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The ARTEMIS trial is for patients who have been diagnosed as having a cancer of the lower bowel, known as the rectum. This study will examine the benefit of adding an additional treatment alongside radiotherapy and chemotherapy with the hope of increasing the chance of curing rectal cancer without the need for surgery.

Submission date 03/02/2023	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 23/10/2023	**Overall study status** Ongoing	
Last Edited 23/02/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Radiotherapy (RT) based treatment for patients with localised rectal cancer can result in long-term cure of the disease, enabling patients to avoid surgery to remove parts of the rectum (known as 'organ preservation' (OP)). Based on our own patient survey, OP is one of the main concerns of the patient population, though with current treatments available it is not an outcome that is available to most patients. Improving OP rate is an important priority of the trial. There is research showing encouraging results when immunotherapy is used in combination with RT treatment. To this end, the trial aims to test the efficacy of a new immunotherapy drug 'AN0025'. Research has shown that it could be an effective treatment which allows patients a better quality of life (QoL). The trial aims to compare what would, effectively, be 'standard care' for patients and 'standard care' in combination with AN0025. There is evidence for the benefits of immunotherapy when treating localised rectal cancer, further research is required as: there is a lack of data relating to OP, new drugs and treatments that may increase rates of OP need to be evaluated, there is little information on health-related QoL and how patients experience treatment and more data is needed to better design methods of assigning patients to treatments that best suit them.

Who can participate?

The trial will be conducted at approximately 15-20 NHS sites in the UK and open to all adults in the patient population (140 patients, 70 patients in each arm).

What does the study involve?
Patients will undergo a regime of either LCCRT or SCRT (dependant on clinician choice) that will take 1-5 weeks, followed by 12 weeks of chemotherapy (this combination is referred to as 'total neoadjuvant therapy'). Patients on the experimental arm will begin taking AN0025 prior to beginning their RT and will stop when their chemotherapy ends. Both arms will then be followed up at 4, 6, 9, 12, 18, 24 and 30 months (post-start of RT) where they will attend clinic and perform assessments.

What are the possible benefits and risks of participating?
Eligibility criteria have been made as inclusive as possible and the trial broadly reflects patients in clinical practice. This study specifically targets an intervention with respect to clinical trials - immunotherapy, and a population which could see great benefit from an increased rate of organ preservation - patients with localised rectal cancer. Participants will be provided with a patient information sheet, along with a consent form (PISICF) which covers the trial information. Patients will have the opportunity to discuss the trial with a member of the local research team. Informed consent will be taken by an authorised clinically and good clinical practice (GCP) trained member of staff who will ensure that the person understands the purpose and nature of the study and what it involves, the benefits, the risks and burdens and the alternative treatments available. Accompanying the PISICF will be a key fact sheet related to the treatment they have been allocated. These act as a condensed document that provides participants with an easy overview of the treatment they will experience. All patient facing documents will ensure that the potential participant is able to retain the information long enough to make an effective decision with free choice. Furthermore, we allow participants as much time as they need to decide whether they would like to participate in the trial. All patients who choose to enter the trial will be fully informed of the potential side-effects of the chemotherapy, radiotherapy and immunotherapy and will be advised on how these can be minimised. A radiotherapy (RT) guideline document has been developed with RTTQA alongside national RT guidance to ensure the safety of participants receiving radiotherapy during the trial. The RTTQA group will monitor quality compliance to ensure the safety of participants. We do not anticipate any significant problems with the administration of chemoradiotherapy in either arm of the trial. Sites must pass pre-trial quality assurance checks prior to opening and additional in-trial quality assurance checks will be incorporated. The doctors and nurses will aim to ensure risks are kept to a minimum. Different people (such as radiographers, physicists, chemotherapy nurses and doctors) check the radiotherapy and chemotherapy treatment before and during treatment, so the chance of it being delivered incorrectly is very small. Should this happen, or an unexpected problem arises during treatment, the treating medical team will discuss the consequences and options with the participant.
The Trial Management Group (TMG) along with the independent committees - Data Monitoring Ethics committee (DMEC) and Trial Steering committee (TSC) will monitor the study on an ongoing basis The DMEC will be presented with treatment compliance and safety data by arm, monitoring and highlighting any potential safety concerns with trial treatment, and allowing the potential to stop the trial. The trial will include an early assessment of safety after 10 patients have been recruited or after 6 months of recruitment, which ever is sooner. If participants experience symptoms or side effects, they must report these to the study nurse or doctor. The side effects of 'standard' RT, chemotherapy and AN0025 are described in detail in documentation provided to the participant. During the trial AN0025 will be closely monitored and side effects that may occur as a result of taking AN0025 will be reported and protocol dose de-escalation or omission will result if deemed necessary. Clinical testing has provided a list of the most commonly occurring side effects when receiving AN0025. Because AN0025 is a relatively new drug, there could be problems and side effects nobody knows about. It is possible that the additional drug treatment (AN0025) may increase side effects of standard RT or

