BMJ Open  Neoadjuvant chemoradiation therapy combined with immunotherapy for microsatellite stable ultra-low rectal cancer (CHOICE II): study protocol of a multicentre prospective randomised clinical trial


ABSTRACT

Introduction  Neoadjuvant chemoradiotherapy (nCRT) could bring tumour shrinking and downstaging and increase the probability of organ preservation for patients with low rectal cancer. But for ultra-low rectal cancer, there is little possibility for organ preservation. Immunotherapy has been shown to have significant survival benefits in microsatellite instability-high patients but poor response in microsatellite stable (MSS) patients. Studies have demonstrated that radiotherapy and immunotherapy have synergistic effects in cancer treatment. There is no existing evidence about the clinical efficacy of immunotherapy combined with nCRT for patients with MSS ultra-low rectal cancer.

Method and analysis  This trial is an open-labelled multicentre prospective randomised controlled trial (NCT05215379) with two parallel groups and allocation ratio 1:1 (nCRT+immunotherapy vs nCRT group).

Eligible participants will be aged 18–75 years, with a desire for anus preservation, confirmed cT_{1,2}, N_{0}, M_{0} rectal adenocarcinoma, confirmed MSS type, inferior margin of ≤5 cm from the anal verge. The primary endpoint of this trial is complete clinical response (cCR) rate. Immunotherapy is added after 1 week of chemoradiotherapy for two cycles, and then the patients will be administered two cycles of immunotherapy and CAPOX. The evaluations will be carried out after the completion of the whole neoadjuvant therapy. We expect the programme to improve the cCR rate and the quality of life for patients with ultra-low rectal cancer.

Ethics and dissemination  This trial was approved by the Ethics committee of Changhai Hospital and other medical centres (Grant number:CHEC2022-118). The results of this study will provide further insight into the clinical efficacy of immunotherapy in combination with nCRT in patients with MSS ultra-low rectal cancer.

Trial registration number NCT05215379.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ CHOICE II will be the first study investigating the clinical complete response rate by combining immunotherapy and neoadjuvant therapy for patients with microsatellite stable rectal cancer.

⇒ CHOICE II will provide new insights into the treatment for ultra-low rectal cancer.

⇒ It is an open-labelled study and the bias of assessment should not be neglected.

INTRODUCTION

The incidence of rectal cancer in China is significantly higher than other countries, accounting for over 50% of all colorectal cancer (CRC) cases. For patients with low rectal cancer, anterior resection and abdominoperineal resection (APR) are the standard surgical approaches, both of which require the resection of rectum and even anus and result in the perioperative mortality, anastomotic leak, sexual problems and extensive effects on quality of life (QoL). Although anus-preserving surgical approaches have been proposed such as intersphincter resection (ISR) and conformal sphincter preservation operation, there is little probability for patients with ultra-low rectal cancer to preserve the rectum and anus.

Neoadjuvant chemoradiotherapy (nCRT) has been recommended as the standard treatment for locally advanced rectal cancer, but the adoption of nCRT in early stage rectal cancer is ambiguous. nCRT could bring tumour shrinking and downstaging, and thus increase the possibility of organ preserving for patients with rectal cancer. But
for patients with ultra-low rectal cancer, the possibility of organ preservation is still rather low even after receiving nCRT. Approximately, 15%–20% patients would occur a pathological complete response (pCR) after nCRT, which is defined as the absence of tumour cells in surgical specimens. Apart from pCR, a phenomenon of complete clinical response (cCR) also exists. cCR is defined as the absence of clinical, endoscopic or radiographic evidence of a tumour. Habr-Gama et al initially reported that patients with cCR could be managed with non-operative ways termed as watch-and-wait (W&W), and the oncological outcomes were identical to those of patients who achieved a pCR. Subsequent studies have supported the finding that W&W is a safe approach for organ preservation and QoL, especially for patients with ultra-low rectal cancer. However, the rate of cCR after nCRT remains unsatisfactory, ranging from 5% to 30%, and improving the cCR rate in patients with ultra-low rectal cancer after nCRT is of great importance to patients’ QoL, particularly those with early stage cancer.

