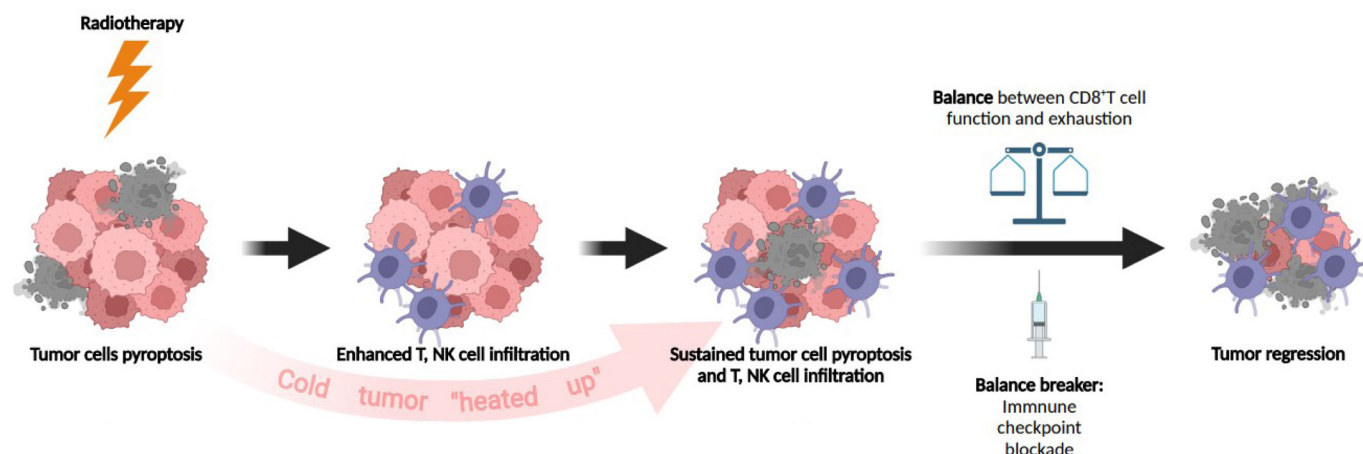


Figure 1 Hypothetical mechanism of tumour regression induced by radiotherapy combined with PD-1 blockade. NK, natural killer; PD-1, programmed death 1.

chemoradiation in locally advanced rectal cancer is merely 11%–15%, 76% and 59.6%, respectively.^{3–5}

Unlike the direct cytotoxic effect of radiation and chemotherapeutic agents, immune checkpoint inhibition (ICI) unleashes the power of cytotoxic T lymphocytes to control tumour.⁶ Currently, MSI-H (microsatellite instability high) status has been widely accepted as the most prominent biomarker to predict positive ICI efficacy.^{7,8} Yet in rectal cancers, only 2% are MSI-H/dMMR (deficient mismatch repair),^{9,10} precluding the majority of patients from ICI benefit. Nevertheless, recent basic researches indicated that radiotherapy has significant synergism effect with ICI (hypothetical mechanism summarised in figure 1).¹¹ And the clinical efficacy and safety of combining radiotherapy and ICI in the neoadjuvant setting of locally advanced rectal cancer (LARC) has been explored by several pioneering teams with phase 2, single arm trials, namely: the Chinese NCT04231552 trial, the Lebanese AVERECTAL trial, the Italian AVANA trial, the Japanese VOLTAGE trial, the Chinese NCRT-PD-1-LARC trial (our team), reporting encouraging pCR rates of 48%, 38%, 23%, 33% and 50%, respectively, as well as acceptable safety profile.^{12–16}

To obtain higher-level evidence, we hereby launched a phase II, multicentre, open-label, three-arm, randomised controlled trial to further clarify the efficacy and safety of neoadjuvant radiotherapy plus anti-PD-1 (Programmed Death 1) immunotherapy (tislelizumab¹⁷) in LARC.

