

Title: Personalized Ultrafractionated Stereotactic Adaptive
Radiotherapy Combined With Penpulimab and Fruquintinib for
Advanced Colorectal Cancer: Phase II Study

Version: 4.0

Document Date: August 6, 2026

Study Design

Non-randomized controlled trial, single-arm study

Sex of study participants:

All sexes

Age of study participants:

Minimum: 18 years

Maximum: 75 years

Healthy volunteers accepted:

No

Vulnerable populations involved:

No

Inclusion Criteria

1.Has fully understood the study and voluntarily signed the informed consent form.

2.Aged 18–75 years, with no restriction on sex.

3.Histologically or cytologically confirmed advanced colorectal adenocarcinoma.

4.Has experienced disease progression after receiving at least two lines of standard therapy, or has developed intolerable toxicity from standard therapy. Standard therapy is defined as prior treatment with fluoropyrimidine plus leucovorin plus a platinum agent or irinotecan, with or without cetuximab or bevacizumab.

5. Has at least one measurable lesion according to RECIST version 1.1.
6. ECOG performance status of 0–1.
7. Estimated life expectancy of at least 3 months.
8. Is willing and able to comply with study procedures and receive treatment, including radiotherapy, immunotherapy, targeted therapy, and follow-up.
9. Has adequate organ function, defined as follows:
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L;
 - Platelet count (PLT) $\geq 80 \times 10^9$ /L;
 - Hemoglobin (Hb) ≥ 90 g/L;
 - Total bilirubin (TBil) $\leq 1.5 \times$ the upper limit of normal (ULN);
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 1.5 \times$ ULN, or $\leq 3 \times$ ULN in patients with liver metastases;
 - Serum creatinine $\leq 1.5 \times$ ULN, or calculated creatinine clearance ≥ 50 mL/min;
 - International normalized ratio (INR) $\leq 1.5 \times$ ULN, and prothrombin time (PT) or activated partial thromboplastin time (APTT) $\leq 1.5 \times$ ULN, unless the participant is receiving anticoagulant therapy;
 - For participants positive for hepatitis B surface antigen (HBsAg), peripheral blood hepatitis B virus DNA (HBV-DNA) $\leq 1 \times 10^3$ copies/L.
- Participants with HBsAg positivity and HBV-DNA $\geq 1 \times 10^3$ copies/L

may be enrolled if, in the investigator's judgment, their chronic hepatitis B is stable and does not pose an increased risk.

10. Women of childbearing potential must agree to use appropriate contraception throughout the study. A serum or urine pregnancy test performed within 24 hours before initiation of chemotherapy must be negative.

11. Female participants must not be breastfeeding.

Exclusion Criteria

1. Receipt of any investigational drug within 4 weeks before the first administration of study treatment.

2. Concurrent participation in another clinical study, unless it is an observational, non-interventional study or the follow-up phase of an interventional clinical study.

3. Receipt of brachytherapy, such as radioactive seed implantation, within 60 days before the first dose.

4. Uncontrolled serious illness that, in the investigator's opinion, may impair the participant's ability to receive protocol-specified treatment, including severe cardiac disease, cerebrovascular disease, uncontrolled diabetes mellitus, uncontrolled hypertension, uncontrolled infection, or active peptic ulcer disease.

5. Active, known, or suspected autoimmune disease, including but not limited to uveitis, enteritis, hepatitis, hypophysitis, nephritis, vasculitis,

hyperthyroidism, hypothyroidism, and asthma requiring bronchodilator therapy. Participants with hypothyroidism requiring hormone replacement therapy and those with skin disorders not requiring systemic treatment, such as vitiligo, psoriasis, or alopecia, may be enrolled.

6. Active tuberculosis infection. Participants with active pulmonary tuberculosis within 1 year before enrollment will be excluded, even if treated. Participants with a history of active pulmonary tuberculosis more than 1 year before enrollment will also be excluded unless they can demonstrate completion of standard anti-tuberculosis therapy.

7. Requirement for long-term systemic corticosteroid therapy at a dose equivalent to >10 mg/day of prednisone, or any other form of immunosuppressive therapy. Participants receiving inhaled or topical corticosteroids may be enrolled.

8. Uncontrolled cardiac disease, including New York Heart Association (NYHA) class II or higher heart failure; unstable angina; myocardial infarction within 1 year; clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention; dementia, altered mental status, or any psychiatric disorder that may impair comprehension, provision of informed consent, or completion of study questionnaires.

9. History of another malignancy within 5 years before enrollment, except for adequately treated basal cell carcinoma or squamous cell carcinoma of

the skin, localized prostate cancer after curative surgery, or ductal carcinoma in situ of the breast after curative treatment.

10. Active gastric or duodenal ulcer, ulcerative colitis, or other gastrointestinal disease; unresected tumors with active bleeding; or any other condition considered by the investigator to pose a risk of gastrointestinal bleeding or perforation. Participants with prior gastrointestinal perforation or gastrointestinal fistula who have not recovered after surgery will be excluded.