Immunotherapy has been shown to have significant survival benefits in deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) metastatic CRC, but poor response in proficient mismatch repair (pMMR)/microsatellite stable (MSS) CRC. However, pMMR/MSS CRC accounts for >90% of all CRC cases, which indicates that most patients with CRC cannot benefit from immunotherapy. Studies have demonstrated that radiotherapy and immunotherapy have synergistic effects in cancer treatment. The expression levels of programmed death ligand-1 (PD-L1) and density of CD8+ tumour-infiltrated lymphocytes were reported to increase after radiation, suggesting the potential benefit of combining radiotherapy and immunotherapy. In the VOLTAGE trial, researchers reported the clinical efficacy and safety of nCRT and subsequent immunotherapies. pCR was confirmed in 30% of the patients with MSS. Given these findings, we hypothesised that nCRT combined with immunotherapy could improve the cCR rate in patients with MSS and benefit organ preservation as well as improve QoL in patients with ultra-low rectal cancer.

### METHODS

#### Study design

This study is an open-labelled multicentre prospective randomised controlled trial (NCT05215379) with two parallel groups and allocation ratio 1:1. Figure 1 summarises the study design. Eligible patients will be randomised into an experimental group (nCRT+immunotherapy) or control group (only nCRT).

Potential participants will be recruited in 18 medical centres across China. This study was approved by the Ethics committee of Changhai Hospital and other medical centres (grant number: CHEC2022-118). All the recruited patients will sign the informed consent.

#### Objectives

The objective of the trial is to determine the clinical efficacy of immunotherapy in combination with nCRT in patients with MSS ultra-low rectal cancer. The primary endpoint of the study was the cCR rate, and the secondary endpoints included the organ preservation (W&W and local excision) rate, anus preservation rate, pCR rate, disease-free survival (DFS), overall survival (OS) and QoL.

#### Eligibility criteria

Eligible participants for this study will be aged 18–75 years, with a desire for anus preservation, confirmed cT1–3aN0–1M0 rectal adenocarcinoma, confirmed MSS type, inferior margin of ≤5 cm from the anal verge. The exclusion criteria will include a history of CRC; intestinal obstruction, intestinal perforation, intestinal bleeding that required emergency surgery; allergy to capecitabine, oxaliplatin, programmed death-1 (PD-1) monoclonal antibody (mAb) or any mAb that targets T cell co-stimulatory molecules; and serious concurrent illness that may affect the outcome of treatment or survival.

---

**Figure 1** Flow chart summarising the study procedures. cCR, complete clinical response; ncCR, near complete clinical response; TME, tumour microenvironment; PR, partial response; PD, progressive disease.
**Inclusion criteria:**

Patients with ultra-low rectal cancer who are initially to receive APR

- With a desire to preserve the anus.
- Aged 18–75 years.
- cT1-3aN0-1M0 rectal adenocarcinoma.
- MSS type.
- Inferior margin of ≤5 cm from the anal verge.
- An Eastern Cooperative Oncology Group performance status of 0–1.
- No antitumour or immunotherapy was received before enrolment.
- Normal laboratory tests.

**Exclusion criteria:**

- Presence of metastasis.
- History of CRC.
- Intestinal obstruction, intestinal perforation, intestinal bleeding that required emergency surgery.
- Allergy to capecitabine, oxaliplatin, programmed death-1 (PD-1) monoclonal antibody.
- History of pelvic radiation.
- Treated with corticosteroids or other immunosuppressive agents within 14 days before the study.
- Presence of autoimmune disease or any other unstable systemic diseases.
- Pregnant or lactating women.

**Experimental group**

Patients will receive 50 Gy (2 Gy/day×25 days) radiotherapy with concurrent capecitabine twice daily. After the radiotherapy, patients will be administered two cycles of CAPOX. And the reassessments will be the same as experimental group.

**Control group**

Patients will receive 50 Gy (2 Gy/day×25 days) radiotherapy with concurrent capecitabine twice daily. After the radiotherapy, patients will be administered two cycles of CAPOX. And the reassessments will be the same as experimental group.

**Follow-up**

Once the cCR was confirmed, the patient was managed using the W&W approach. Endoscopy and a series of examinations, including DRE, pelvic MRI and carcinoembryonic antigen, were performed every 3 months for the first 2 years and then every 6 months. Chest CT and abdominal CT or MRI were performed every 6 months. Local regrowth was defined as any sign of tumour recurrence, such as new rectal wall thickening and an enlarged mesorectal mass, in the rectal wall on DRE, endoscopy or imaging findings. Local regrowth was an indication for salvage surgery via TME. Patients were examined using chest CT, liver MRI and abdominal and pelvic CT or MRI to fully detect metastases.