METHODS AND ANALYSIS

Study objectives and endpoints

The primary endpoint of this study is rate of pCR, with the objective being to compare pCR rate between two experiment arms and the control arm, respectively. Secondary endpoints include: NAR score (Neoadjuvant Rectal Score),¹⁸ 2-year OS rate, 2-year DFS (disease-free survival) rate, 3-year OS rate, 3-year DFS rate, 5-year OS rate, 5-year DFS rate, median OS time, median DFS time, R0 resection rate, sphincter preserving rate, nearly pCR

rate, objective response rate, immune-related adverse event rate, Grade 3+ immune-related adverse event rate, neoadjuvant-treatment-related adverse event rate, Grade 3+ neoadjuvant-treatment-related adverse event rate, clinical complete response (cCR) rate, incidence rate of surgical complications, incidence rate of Grade 3+ surgical complications, quality of life score.¹⁹

Study design and registration

This study is a phase 2, multicentre, open-label, randomised, controlled trial consisting of two experiment arms and one control arm, which will be conducted in eight academic hospitals in Beijing, China (names of the study sites can be found on ClinicalTrials.gov).

Patient eligibility

Inclusion criteria

1. Aged 18–75.
2. ECOG (Eastern Cooperative Oncology Group) score 0–2.
3. Biopsy diagnosed rectal adenocarcinoma, distal margin within 10 cm to anal verge.
4. No distant metastasis, staged II/III (T4b excluded) by MRI.
5. Maximum diameter of rectal cancer lesion ≥ 10 mm according to baseline CT or MRI diagnosis (ie, a 'measurable lesion' as per Response Evaluation Criteria in Solid Tumors V.1.1).
6. Willing and able to comply with study protocol.
7. Consent to the use of blood and tissue specimens for study.
8. No history of previous antitumour treatment (eg, radiation, chemo, immuno, bio, herbal).
9. No disorders/diseases of immune system (eg, systemic lupus erythematosus, rheumatoid arthritis, systemic vasculitis, scleroderma, pemphigus, dermatomyositis, mixed connective tissue disease, autoimmune haemolytic anaemia, hyperthyroidism/hypothyroidism, ulcerative colitis, autoimmune haemolytic anaemia, HIV infection).

10. No significant dysfunction of major viscera (eg, heart, lung, liver, kidney).
11. No jaundice or gastrointestinal obstruction.
12. No acute/on going infection.
13. No significant irregularities in blood routine test and biochemical test results, particular requirements include: neutrophils $\geq 1.5 \times 10^9/L$, HGB (Hemoglobin) $\geq 80 g/L$, platelet $\geq 100 \times 10^9/L$, serum creatinine $\leq 1.5 \times ULN$ (upper limit of normal), total bilirubin $\leq 1.5 \times ULN$, ALT (alanine transaminase) and AST (aspartate transaminase) $\leq 2.5 \times ULN$.
14. No social or mental disorder.
15. For women of childbearing age, a negative result of serological pregnancy test is required, and effective contraception measures from inclusion till 60 days after the last dose of study drug is required.
11. With other conditions/issues that may affect the study results or cause the study treatment to be terminated halfway (eg, alcoholism, drug misuse).
12. Pregnant or lactating women, or women intending on conception during treatment period.

Protocol treatments

Experiment arm 1

Patients will receive long-course chemoradiation (long-course radiotherapy plus capecitabine tablets) concurrently combined with tislelizumab (200 mg \times 3 times, 3-week interval), as well as radical surgery. The first dose of tislelizumab will be given on Day 8 of radiation, with radical surgery planned 8–12 weeks after completion of radiotherapy (figures 2 and 3).

Experiment arm 2

Patients will receive long-course chemoradiation (long-course radiotherapy plus capecitabine tablets) sequentially combined with tislelizumab (200 mg \times 3 times, 3-week interval), as well as radical surgery. The first dose of tislelizumab will be given 2 weeks after completion of radiotherapy, with radical surgery planned 8–12 weeks after completion of radiotherapy (figures 2 and 3).

Control arm

Patients will receive long-course chemoradiation only (long-course radiotherapy plus capecitabine tablets, with no neoadjuvant immune therapy). Radical surgery will be performed 6–12 weeks after completion of radiotherapy (figures 2 and 3).

Specifications

Radiotherapy: total dosage 45–50.4 Gy, 25–28 fractions, 5 days/week, duration 5–5.5 weeks.