chemoradiotherapy and the following chemotherapy. Smaller studies carried out suggest that the side effects caused by AN0025 are mild and well-tolerated. Measuring these potential side effects precisely is a very important part of the ARTEMIS study. That is why we will make sure that we regularly assess side effects and ask participants about their symptoms and quality of life, each time the patient attends a clinic visit during treatment and afterwards in the 'follow-up' period. The trial design includes an interim assessment for futility so that if there is evidence that the treatment arm response is no better than the control then the trial will stop for futility. This prevents any further patients taking an additional agent that does not add benefit. Data on the treatment participants receive will be collected weekly during radiotherapy. Information will be recorded on the total dose of radiotherapy received (dose and fractions), the overall treatment time (i.e. start and end date), details of any interruptions to the radiotherapy and the reasons for these interruptions (i.e. toxicity or other).

Where is the study run from?
Clinical Trials Research Unit (CTRU) at University of Leeds (UK)

When is the study starting and how long is it expected to run for?
January 2023 to September 2026

Who is funding the study?
Adlai Nortye (USA)

Who is the main contact?
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Additional identifiers

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Integrated Research Application System (IRAS)
1004319

ClinicalTrials.gov (NCT)
Nil known

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MO21/118263

Central Portfolio Management System (CPMS)
58458

Study information

Scientific Title
Augmenting RadioTherapy in REctal Cancer to Minimise Invasive Surgery

Acronym
ARTEMIS

Study objectives
Radiotherapy (RT) for localised rectal cancer can result in long-term cure, enabling avoidance of surgery and 'organ preservation' (OP). Based on our own survey of patients, this is one of the main priorities from a patient's perspective. This option is only achievable in a minority of patients. Improving the OP rate is the main objective of the trial. Studies have shown encouraging results for the things we are testing (the use of chemotherapy after radiotherapy treatment and immunotherapy) in relation to OP, however further research is required because there is a lack of rigorous test data evaluating their effectiveness. There is a need to evaluate the newly developed immunotherapy drug that may increase the OP rate. The primary objective of the ARTEMIS trial is to determine whether the addition of AN0025 to SCRT/LCCRT + FOLFOX /CAPOX improves the cCR rate for patients with moderate to high risk rectal cancer, at 6 months post start of radiotherapy, compared to standard SCRT/LCCRT + FOLFOX/CAPOX.

To evaluate the impact of the addition of a new drug 'AN0025' to standard total neoadjuvant treatment (radiotherapy in conjunction with chemotherapy) on the following outcomes: Acute and late toxicity; Treatment compliance; Patient Reported Outcomes and HRQoL; Surgical

outcomes; Clinical, radiological and pathological response rates; Stoma rates; Locoregional regrowth following a cCR; Organ preservation; Organ preservation adapted disease-free survival; Metastasis- free survival; and Overall survival.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 28/09/2023, North East - Newcastle & North Tyneside 1 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8077; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 23/NE/0029

Study design
Interventional randomized parallel group controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Locally advanced rectal cancer

Interventions
Radiotherapy: All patients will receive standard radiotherapy delivered using intensity-modulated radiotherapy (IMRT), Volumetric-modulated arc therapy (VMAT) or TomoTherapy to treat an elective pelvic clinical target volume (CTV) to one of two standard regimens (clinician choice on an individual patient basis).
1) Long-course chemoradiation (LCCRT) - 45 Gy in 25 daily fractions treating once per day Monday-Friday over 5 weeks, with a synchronous integrated small volume boost to the gross tumour volume (GTV) of 50Gy in 25 fractions. Concurrent capecitabine will be given on the days of radiotherapy orally at 825mg/m2 twice daily (BID) throughout the radiotherapy course.
2) Short-course radiotherapy (SCRT) - 25 Gy in 5 daily fractions treating once per day Monday-Friday over 5 days (without concurrent chemotherapy).

Chemotherapy: All patients will receive 12 weeks of FOLFOX or CAPOX starting 3 weeks after the last radiotherapy treatment (clinical choice on a patient-by-patient basis).