**Data collection and management**

A group of researchers will be responsible for contacting patients to assess outcomes at baseline and at follow-up visits. Data will be stored in Electronic Data Capture (EDC) system developed by Healife Group with access to all the researchers. For security reasons, an external hard drive will be used to back up the database regularly. Another group of researchers will be responsible for assessing outcomes and data analysis. Personal information will be maintained only by the researchers at the institution where data will be collected.

**Management of adverse event**

Adverse event (AE) will be rated following the Common Terminology Criteria for Adverse Events (V5.0). Any AEs
Table 1  Pathological assessment of tumour regression grading (TRG) after neoadjuvant therapy

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRG 0</td>
<td>No residual tumour cells</td>
</tr>
<tr>
<td>TRG 1</td>
<td>Single cell or small group of cells</td>
</tr>
<tr>
<td>TRG 2</td>
<td>Residual cancer with desmoplastic response</td>
</tr>
<tr>
<td>TRG 3</td>
<td>Minimal evidence of tumour response</td>
</tr>
</tbody>
</table>

including dermatologic, gastroenterological, endocrine, pulmonary, rheumatological, musculoskeletal, infusion reactions, cardiovascular, haematologic, renal, neurological and ophthalmological events that occurred during the study will be monitored and followed up until the end of the study. The detailed management of AE and immune-related AEs will be documented.

Quality control

In order to ensure the quality of this trial, all the clinical data unloaded to the EDC system will be re-evaluated and verified. All the researchers will be trained in the principal centre, especially researcher of the imaging department and pathology department.

All the recruited patients will be examined, treated and evaluated strictly according to this study protocol. The clinical data will be documented correctly by the researchers in each medical centre through the EDC system. The clinical research associate will check the documented data every month to confirm the accuracy of all the data.

The parameters of MRI staging and cCR will be standardised (online supplemental materials 2 and 3). Every diagnosis of cCR and the adoption of W&W will be discussed and reassessed by the MDT in the principal centre.

Surgery will be performed by experienced surgeons in each centre. Radical surgery will follow the principles of TME. The video of the whole surgical procedure will be submitted and reviewed by the professional surgeons in the principal centre. Local excision will be a surgical transanal traditional or endoscopic full thickness rectal wall excision, with a bowel margin of 1 cm. All the specimens will be processed and examined by professional pathologists.

Sample size

This is a multicentre, prospective, randomised controlled trial. The significance level of the sample size estimation hypothesis test is unilateral $\alpha=0.05$, and the test power is 0.80. According to literature and clinical practice, the proportion of cCR after neoadjuvant therapy is 20%. In the single-arm study of nCRT combined with immunotherapy carried out by our centre, the cCR rate reached 40%. Using the PASS 2021 software, assuming a cCR of 40% in the experimental group and 20% in the control group, considering that 10% of cases will be lost, the sample size required for each group is 90 cases.

Statistical analysis

Clinical data will be analysed using SPSS software (V.26.0). Continuous variables are summarised using medians and ranges, and categorical variables are described using frequencies and percentages. Comparisons between groups were performed using Fisher’s exact test or the $\chi^2$ test. Statistical significance was set at $p<0.05$. DFS was defined as the duration from the date of randomisation to the date of the first recurrence (local, distant or mixed) or death. Recurrence was defined as the identification of suspicious imaging findings or a biopsy-proven tumour. OS was calculated from the date of randomisation. The QoL was assessed by EORTC QOL Core Questionnaire (EORTC QOL-C30). The populations analysed for efficacy will be patients who complete the whole neoadjuvant therapy, and the population analysed for safety will be the patients who have ever received immunotherapy. Subgroup analysis towards the gene status will be carried out.

Allocation sequence

Permuted block randomisation using computer-generated random numbers will be used to produce the randomisation sequence, and the treatment arm will be decided by opening the randomisation envelope at the time of successful screening. The randomisation is stratified by T stage and N stage. The randomisation process will be performed by someone who is not part of the research team. Due to the nature of the intervention, participants and clinicians could not be blinded. The results will be analysed by statisticians independent of the research team.

Patient and public involvement

No patient involved.