Capecitabine tablets: 825 mg/m² orally, two times per day, 5 days/week (synchronous with radiotherapy), duration 5 weeks.

Tislelizumab: 200 mg (fixed dosage) ivgtt (intravenously guttae), one time every 3 weeks. In both experiment

Exclusion criteria

1. Multiple cancers, or with concomitant malignant tumours besides rectal cancer.
2. Having received any anticancer treatment (surgery, drugs, etc) in the past 5 years.
3. History of recent major surgery.
4. With conditions that affects the absorption of capecitabine via gastrointestinal tract (eg, inability to swallow, nausea, vomiting, chronic diarrhoea).
5. With uncontrolled, severe, concomitant diseases of any sort.
6. Allergic to any of the ingredients under study.
7. Estimated survival period ≤ 5 years due to any reason.
8. Preparing for or having previously received organ or bone marrow transplantation.
9. Having received immunosuppressive or systemic hormone therapy for immunosuppressive purposes within 1 month prior to inclusion.
10. For patients with history of disorder of central nervous system, investigator discretion is required as to whether the clinical severity prevents the signing of informed consent or affects the patient's oral medication compliance.

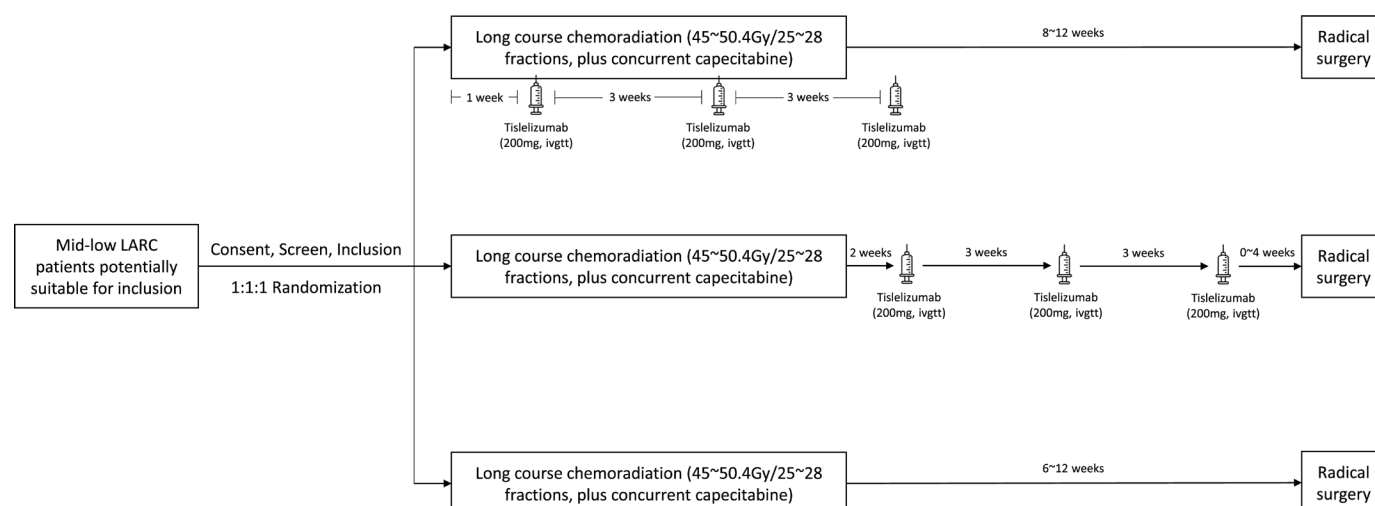


Figure 2 Study flowchart. LARC, locally advanced rectal cancer; ivgtt, intravenously guttae.