Participants will be randomised (1:1) intervention to control arm.
Control Arm: LCCRT or SCRT followed by FOLFOX or CAPOX.
Intervention Arm: LCCRT or SCRT followed by FOLFOX or CAPOX with the addition of immunotherapy agent, AN0025.

AN0025 is given orally at a dose of 500mg once a day (QD) continuously, 7 days a week starting two weeks before SCRT/LCCRT and continuing until the end of the 12 week course of FOLFOX /CAPOX.
1) LCCRT - AN0025 starts 14 days prior to start of LCCRT and continues for ~22 weeks*, QD, 7 days per week.
2) SCRT - AN0025 starts 14 days prior to start of SCRT and continues for ~18 weeks*, QD, 7 days per week.

*Please note this is dependent on a 3 week gap between completion of SCRT/LCCRT treatment and start of CAPOX/FOLFOX chemotherapy treatment, therefore number of weeks will change dependent on the gap (maximum one extra week permitted).

Patients will be followed up at 4, 6, 9, 12, 18, 24 and 30 months from the start of radiotherapy.

a. ELIGIBILITY AND BASELINE ASSESSMENTS:
Participants must have provided written informed consent before being formally assessed for eligibility, and prior to the commencement of any trial-specific assessments. The following investigations and assessments must be carried out prior to randomisation. Some of the following assessments may have been completed as part of standard clinical care within the timelines specified below, if this is the case they do not need to be repeated specifically for the trial, and can be used to establish eligibility:
No specific time limit:
• DPD Testing
• Diagnostic biopsy (proving rectal adenocarcinoma)

Within 63 days prior to randomisation:
• CT Scan thorax, abdomen and pelvis (Some centres may have access to PET-CT scanning on an individual patient basis. These scans are not a mandatory part of routine care, nor are they required as part of this trial protocol. If a PET-CT has been performed, it is reasonable that this is fused with the planning CT as per local practice)
• Pelvic MRI
• Flexible sigmoidoscopy
• DRE

Within 14 days prior to randomisation:
• Medical history (concomitant disease and concomitant treatments, including review of steroid use and contraindicated medications)
• Physical examination (including ECOG PS, height and weight, vital signs and BSA)
• ECG
• Carcinoembryonic antigen (CEA)
• Baseline CTCAE assessment (adverse events)
• Haematology (FBC) and biochemistry (urea and electrolytes (U&Es), bone profile (calcium and phosphate), liver function tests (LFTs))
• Pregnancy test (if patient of childbearing potential) as per local practice

In addition to the above eligibility assessments, data collected on the pre-randomisation eCRFs (Baseline Assessments and Randomisation eCRFs) will also include (but will not be limited to):
• Confirmation of written informed consent
• Planned start date of trial treatment
• Completion of the baseline QoL questionnaires by the patient

b. PRE-TREATMENT ASSESSMENTS (DEPENDENT ON WHAT ARM THE PARTICIPANT IS RANDOMISED TO)
For participants randomised to the intervention arm, pre-treatment data collected following randomisation must take place no longer than 7 days prior to the start of AN0025.
Where any assessments carried out for eligibility/baseline (pre-randomisation) are more than 7 days prior to the start of AN0025, these must be repeated and entered on the Pre-treatment eCRF. The following data will be collected:
• ECOG PS

• Haematology and biochemistry
• Review of potential contraindicated medications

For participants randomised to the standard control arm, their pre-treatment assessments including biochemistry and haematology, will occur within 14 days of starting SCRT or LCCRT. Please note, any investigations/assessments carried out at eligibility/baseline (pre-randomisation), do not need to be repeated if done within 14 days of the start of trial treatment.

c. ASSESSMENTS AND DATA COLLECTION FOR PATIENTS RECEIVING AN0025
A telephone-based assessment will be carried out 7 days (1 week) after starting AN0025, to record treatment compliance and toxicity assessment (including AEs and ARs) using CTACE v5.0. This can be done by a trial nurse.
During planned clinic visits during RT and FOLFOX/CAPOX, compliance checks for AN0025 will be performed. No specific assessments, other than what has been indicated on the schedule of events, are required for patients randomised to receive AN0025. Data collected will include (but will not be limited to):
• Date treatment started
• Immunotherapy agent details (number of days tablets taken, doses, dose delays, omissions or reductions or extra doses that have occurred, and reason(s) for these)
Further compliance checks for AN0025 will be performed when the participant is seen to start RT, including details of any doses omitted, doses reductions or extra doses that have occurred.