DISCUSSION

The probability of organ preservation for low rectal cancer has improved with the advances in surgical techniques and the adoption of nCRT. But little is the possibility of patients with ultra-low rectal cancer for organ preservation. The new concept of W&W by identifying cCR at restaging and avoiding surgery has been proved to be oncologically safe and could improve functional outcomes. However, the cCR rate after nCRT was still low. Here, in this, we aim to elevate the cCR rate for patients with ultra-low rectal cancer by combining immunotherapy and nCRT.

nCRT is much better tolerated than postoperative chemoradiotherapy and has proven to be very effective in downstaging rectal cancer. nCRT followed by TME has improved surgical quality and decreased the local relapse rate. As a result, local control is no longer the Achilles heel in rectal cancer treatment, it is time to focus to improve functional outcomes. Especially for the elderly and for those with several comorbidities, radical resections are major procedures with substantial morbidity.
and mortality. More than half of patients undergoing TME surgery and nCRT will have long-term anorectal and urogenital dysfunction. Habr-Gama et al first reported the implementation of W&W in patients who achieved a cCR after nCRT. This specific strategy has been shown to significantly improve the QoL of patients without affecting long-term survival. However, the current cCR rate following nCRT remains low. Martens et al reported that of 141 patients with rectal cancer who underwent nCRT, only 24 (17%) achieved a cCR. Perez et al showed that for patients with cT2–4 N0/+ , only 16 (16.2%) achieved a cCR following nCRT. In a meta-analysis by Dattani et al, 692 patients were included in 17 studies, of which the proportion of patients with cCR was 22.4%.

Immunotherapies that target the interaction of PD-1 with its ligand, PD-L1, have ushered in the modern oncology era. Anti-PD-(L)1 rejuvenates tumour-specific cytotoxic T cells that already reside in the TME, causing their activation, proliferation and trafficking to micrometastatic deposits. Immunotherapy has shown promising results in patients with dMMR/MSI-H metastatic CRC. However, little is known regarding neoadjuvant immunotherapy in patients with pMMR/MSS. Although neoadjuvant chemotherapy can downstage tumours preoperatively, neoadjuvant immunotherapy aims to enhance systemic immunity against tumour antigens, eliminating micrometastatic tumour deposits that would otherwise be the source of postsurgical relapse. Moreover, neoadjuvant immunotherapy, while the primary tumour is in place, as opposed to adjuvant therapy directed only against micrometastatic disease after resection, leverages higher levels of endogenous tumour antigens present in the primary tumour to enhance T cell cytotoxicity. Recent studies have shown that radiotherapy and immunotherapy have synergistic effects in cancer treatment. The expression levels of PD-L1 and density of CD8+ tumour-infiltrating lymphocytes were reported to increase after radiation, suggesting the potential benefit of combining radiotherapy and immunotherapy. The Japanese VOLTAGE trial initially reported the results of nCRT followed by nivolumab and surgery in patients with locally advanced rectal cancer, and a 30% pCR rate was observed in patients with MSS, indicating the potential advantage of immunotherapy in nCRT but further randomised controlled trials are still required.

To conclusion, this trial intends to verify the efficacy of combining nCRT and immunotherapy in patients with MSS ultra-low rectal cancer. To our knowledge, this will be the first randomised controlled trial by adding immunotherapy into nCRT, and hope this trial will provide high level evidence to the organ preservation strategy of patients with ultra-low rectal cancer.

Contributors LZ, GY and RW drafted the manuscript. HJ, TZ, ZP, HF and AP contributed to the methodology, YY, XZ, HG, XG and ZL contributed to revise the manuscript. WZ contributed to the design and funding of the study.

Funding This work was supported by National Natural Science Foundation of China (82072750), Natural Science Fund of Shanghai (20ZR1457200), Shanghai Sailing Program (21YF1459300), Shanghai Municipal Health Commission Health Industry Clinical Research Project(2024Y0348).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID ID
Tianshuai Zhang http://orcid.org/0000-0002-4596-6832

REFERENCES


Supplemental Material 1

Multicenter prospective randomized clinical trial of neoadjuvant chemoradiation therapy combined with immunotherapy for MSS ultra-low rectal cancer (CHOICE II)

INFORMED
CONSENT FORM

Version NO.1.3(20230210)
Research Institute: Shanghai Changhai Hospital
Principal Investigator: Prof. Wei Zhang
1. Purpose of the study