11. Positive hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) antibody.

12. Active infection requiring systemic treatment.

13. Contraindication to finotolimab or fruquintinib, including a history of allergy or hypersensitivity to any component of either drug.

14. Contraindication to radiotherapy, including prior adequate-dose radiotherapy to the same site, severe radiation injury to the skin or local tissues/organs, or inability to tolerate re-irradiation.

15. Any other condition that, in the investigator's judgment, makes the participant unsuitable for enrollment.

Sample Size

Planned sample size: 32 participants

Basis for sample size calculation:

The sample size was calculated with reference to the phase II FRESCO study of fruquintinib monotherapy for third-line treatment of advanced colorectal cancer under its currently approved indication, in which the median progression-free survival was 3.7 months. This study is expected to extend median progression-free survival to 6.2 months. With β set at 0.20 and a one-sided α of 0.05, the sample size was estimated using the log-rank method in PASS. Assuming a 5% dropout rate, at least 32 participants are required.

Anticipated date of first informed consent:

Study Arm Information

Arm name:

Single-arm study

Sample size:

32

Control group:

No

Intervention

Intervention name:

Radiotherapy + immunotherapy + targeted therapy

Combination intervention:

Yes

Intervention type:

Approved marketed product, drug

Drug name:

Finotonlimab + fruquintinib

Traditional Chinese medicine:

No

Biological product:

No

Off-label use:

Yes

Dosage and administration:

Fruquintinib 5 mg orally once daily for 14 consecutive days, followed by a 7-day treatment-free interval. Each treatment cycle is 21 days.

Finotonlimab 200 mg administered once every 21 days. Each treatment cycle is 21 days.

Combination treatment without prior safety data:

No

Intervention description:

PULSAR will be delivered at a dose of 25–50 Gy in 5 fractions, with a dose of 5–10 Gy per fraction and an interval of 3 weeks between radiotherapy courses.

Finotonlimab and fruquintinib will be administered at fixed doses until disease progression or unacceptable toxicity, whichever occurs first.

This study uses an integrated treatment approach consisting of fruquintinib, finotonlimab, and PULSAR radiotherapy. The treatment regimen was designed with reference to previous clinical studies of fruquintinib combined with immunotherapy, the recommended use described in the product labeling, the implementation characteristics of PULSAR radiotherapy, and the feasibility of clinical implementation.

Each treatment cycle lasts 21 days. The study treatments will be administered in a predefined sequence within each cycle to ensure treatment safety, adherence, and feasibility of clinical implementation.

1. Fruquintinib administration regimen

With reference to previous clinical studies of fruquintinib combined with immunotherapy, and considering the safety of combination treatment, patient tolerability, and convenience of clinical drug administration, fruquintinib will be administered at a fixed dose in this study.

Drug name: Fruquintinib

Dose: 5 mg

Route of administration: Oral

Frequency: Once daily

Dosing schedule: Administered for 14 consecutive days, followed by a 7-day treatment-free interval

Treatment cycle: 21 days

After eligibility has been confirmed and the participant has been enrolled, oral fruquintinib treatment may be initiated. Fruquintinib should be taken at approximately the same time each day and may be taken with or without food. Specific administration requirements should follow the study drug management procedures and product labeling.

During the study, adverse events associated with fruquintinib will be closely monitored, particularly hypertension, proteinuria, hand-foot skin reaction, bleeding risk, abnormal liver function, gastrointestinal adverse events, and other toxicities associated with antiangiogenic agents.

If a participant develops intolerable toxicity or meets protocol-specified criteria for dose modification, treatment interruption, dose reduction, or other management measures should be implemented according to the prespecified principles of the study protocol.

Randomization

Randomized allocation:

No

Statistical Analysis Methods

1. Analysis populations

The intention-to-treat (ITT) principle will be used. All participants who sign informed consent and are enrolled will be included in the analysis.

The analysis populations include the Full Analysis Set (FAS), Per-Protocol Set (PPS),

and Safety Analysis Set (SAS). Efficacy analyses will be conducted in the FAS and PPS populations. Safety analyses will be conducted in the SAS population.

Full Analysis Set: All enrolled participants who have received at least one dose of study treatment.

Per-Protocol Set: A subset of the FAS consisting of participants who received study treatment and did not have any major protocol deviations.

Safety Analysis Set: All participants who signed informed consent and received at least one dose of study treatment.

2. Statistical methods

For baseline characteristics, continuous variables will be summarized using appropriate descriptive statistics.

Outcome Measure

Outcome measure name:

Progression-Free Survival

Type:

Primary outcome, treatment outcome, clinical event

Time frame:

From the date of first administration of study treatment to the date of first documented tumor progression or death from any cause, whichever occurs first.

Measurement method:

From the date of first administration of study treatment to the date of first documented tumor progression or death from any cause, whichever occurs first.