d. ASSESSMENT AT THE END OF RADIOTHERAPY FOR SCRT PATIENTS (COLLECTED WHEN ATTENDING CYCLE 1 OF CHEMOTHERAPY)
Participants receiving SCRT will be assessed clinically for symptoms and toxicity at the end of RT treatment on the SCRT Treatment eCRF. Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0). A copy of NCI-CTCAE is provided in the ISF. Data collected will include (but will not be limited to):
• Date treatment started and ended
• Number of fractions and weekly dose of radiotherapy given
• Details of any interruptions to radiotherapy, including reason(s)
• ECOG PS
• Weight
• Acute toxicity scores (including AEs and ARs) using CTCAE v5.0

e. WEEKLY ASSESSMENTS DURING CHEMORADIOTHERAPY FOR LCCRT PATIENTS
For participants receiving LCCRT, details of RT treatment will be collected by completing the LCCRT Treatment eCRF weekly during RT. Data collected will include (but will not be limited to):
• Date treatment started and ended
• Weekly number of fractions and weekly dose of radiotherapy given
• Details of any interruptions to radiotherapy, including reason(s)
• Chemotherapy details (doses, interruptions and any dose delays or dose reductions that have occurred, and reason(s) for these)
• ECOG PS (during last week of RT only)
• Weight (during last week of RT only)
• Acute toxicity scores (including AEs and ARs) using CTCAE v5.0

Haematology and biochemistry assessments during LCCRT should be conducted following standard of care at participating sites, including at the start of week 4 as a minimum and entered on the appropriate eCRF.

f. ASSESSMENTS DURING CHEMOTHERAPY
Participants will be assessed on day 1 at the start of each treatment cycle, either every 2 weeks for participants receiving FOLFOX for a maximum of 6 cycles, or every 3 weeks for those receiving CAPOX for a maximum of 4 cycles. Data collected will include (but will not be limited to):
• Date treatment started and ended
• Chemotherapy details (doses and any dose delays, omissions or dose reductions that have occurred, and reason(s) for these)
• AN0025 details (if applicable), including the number of days tablets taken, doses and any dose delays, doses omitted, dose reductions or extra doses that have occurred, and reason(s) for these
• ECOG PS and weight
• Acute toxicity scores (including AEs and ARs) using CTCAE v5.0

g. FOLLOW-UP ASSESSMENTS FOR THOSE ON ACTIVE SURVEILLANCE
After completion of RT treatment, follow-up visits will take place at 4, 6, 9, 12, 18, 24 and 30 months, post start of RT (+/- 14 days). Details of assessments are included in the Follow-up Schedule of Events.
Follow-up data will be collected at the above time points by completing the relevant eCRF. At follow-up visits, data collected will include (but will not be limited to):
• Presence and details of stoma
• Response to treatment (including details on cCR, definite local regrowth/residual disease or distant relapse)
• Details of any further cancer-specific treatment such as systemic anti-cancer treatment (SACT) or surgery
• CEA
• Toxicity assessment (CTCAE) (AEs collected up to 30 days post end of treatment, ARs collected up to 30 months)
• Disease status
• DRE
• CT scan thorax, abdomen and pelvis (Some centres may have access to PET-CT scanning on an individual patient basis. These scans are not a mandatory part of routine care, nor are they required as part of this trial protocol.) at 6, 18 and 30 months
• Pelvic MRI
• Flexible sigmoidoscopy
• HRQoL
Trial specific follow-up assessments should, if at all possible, be conducted irrespective of any subsequent rectal cancer progression or recurrence or any new primary cancers.
In the case of patients with an ‘uncertain cCR’ at 6 months, defined as a patient where the criteria for a cCR (primary endpoint) are mostly fulfilled however has the presence of superficial mucosal ulceration, teams may consider continuation of active surveillance to help decide whether such patients have in fact had a cCR. If such patients show improving appearances (epithelialising mucosal ulcer), a deferral of surgery path can continue to be followed.
Clinical management beyond 30 months is at the discretion of the local treating team.

h. FOLLOW-UP ASSESSMENTS FOR PATIENTS WHO HAVE SALVAGE SURGERY
Participants who demonstrate tumour progression, no response or poor response at 4 months will undergo radical surgery. Participants who do not achieve cCR at 6 months may be considered for radical surgery and those who do will be followed up according to the post-surgery follow-up schedule of events.
Patients will join this assessment schedule after they have surgery to remove relapsed or residual disease. All times for follow-up will remain calculated from start of RT in line with active surveillance pathway.