Background

Ultra-low rectal cancer refers to tumors whose lower edge is within 2 cm of the dentate line. Surgical treatment for these patients requires removal of the rectum or anus, which has a high disability rate and disease burden. Neoadjuvant radiotherapy can significantly reduce the size of the tumor, thereby increasing the patients’ chances of preserving the anus. Approximately 20% of patients will experience complete tumor disappearance (complete clinical response) after neoadjuvant radiotherapy. The Watch & Wait nonsurgical strategy for these patients can effectively increase the rate of anus preservation and rectum preservation, and thus improve the quality of patients’ life. The proportion of patients who achieve complete clinical response under current neoadjuvant treatment modalities is still low; therefore, improving neoadjuvant treatment strategies for rectal cancer is the focus of improving the rate of anus and rectum preservation in rectal cancer patients. The effectiveness of immunotherapy in treating malignant tumors is obvious and has changed the traditional anti-tumor treatment paradigm. However, in colorectal cancer, immunotherapy is limited to a specific group with a small proportion of MSI-H/dMMR, and there is no effective immune response for the majority of MSS/pMMR patients. Radiotherapy has been shown to enhance the efficacy of immunotherapy and promote its antitumor effects.

Sintilimab (development code: IBI308) is a recombinant fully human IgG4-type

Please read the following carefully

You are being invited to participate in a clinical study. This informed consent form gives you some information to help you decide whether to participate in this clinical study. Please read it carefully and feel free to ask any questions you may have to the investigator in charge of the study, who will provide you with detailed answers. You can make a decision based on your own situation and you will have ample time to consider it.
anti-PD-1 monoclonal antibody developed by Innovent Biologics (Suzhou), Inc. Meanwhile, the available safety data and pharmacokinetic data demonstrate that the safety of Sintilimab in patients is acceptable. Therefore, it is safe and feasible to use Sintilimab as the immunotherapy drug in this study.

The Department of Anorectal Surgery of Changhai Hospital is a national key discipline, a key discipline of Chinese and Western medicine combined with anorectal disease of the State Administration of Traditional Chinese Medicine, a key discipline of anorectal disease of the Chinese People’s Liberation Army, and a key discipline of the Second Military Medical University. At present, there are 104 beds in the whole department, and the annual average rectal cancer surgery volume has been ranked among the top in Shanghai in the past three years. The Department has carried out a preliminary study of neoadjuvant radiotherapy combined with immunotherapy, the results of which showed that 40% of patients with MSS-type ultra-low rectal cancer were in complete clinical response. Accordingly, this study intends to investigate the effect of neoadjuvant radiotherapy combined with immunotherapy on the rate of clinically complete patients with MSS-type ultra-low rectal cancer who cannot conserve anus, with the hope that this treatment mode will improve the rate of organ preservation, enhance the overall treatment effect, and improve the quality of life and long-term survival of these patients.

**Purpose**

We intend to investigate the effect of neoadjuvant radiotherapy combined with immunotherapy on the clinical complete remission rate of MSS-type ultra-low rectal cancer without anus preservation, with the clear expectation that this treatment modality will improve the rate of anus and rectum preservation, enhance the overall treatment effect, and improve the quality of life and long-term survival of patients.

**2. Research Process**

This clinical trial is an open label multicenter randomized controlled clinical study,
consisting of 2 treatment regimens: neoadjuvant radiotherapy combined with immunotherapy and neoadjuvant radiotherapy alone. 180 patients will be enrolled in this study, which will be divided into 3 parts: screening, treatment and follow-up.

Screening

Screening is to assess your suitability for this study and to carefully document your general health status by your physician. You will undergo a physical examination, provide past and current medical history and specific treatment, provide for collection of routine blood/blood biochemistry/coagulation/cardiac enzymes/tumor markers/thyroid function; routine urine testing; routine stool; imaging (CT thorax and abdomen, pelvic MRI, colonoscopy); and mismatch repair proteins (MSI status, etc.). You will be enrolled in our study after the screening period if you meet all the inclusion criteria, do not meet any of the exclusion criteria, and agree to continue in the study.

However, your doctor will terminate your continued participation in the trial if:
- Requesting to withdraw from the study for various reasons after being enrolled in the study;
- You are unable to complete the study for various reasons after enrollment in the study
- You are a patient with postoperative imaging and pathology confirmed local recurrence or distant metastases, including liver, pelvis, ovaries, peritoneum.