| Time | | Screening/Baseline | | | Neoadjuvant treatment | | Pre-operative | Post-operative (Within 1 week) |
|-------------------------|------------------|------------------------|-----------|---|--|--|---------------|-----------------------------------|
| | | -14~8 days | -7~1 days | | Radiotherapy (Within 1 week after completion) | PD1 blockades (Before and after, within 1 week) | | |
| Items | | | | | | | | |
| Quality of life score | | ✓ | | | | | | |
| Lab tests | Blood routine | | ✓ | R A N D O M I Z E | ✓ | ✓ | ✓ | ✓ |
| | Biochemical | | ✓ | | ✓ | ✓ | ✓ | ✓ |
| | Thyroid function | | ✓ | | | ✓ | | |
| | HIV | | ✓ | | | | | |
| | Tumor markers | | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Chest CT | | ✓ | | | | | ✓ | |
| Abdominal and pelvic CT | | ✓ | | | | | ✓ | |
| Rectal MRI | | ✓ | | | | | ✓ | |
| Colonoscopy | | ✓ (with MMR diagnosis) | | | | | ✓ (optional) | |

Figure 3 Patient work-up during treatment period. MMR, mismatch-repair; PD1, programmed death 1.

groups, patients are designated to receive three times of tislelizumab treatments (200mg each time, 3-week interval) before surgery. However, if a serious adverse event (Common Terminology Criteria for Adverse Events Grade 3 or above) occurred after any one of the three times of immunological treatments, the residue doses will be cancelled and the patient will wait for the initially designed time window to receive radical surgery.

Adjuvant therapy: all included patients will receive none, capecitabine only or CAPOX therapy based on their baseline tumour staging.

Consent, randomisation and blinding

As a multicentre study, patient consent and enrolment is conducted at outpatient or ward of our eight study sites by attending surgeons. Our randomisation procedure adopted a 'center-stratified, block randomization' approach, with a block size of 6. The randomisation procedure is performed by an external CRO (clinical research organisation) company using a specially designed online system (<https://www.larc-crt-pd1.com/user/login>), with the allocation sequence being computer-generated random numbers from CRO company, which is concealed from all clinical staff or researchers. As an open-label trial, the surgeons, patients and coordinating researchers will not be blinded for the allocated treatment, for the fact that treatment schedules of different arms are distinct and easily recognisable.

Criteria of tumour response and adverse events

Tumour response and adverse events will be closely followed-up and recorded by specially assigned personnel from each study site.

Tumour response

Responses to neoadjuvant therapy of all arms are performed in accordance with RECIST V.1.1 criteria.²⁰ This assessment is performed when patients have finished preoperative rectal MRI examinations. Notably, for

patients achieving cCR, surgery will still be recommended unless patients insist on a non-surgical approach.

Toxicity

Adverse reactions to neoadjuvant treatments (including immune-related adverse reactions) are strictly recorded and graded according to CTCAE V.5.0 criteria. The time window for this evaluation ranges from the start of radiation to perioperative phase.

Surgical complication

Surgical complications (within 30 days after operation) are strictly recorded and graded according to Clavien-Dindo criteria.

Sample size

Calculation of sample size

As a parallel group, superiority trial, sample size calculation is performed with the TEST FOR TWO PROPORTION function of PASS software (V.21.0.3), with the parameters set as follows:

1. $p_1=0.4$ (assuming the pCR rate of both experiment arms to be 40%, considering current evidences).
2. $p_2=0.16$ (assuming the pCR rate of control arms to be 16%, considering the actual pCR rates of participating centres).
3. $\alpha=0.05$ (two-sided).
4. $\beta=0.2$.
5. Drop-out rate=0.15.

On calculation, each arm requires 62 patients, totalling 186 patients.

Reasons for mid-way sample size expansion

In our initial sample size calculation, we assumed p_2 to be 0.10 based on the regular pCR rate of chemoradiation in the primary centre (Beijing Friendship Hospital). However, after the first routine multicentre investigator meeting, where the regular pCR rate of the control group was discussed, consensus was reached that 0.16 is more

| Time after surgery | | 3 months | 6 months | 1 year | 1.5 year | 2 years | 3 years | 4 years | 5 years |
|------------------------------|------------------|----------|----------|--------|----------|---------|---------|---------|---------|
| Items | | | | | | | | | |
| Survival status | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Quality of life score | | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ |
| Lab tests | Blood routine | ✓ | | | | | | | |
| | Biochemical | ✓ | | | | | | | |
| | Thyroid function | ✓ | | | | | | | |
| | Tumor markers | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Tumor evaluation (CT or MRI) | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Adverse events | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Accompanying drugs | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Accompanying treatments | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

Figure 4 Follow-up plan.

representative as the pCR rate of the control group.²¹ Therefore, we revised the protocol and changed p_2 from 0.10 to 0.16.