Follow-up data will be collected at the above time points by completing the relevant eCRF. At follow-up visits, data collected will include (but will not be limited to):
• CEA
• Post-surgery complications (Clavien-Dindo Classification to be completed once, 90 days post-surgery)
• Details of any further cancer-specific treatment such as systemic anti-cancer treatment (SACT) or surgery
• Disease status
• CT scan thorax, abdomen and pelvis (Some centres may have access to PET-CT scanning on an individual patient basis. These scans are not a mandatory part of routine care, nor are they required as part of this trial protocol) at 6, 12 and 24 months
• HRQoL

Trial specific follow-up assessments should, if at all possible, be conducted irrespective of any subsequent rectal cancer progression or recurrence or any new primary cancers.

i. BASELINE AND FOLLOW-UP MRI
Imaging using MRI is of importance in ARTEMIS because it partly defines the primary endpoint. MRIs should be reported by a local radiologist expert in rectal cancer pelvic imaging.
Central review of pre- and post-treatment MRI scans may be performed for all patients who receive them in batches retrospectively although no 'real time' central review will take place. CTRU may request these images for quality assurance purposes, however these images will remain at site until requested.
The MRIs use the same imaging protocol, adhering to consistent parameters, including diffusion weighted imaging. Reporting of MRI scans will include mrTRG. Follow-up MRI (pelvis) for participants on active surveillance will be carried out at 9, 12, 18, 24 and 30 months. All time points are from the post-start of RT.

j. BASELINE AND FOLLOW-UP FLEXIBLE SIGMOIDOSCOPY
Examination of tumour response via flexible sigmoidoscopy is of importance in ARTEMIS because it partly defines the primary endpoint.
A flexible sigmoidoscopy assessment will be carried out by an endoscopist experienced with post-radiotherapy rectal endoscopy during follow-up active surveillance beyond 6 months at 9, 12, 18, 24 and 30 months. All time points are from the post-start of RT.
Central review of pre- and post-treatment sigmoidoscopies may be performed for all patients in batches retrospectively although no 'real time' central review will take place. CTRU may request these photos for quality assurance purposes, however these images will remain at site until requested.

k. ASSESSMENT OF PRIMARY ENDPOINT/ RESPONSES TO TREATMENT
All patients will be assessed for whether or not they have achieved a cCR at 6 months post start of RT. This will be entered on the relevant 6 Months Response Assessment eCRF.
Response to treatment will be assessed via a composite of:
1. digital rectal examination,
2. high resolution pelvic MRI (participants on active surveillance who do not undergo surgery) and
3. sigmoidoscopy, with a declaration of cCR based on the combined assessment not indicating any remaining active tumour.

Assessment of the primary endpoint will be based solely on these criteria. More proximal tumours may not be reachable with DRE and in those, assessment will depend on MRI and sigmoidoscopy alone.

Occasionally centres may wish to perform an examination under anaesthetic to assess the response. However, this is not formally part of the ARTEMIS primary endpoint assessment. Routine biopsies to assess response are not recommended because biopsy sampling does not provide additional value and could lead to false-negative results.

l. DIAGNOSIS AND MANAGEMENT OF UNCERTAIN CCR
There may be cases where the MDT is uncertain whether a cCR has been achieved. In these cases the criteria for a cCR are fulfilled but in addition there may be some small smooth mucosal nodules or minor mucosal abnormalities. Such patients will be deemed to have an 'uncertain cCR' (ucCR).
When considering lymph nodes in the assessment of cCR and ucCR, the assessment should take into account both lymph node regression relative to pre-treatment MRI and the presence of morphological features associated with node positivity (such as an irregular border and heterogeneous signal combined with a diameter of ≥5 mm).
m. Patients with an ucCR at 6 months may continue to undergo active surveillance, following assessment at MDT. Those who are subsequently thought to have regrowth/residual disease in the opinion of the local MDT will be considered for salvage TME surgery.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AN0025

Primary outcome(s)
Clinical complete response (cCR) rate at 6 months post-start of treatment assessed via a composite of digital rectal examination (DRE), high resolution pelvic Magnetic Resonance Imaging (MRI) and sigmoidoscopy, defined as:
1. No evidence of either mucosal tumour or submucosal swelling on white light endoscopy. A flat white scar remains, with or without telangiectasia or a small residual mucosal ulcer and
2. No palpable tumour upon DRE, and
3. High resolution pelvic MRI scanning shows complete response in both the primary tumour and involved nodes (participants on active surveillance who do not undergo surgery).
(If the tumour is too proximal to reach with DRE then assessment will be via MRI and sigmoidoscopy alone).