Treatment

1. Neoadjuvant radiotherapy + immunotherapy: using long-course radiotherapy mode, irradiate the primary tumor and high-risk area with a tumor dose of 50 Gy (2 Gy/dose \times 25 times); give capecitabine and 2 courses of PD-1 antibody (200 mg/3 weeks) simultaneously during radiotherapy. Two courses of PD-1 antibody (200 mg/3 weeks) and capecitabine alone or Capeox regimen chemotherapy were applied for 2 cycles after the completion of radiotherapy. At the end, pelvic MRI, endoscopy and digital rectal examination were performed to assess the tumor regression grade. Patients with poor tumor regression or even progression were treated surgically as appropriate; patients with good tumor regression and near complete regression (ncCR) were decided after MDT discussion whether to undergo total transanal tumor resection or to enter the Watch & Wait cohort; patients with complete tumor response were entered into the
Watch & Wait cohort.

2. Neoadjuvant radiotherapy: using long-course radiotherapy mode, irradiating tumor dose of 50 Gy (2 Gy/dose × 25 times) to the primary tumor and high-risk area; giving capecitabine monotherapy simultaneously during radiotherapy, followed by capecitabine monotherapy maintenance or Capeox regimen chemotherapy treatment for 2 cycles. At the end of the treatment, pelvic MRI, endoscopy and anal finger examination were performed to assess the tumor regression grade. Patients with poor tumor regression or even progression were treated surgically as appropriate; patients with good tumor regression and near complete response (ncCR) were decided after MDT discussion whether to undergo surgery or to enter the Watch & Wait cohort; patients with clinical complete response (cCR) entered into the Watch & Wait cohort.

**Follow-up**

For patients entering the Watch & Wait cohort, we will perform digital rectal examination and colonoscopy every 2 months for the first 2 years, and need to combine with endoscopic narrow band imaging (NBI) observation; pelvic MRI every 4-6 months; blood carcinoembryonic antigen every 4 months; chest and abdominal CT every 6 months. Colonoscopy was performed according to the current oncology follow-up guidelines. If cCR is still maintained after 2 years, colonoscopy and digital rectal examination can be performed every 6 months, and after 3 years, it can be changed to once a year.

If local regrowth of the tumor occurs during the Watch & Wait process, we will perform radical surgery and determine the margins of local resection according to the original tumor borders before treatment; patients who undergo local resection are re-admitted to the Watch & Wait follow-up program for meticulous follow-up; patients with the following high-risk factors for local resection are recommended to undergo radical surgery again: ypT stage $\geq T2$, hypofractionated adenocarcinoma, indolent cell carcinoma mucinous adenocarcinoma, choroidal carcinoma, nerve infiltration, and positive cut margins. In case of distant metastases during Watch & Wait, if the local lesion continues to remain in complete respondr but distant metastases occur, we will prioritize the distant metastases and the primary lesion can continue to Watch & Wait.
If you have completed study treatment or terminated treatment early, survival follow-up begins every 12 weeks after disease progression or termination of treatment, and your physician will continue to collect information on your serious adverse events related to the study drug, subsequent antitumor therapy, and survival follow-up. If you discontinue study treatment for reasons other than disease progression, your physician will also recommend periodic tumor imaging to assess the current status of your disease.

All tests performed throughout the study are to determine your suitability to continue in the study and to ensure your safety. You will need to tell your doctor about any medications and treatments you are using and receiving. Your doctor will ask you throughout the study if you are experiencing any discomfort with your medications and if you are taking them as prescribed, and your doctor will make detailed notes and give you appropriate treatment.

The blood samples and related test reports you provide will be used for this study only and will not be used for other studies. Blood samples tested in our hospital will be tested in accordance with the relevant hospital regulations and the corresponding reports will be issued. Some blood samples will be collected and sent to the central laboratory for testing in accordance with the study regulations. After laboratory testing is completed, the remaining samples will be destroyed after testing is completed and will not be stored further or used for other studies.
3. Research risks and discomfort

During the screening period you will need to complete a number of tests and examinations. Complications and tissue damage may occur due to individual patient specificity, disease differences, age and other factors.

Neoadjuvant radiotherapy may lead to the accumulation of toxic side effects of chemotherapy drugs and increase the probability of cytotoxic reactions, bone marrow suppression, peripheral neurotoxicity, cardiotoxicity, gastrointestinal reactions and allergic reactions; skin ulceration, injury and poor anal function caused by radiotherapy; the occurrence of disease progression and distant metastasis; and the possible increase in the difficulty of surgery due to neoadjuvant radiotherapy.

Immunotherapy is a relatively new treatment with certain risks associated with immunotherapy. adverse events with PD1 monoclonal antibody include the following, most of which are mild or moderate and reversible.