Along with p_2 , we also revised the value of α , β and drop-out rate: α was revised from 0.05 (one-sided) to 0.05 (two-sided) to reduce false positive rate; β was revised from 0.1 to 0.2 for the fact that setting power to 0.8 was a common practice, and a power of 0.9 was unnecessary; drop-out rate was revised from 0.20 to 0.15 for the fact that the primary endpoint of this study (pCR rate) is a short-term endpoint, a drop-out rate of 0.20 (as in those studies with 3-year or 5-year endpoints) was considered highly unlikely.

After recalculation, sample size was expanded from 120 to 186. Revision of study protocol and update of online registry information are completed on 10 May 2023, while enrolment is still ongoing.

Postoperative follow-up

Postoperative follow-up period starts on operation day and ends till 5 years postoperation, by specially assigned personnel of each study site. Time points of follow-up include: 3 months, 6 months, 1 year, 1.5 years, 2 years, 3 years, 4 years, 5 years. Primary items of follow-up include: survival status, quality of life score, blood routine test and biochemical test, tumour biomarkers, radiological tumour assessment, adverse events, accompanying drugs/treatments (figure 4).

Trial status and study timeline

This trial was conceived and designed in February 2022. Enrolment started on 1 April 2022, and is scheduled to close by June 2023. Revision of protocol started on 1 March 2023 and was completed on 10 May 2023 to expand sample size from 120 to 186. Current protocol version and date: V.4.0, 10 May 2023. Analysis of short-term endpoints (including the sole primary endpoint pCR rate) will be completed before December 2023. Analysis of long-term follow-up results will be completed roughly around 2029.

Data management

A trial-specific database has been developed and validated based on standard operating procedures at the Clinical Trial Center of Beijing Friendship Hospital. The database (<https://www.larc-crt-pd1.com/user/login>) has been integrated into a general information technology infrastructure with a firewall and backup system. Patient de-identified data are digitalised from paper CRF (case report forms) into the database by an external CRO company. Changes made to the originally input data will be documented and audited by a data monitoring committee composing of staff from all eight study sites, which is independent from the sponsor. The committee will conduct periodical checks for completeness and plausibility of the input data. All participating centres will be closely monitored to ensure data quality. The database is accessible only to the principal investigator, specific members of the research team and the data monitoring committee.

Plans and methodology for statistical analysis

As a phase 2 trial, we set no plans for an interim analysis. In the final analysis, an intention-to-treat approach will be adopted. When describing statistical data, count variables will be described as rate, measurement variables will be described as mean with 95% CI. When comparing data of two or more groups, χ^2 test will be adopted for count data and t-test for measurement data. The Kaplan-Meier method will be applied to generate a survival curve, where a log-rank test will be adopted for comparisons between groups. Level of statistical significance is defined as $p < 0.05$.

Ethics

This protocol has been approved by the institutional ethical committee of Beijing Friendship Hospital (the primary centre) with an identifying serial number of 2022-P2-050-01. Any amendments to the protocol will be updated on ClinicalTrials.gov. Clinical investigators' trial conduct will be audited by the ethical committee of each study site through compulsory briefing sessions once every 6 months. Patients having suffered from

adverse reactions of Grade 3 or above due to neoadjuvant treatment will be compensated by our clinical insurance agreement with Ping An Insurance (Group) Company of China. Before publication, data of this research will be stored in a specially developed clinical trial database.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Role of study sponsor and funder

This is an investigator-initiated clinical trial. The study sponsor and funder, BeiGene, have no role in study design, data management, report writing or publication decision-making, nor will they have any authority over any of these activities.

Dissemination

Results of the primary endpoint (pCR rate) as well as other short-term endpoints will be published in peer-reviewed journals focusing on the immunological treatment of solid tumours. Results at 3 and 5 years will be published separately. The final manuscripts will be drafted by the first author of this protocol, and the authorship of the final manuscripts will depend on investigators' actual contribution to the trial. Trial participants will not be informed on the results.

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