Key secondary outcome(s))
1. Acute & Late toxicity:
The acute toxicity period has been defined from randomisation (AN0025 or RT) to the 6 month post start of RT primary endpoint assessment. Clinician assessment of acute toxicities will take place on each week of treatment during clinic, including the 4 and 6 month follow-up assessments. The late toxicity period will be defined as 6 months post-start of RT until the final follow-up visit at 30 months post start of RT. Clinician assessment of late toxicity will take place during each of the follow-up visits and will be recorded at 9, 12, 18, 24 and 30 months post start of RT.
All adverse events will be evaluated using the CTCAE criteria (V5.0) and include all AEs, SAEs, ARs, SARs and SUSARs. The CTCAE criteria will only be used and collected prior to patients receiving surgery.

2. Treatment compliance:
Data on the treatment which participants receive will be collected weekly during radiotherapy and during weeks of chemotherapy. Compliance to the treatment will be assessed and include adherence to both the radiotherapy, chemotherapy, and if received AN0025.
Information will be recorded on the total dose of radiotherapy received (dose and fractions), the overall treatment time (i.e., start and end date), details of any interruptions to the radiotherapy and the reasons for these interruptions (i.e., toxicity or other). Chemotherapy treatment compliance data will be recorded on the number of cycles received, any treatment modifications, including delays, omissions or reductions, and their associated reasons. Details of any dose reductions or omissions of AN0025 and associated reasons for participants in the intervention arm will also be recorded.
Adherence to the radiotherapy schedule will be defined as a participant that has completed their scheduled course of radiotherapy with no more than three treatment days of interruptions due to toxicity. Adherence to the chemotherapy and AN0025 will be defined as a participant that completes > 80% of the original prescribed dose.
3. Patient reported outcomes (PROs) and Health Related Quality of Life (HRQoL):
PRO and HRQoL data will be captured via the EORTC QLQ-C30, QLQ-CR29, EQ-5D-5L and LARS questionnaires, and additional items relevant to an organ sparing approach to treatment using the EORTC-QLQ item library. HRQoL will be requested at baseline, 3 weeks post end of RT, and 4, 6, 12, 24 and 30 months post-start of RT treatment. PRO results will describe the treatment impact on patient experience over the course of the study. The goal of the PRO assessment is to assess tolerability from the patient's perspective; i.e., how patients are feeling and functioning (descriptive objective), encompassing both early and late effects. To ensure high quality data and interpretation, PRO data will be implemented and analysed using international consensus guidelines. The data will capture early effects of treatment, and long term patient experience.
4. Surgical outcomes:
Details on any surgery performed will be collected including the type, approach and outcome (residual tumour R classification). Post-surgical outcomes will also be collected including length of hospital stay, surgical complications measured by the Clavien Dindo classification system 90 days post-operatively, and any reoperation details where appropriate.
5. Response assessment:
Local control data will be collected for all patients. Assessments of cCR and mrTRG will be collected in patients on active surveillance at 4, 6, 9, 12 months post start of RT. Continued cCR confirmation will be collected at 18, 24, 30 month post start of RT.
A pathological Complete Response (pCR) is defined as the absence of any viable tumour cell on the resected specimen, irrespective of the proportion of necrosis and fibrosis (Quah et al., 2008). The five point Mandard Tumour Regression Grade (TRG) (Mandard et al., 1994) is a measure of histopathological response of rectal cancer and will be assessed in patients after surgery in addition to the current standard of care four point AJCC Tumour Regression Score system. pCR TRG and TRS will be assessed once after surgery.
6. Stoma rates:
Stoma data will be collected at standard follow-up visits. Date of stoma formation, type of stoma and reason for defunctioning will be collected. Stoma rates will be presented and analysed as a time-to-event outcome i.e., the time from randomisation to the fashioning of a stoma.
7. Locoregional regrowth after cCR:
Locoregional regrowth is defined as the detection of a tumour involving either the bowel wall, mesorectum or pelvic organs that occurs after an initial cCR. Date of confirmed regrowth will be collected.
8. Organ preservation rates:
Organ preservation in the setting of ARTEMIS is defined by intact rectum, absence of stoma and free of locoregional failure. Where locoregional failure is detection of any un-resectable

regrowth or recurrence involving either the bowel wall, mesorectum and/or pelvic organs. Data on surgery, stomas and locoregional disease will be collected on all patients. Organ preservation rates will be assessed over time.
9. Organ-preservation-adapted Disease-free survival:
Organ-preservation-adapted Disease free survival (OP-DFS) is defined as the time from randomisation, to the first confirmed evidence of un-resectable regrowth or locoregional recurrence after TME, any distant metastasis, any second primary cancer (including non-colorectal) or death from any cause. First confirmed evidence can include imaging, histology or endoscopy.
10. Metastasis free survival:
Metastasis free survival (MFS) is defined as the time from randomisation, to the first confirmed evidence of metastatic disease or death from any cause. First confirmed evidence can include imaging or histology.
11. Overall survival (OS):
Overall survival (OS) is defined as the time from randomisation to the date of death from any cause. Survival data will be collected at standard follow-up visits