- Serious immunotherapy-related serious adverse reactions (low incidence, about 1-2%, PD-1 associated immune myocarditis, pneumonia, hepatitis, colitis, death)
- Common adverse events: malaise, dizziness, fever, myelosuppression, loss of appetite, nausea, vomiting, diarrhea, constipation, gastritis, alopecia, rash, pruritus, limb edema, peripheral neuropathy, elevated blood glucose, hypothyroidism, hyperthyroidism
- Rare adverse events: allergic reactions, abnormal liver function, elevated creatinine levels, proteinuria, hematuria, renal failure, neuromuscular toxicity, drowsiness, disorientation, lower extremity weakness, motor speech disorders, hyponatremia, pneumonia, etc;
- Very rare adverse events: impaired consciousness, convulsions, myocardial infarction, arrhythmias, death.

In addition to the above adverse events, other adverse events may occur. Although Sintilimab has completed phase I/II clinical studies with controlled safety and is available, some unintended adverse reactions may occur. Prior to the start of treatment, we will actively pre-treat anti-allergy, strengthen cardiac monitoring, closely observe vital signs, discontinue treatment as soon as possible if serious adverse reactions occur, and provide active rescue treatment such as cardiopulmonary function protection.
support and anti-inflammatory storm treatment. Medical staff will closely observe and prevent toxic side effects as much as possible during treatment, actively give appropriate therapeutic measures, and strictly control the application indications and termination conditions to reduce accidents. Because study drugs may disrupt embryonic development, sperm or eggs, women who are pregnant or may become pregnant should not use these study drugs and both men and women should use effective contraception. If you do not agree to use effective contraception during the study and for 6 months after the study is completed, you cannot participate in this study. You should tell your doctor immediately if you or your partner are pregnant or may become pregnant. If you are a woman, you will be excluded from the study after your pregnancy is confirmed.

The protocol will likely result in a better quality of clinical survival for patients who meet the enrollment criteria, but the possibility of recurrence cannot be ruled out: patients with local recurrence or distant metastases will be withdrawn from the study in the presence of either local recurrence with radical resection; patients with distant metastases will be treated according to guidelines. These two treatment options after recurrence did not significantly increase the associated surgical risks and treatment costs for patients, and had no significant impact on the survival benefit.

4. Possible benefits of participating in the study

The investigator will introduce you to the study drugs and the study schedule, and participation is completely voluntary. Given the results of existing clinical studies, it is possible that your condition may improve through this study and lead to preservation of the rectum and anus. Your condition will be closely monitored by your doctor after you participate in the study. You may not benefit from this treatment due to treatment failure or other potential disease deterioration, but you and other patients will benefit from the new information about the study drug that will be obtained through this study.

5. Research-related costs

Participate in this study will provide you with 4 courses of PD-1 monoclonal antibody for free, and you will be closely monitored by a physician. If the tumor is not in complete clinical remission at the end of the 4 courses, patients will be responsible for
the cost of radical resection or continued use of PD-1 monoclonal antibody. Patients are responsible for the cost of any treatment other than PD-1 monoclonal antibody required during the course of treatment.

Patients with local recurrence or distant metastases will be followed up according to the guidelines, and any treatment options after recurrence will be the responsibility of the patient. All tests, drugs and surgeries in this study are routine clinical examinations and treatments, and will not increase the cost of patients beyond the routine clinical treatment.

6. Subjects' duties

As a study subject, you have the following responsibilities: to provide truthful information about your medical history and current medical condition; to tell the study doctor about any discomfort you have experienced during this study; not to take restricted medications, foods, etc.; to tell the study doctor if you have participated in other studies recently or are currently participating in other studies. In relation to that, you are expected to inform us of any symptoms that occur to you. Please inform us of any increases and changes in taking your regular medications during your participation in the trial.

7. Voluntary participation

You may choose not to participate in the study or request to withdraw from the study at any time by notifying the investigator that your data will not be included in the study results and that any of your medical treatment and rights will not be affected as a result. Your participation in the study may be terminated by the study physician if you require additional treatment, if you fail to comply with the study plan, if a study-related injury occurs, or for any other reason.

8. Privacy

If you decide to participate in this study, your participation in the trial and your personal information during the trial will be confidential. Your blood/urine specimen
will be identified by the study number digit and not by your name. Information that 
identifies you will not be disclosed to members outside the study team unless your 
permission is obtained. All study members and study sponsors are asked to keep your 
identity confidential. Your file will be kept in a locked file cabinet and will be accessible 
only to the researcher. To ensure that the research is conducted in accordance with 
regulations, members of the government administration or ethics review committee will 
have access to your personal information at the research unit, as required. No personal 
information about you will be disclosed when the results of this study are published.