Completion date
30/09/2029

Eligibility

Key inclusion criteria
1. Patients age ≥18 years old
2. ECOG PS 0 or 1
3. Capable of informed consent
4. Able to fully understand trial treatment enough to provide informed consent
5. Biopsy-proven rectal adenocarcinoma
6. Staged on high-resolution MRI as: T3b-4a or TanyN1-2 or TanyEMVI+ or with a threatened (<1mm) or involved mesorectal fascia resection margin or breached but not invading other organs or definite pelvic side wall lymph nodes involved (that the MDT feel are not resectable)
7. Low tumours with involvement of the anal intersphincteric plane or with levator involvement. The superior extent of macroscopic tumour (primary, EMVI or nodes) is no higher than the S1/2 junction on sagittal MRI.

Within 14 days pre-randomisation the following must be met:
8. Estimated creatinine clearance ≥50 mls/min (using a validated creatinine clearance calculation e.g. Cockcroft-Gault or Wright formula)
9. Haemoglobin ≥ 9.0g/dL
10. Neutrophils >1.5 x 10^9/l
11. Platelets >100 x 10^9/l
12. Adequate blood coagulation function as evidenced by a prothrombin time (PT) <1.5 x normal
13. Alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN)
14. Serum transaminase (either alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) ≤ 2.5 × ULN
15. Total bilirubin ≤1.5 × ULN except for unconjugated hyperbilirubinemia or Gilbert’s syndrome

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Unequivocal distant metastatic disease
2. Previous pelvic radiotherapy
3. MRI defined predominantly mucinous tumour i.e. more than one third of tumour volume assessed to consist of mucin
4. Biopsy-proven neuroendocrine tumour
5. Definite MRI pelvic side wall lymph node involvement, invasion of adjacent organ, ischio-rectal fossa involvement
6. Pre-existing faecal incontinence for solid stool or chronic diarrhoea (> grade 1 according the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE))
7. Defunctioning colostomy or ileostomy
8. Prior antineoplastic therapy for rectal cancer
9. Pregnant or breast feeding or of child bearing potential and unwilling to use effective contraceptive methods
10. On-treatment participation in an interventional clinical study 30 days prior to randomisation
11. Other concomitant antineoplastic therapy
12. Inability to comply with taking oral capecitabine/AN0025 medication
13. Active, uncontrolled infections
14. Active, disseminated coagulation disorder
15. Clinically significant cardiovascular disease ≤ 6 months before randomisation
16. Prior invasive malignancy unless disease free >3 years (excluding basal cell carcinoma of the skin or carcinoma in situ)
17. Known allergic reactions to either oxaliplatin or AN0025 or both capecitabine and 5-FU
18. On medication with inhibitors of DPD
19. Psychosocial issues which may affect treatment compliance
20. Prolongation of corrected QT (QTc) interval to >480 msec when electrolyte balance is normal
21. Recent occurrence (within 3 months prior to randomisation) of a major thromboembolic event, such as pulmonary embolism or proximal deep vein thrombosis, unless stable on (>14 days) therapeutic anticoagulation (aspirin ≤325 mg daily or low-molecular-weight heparin (LMWH). Subjects with a history of clinically non-significant thromboembolic events, not requiring anticoagulation, are allowed on study
22. Subjects receiving oral warfarin are not eligible for this study (unless warfarin is discontinued at least 7 days prior to commencement of treatment and for the duration of the study, or oral warfarin is converted to LMWH, where local clinical opinion considers this an acceptable option)

23. Other systemic and local antitumor therapies such as chemotherapy, anti-tumour immunotherapy, radiotherapy or surgical interventions that may interfere / interact with the proposed treatment as part of the ARTEMIS trial
24. Other investigational drugs.