9. Treatment of Subjects’ Injuries

In addition to the necessary transportation and nutrition benefits, if you have an 
adverse event during the study period that is related to this study and the diagnostic 
tests required by the study protocol, you will be reasonably compensated based on an 
objective, comprehensive and scientific definition and assessment of the actual 
situation in accordance with the "Administrative Measures for Conducting Investigator-
Initiated Clinical Research in Medical and Health Institutions (Draft for Comments)"
issued by the National Health Care Commission on December 30, 2020 and the 
requirements of the Changhai Ethics Committee.

10. Other treatment options available

Patients with ultra-low rectal cancer may be treated with surgery and a transverse 
colostomy; you should consult your study doctor for more information.

You may discuss other treatment options with your doctor to decide whether you will 
participate in this study. If you decide not to participate in this study, your doctor will 
still suggest other treatment options that are appropriate for you.

Information about this study and the informed consent form have been reviewed by the 
institutional ethics review committee of this study. If there is any violation of the study 
protocol during the trial, you may file a complaint directly with the hospital ethics 
committee.

If volunteering to participate in this study, you will be required to sign an informed 
consent form certifying that you have been informed about the study and are
volunteering to participate in this study. If you have questions about the study, or if you experience any discomfort or injury during the study, or if you have questions about the rights of participants in the study, you can contact Dr. Guangyu Yu or the Institutional Ethics Committee at 18801765121 or 021-31162338.
Informed consent form signature page

I have read this informed consent form.

I have been given the opportunity to ask questions and all questions have been answered.

I understand that participation in this study is voluntary.

I may choose not to participate in this study or withdraw at any time with notice to the investigator without discrimination or reprisal, and any of my medical treatment and rights will not be affected as a result.

The investigator may terminate my participation in the study if I require other treatment, or if I fail to comply with the study plan, or if a study-related injury occurs, or for any other reason.

I will receive a signed copy of the "Informed Consent form".

Subject's name: ______________________
Subjects' contact information: ______________________
Date: ______________________

Agent's name: ______________________
Agent's contact information: ______________________
Date: ______________________

I have accurately informed the subject of this document, he/she has accurately read this informed consent form, and I certify that the subject has had the opportunity to ask questions. I certify that he/she has given voluntary consent.

Researcher's name: ______________________
Researcher's contact information: ______________________
Date: ______________________

(Note: If the subject is illiterate, the signature of a witness is required, and if the subject is incapacitated, the signature of a proxy is required.)
Supplemental Material 2

cCR was mainly evaluated based on digital rectal examination, endoscopy and high-resolution MRI findings.
(1) Digital rectal examination: local smooth, no mass or only local stiffness in the original tumor site.
(2) Endoscopy: the mucosa was pale, complete and smooth, and the proliferation of capillaries was visible; Or visible scar changes; There are also patients whose tumors disappear completely.
(3) High resolution magnetic resonance imaging: T2-weighted low signal in the original tumor site, no diffusion limitation in mrTWI, mrTRG was 1.
(If digital rectal examination conflicts with MRI, endorectal ultrasound is recommended)

There is an intermediate state between cCR and definite residual tumor, namely ncCR, which is judged by the following criteria:
(1) Locally normal in digital rectal examination, or only touch less than 2cm of uneven or nodules;
(2) Mucosa whitening and/or telangiectasia were observed by endoscopy, but mild mucosal unevenness was observed;
(3) High resolution magnetic resonance imaging showed low signal in the original tumor site on T2-weighted, and the mrTRG was 1-2.
### Supplemental Material 3

**MRI tumor regression grade (mrTRG)**

<table>
<thead>
<tr>
<th>TRG scale</th>
<th>mrTRG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No/minimal fibrosis visible (tiny linear scar) and no tumor signal</td>
</tr>
<tr>
<td>2</td>
<td>Dense fibrotic scar (low signal intensity) but no macroscopic tumor signal (indicates no or microscopic tumor)</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosis predominates but obvious measurable areas of tumor signal visible</td>
</tr>
<tr>
<td>4</td>
<td>Tumor signal predominates with little/minimal fibrosis</td>
</tr>
<tr>
<td>5</td>
<td>Tumor signal only: no fibrosis, includes progression of tumor</td>
</tr>
</tbody>
</table>