25. The following are prohibited during AN0025 therapy and therefore render patients ineligible for randomisation unless these can be switched to alternative medication prior to trial drug dosing:
25.1. Non-steroidal anti-inflammatory drugs (NSAIDs)
25.2. Aspirin at doses of higher than 325 mg daily
25.3. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)
25.4. Uridine’5 diphospho-glucuronosyl transferase (UGT) inducers or inhibitors (atazanavir, probenecid, valproic acid, mefenamic acid, quinidine)
25.5. Anticoagulation with anti Xa agents (i.e.:Novel oral anticoagulants (NOACs): apixaban, rivaroxaban): Low Molecular Weight Heparin (LMWH) is the preferred form of initial anticoagulation. However, if, in the assessment of the investigator, changing to a NOAC is considered appropriate, then this is acceptable assuming the thrombotic event is medically controlled.
26. We recommend that patients DO NOT receive concomitant capecitabine and warfarin as the disturbance in warfarin metabolism during capecitabine treatment is unpredictable and difficult to manage. Wherever possible we would recommend either treating the patient with low molecular weight heparin instead of warfarin, or changing the patient to OxMdG treatment rather than CAPOX. If the Local Investigator feels there is no alternative to giving capecitabine and warfarin concurrently then these patients MUST have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Unless: A patient, in the assessment of the investigator, requires the use of prohibited anti-Xa anticoagulants for clinical management and are unable to find alternative treatments, they may be allowed to participate in the trial if the following are met: The patient has been receiving anticoagulant treatment for venous thromboembolism continuously for at least 1 month and has, in the opinion of the investigator, achieved stable response in keeping with the community standards of medical care
27. Leeds CTRU is notified prior to screening/consent of the patient’s requirement for anticoagulants and received approval by Leeds CTRU.

Added 19/05/2025:
28. Known complete DPD deficiency
29. Known deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H)

Date of first enrolment
22/03/2024

Date of final enrolment
21/03/2026

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
The Christie Hospital
Wilmslow Road
Withington
Manchester
England
M20 4BX

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Centre for Oncology NHS Foundation Trust
Clatterbridge Road
Bebington
Wirral
England
CH63 4JY

Study participating centre
Darlington Memorial Hospital
County Durham and Darlington NHS Foundation Trust
Hollyhurst Road
Darlington
England
DL3 6HX

Study participating centre

Glan Clwd Hospital
Ysbyty Glan Clwydd
Bodelwyddan
Rhyl
Wales
LL18 5UJ

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
England
HU3 2JZ

Study participating centre
Imperial College London
Central and North West London NHS Foundation Trust
Du Cane Road
London
England
W12 0NN

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
England
NE7 7DN

Study participating centre
Royal Preston Hospital
Sharoe Green Lane North
Fulwood
Preston
England
PR2 9HT

Study participating centre

The Royal Wolverhampton NHS Trust
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
England
WV10 0QP

Study participating centre
Southampton General Hospital
University of Southampton and University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
England
SO16 6YD

Study participating centre
St James's University Hospital NHS Trust
St James's University Hospital
Gledow Wing
Beckett Street
Leeds
England
LS9 7TF

Study participating centre
Taunton Hospital
Musgrove Park Hospital
Taunton
England
TA1 5DA

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre

Weston Park Hospital
Whitham Road
Sheffield
England
S10 2SJ

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
Scotland
AB25 2ZN

Study participating centre
Colchester General Hospital
Colchester District General Hosp.
Charter Way
Turner Road
Colchester
England
CO4 5JL

Study participating centre
Ipswich Hospital
Heath Road
Ipswich
England
IP4 5PD

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
England
OX3 7LE

Study participating centre
Royal Shrewsbury Hospital
Mytton Oak Road

Shrewsbury
England
SY3 8XQ

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast
Northern Ireland
BT9 7AB

Study participating centre
Velindre Cancer Centre
Velindre Road
Cardiff
Wales
CF14 2TL

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
Scotland
G12 0YN

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Adlai Nortye

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3.0	20/09/2023	20/06/2024	No	Yes
Participant information sheet	version 7.0	29/04/2025	19/05/2025	No	Yes
Participant information sheet	version 9.0	01/09/2025	17/09/2025	No	Yes
Participant information sheet	version 10.0	17/10/2025	08/01/2026	No	Yes
Protocol file	version 2.0	20/09/2023	20/06/2024	No	No
Protocol file	version 5.0	25/01/2022	19/05/2025	No	No

Protocol file	version 6.0	25/06/2025	17/09/2025	No	No
Protocol file	version 8.0	17/10/2025	08/01/2026	No	No
Study website		11/11/2025	11/11/2025	No	Yes