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Comparing two different regimens of radiotherapy, combined with durvalumab immunotherapy and chemotherapy, in improving the response of rectal cancer to treatment

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Registration date 27/10/2020	**Overall study status** Ongoing	
Last Edited 05/09/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-durvalumab-for-rectal-cancer-prime-rt (added 21/12/2021)

Background and study aims
Locally advanced rectal cancer is usually treated with radiotherapy and chemotherapy first followed by surgery. The treatment is important as it shrinks the tumour making surgery more successful. In a small proportion of patients, there is the potential to avoid surgery altogether if there is evidence of a complete response. This trial will recruit patients who require radiotherapy prior to surgery to cure their disease. We will investigate whether a combination of chemotherapy, radiotherapy in addition to immunotherapy can achieve higher rates of complete response allowing more patients to be managed with organ preservation avoiding radical surgery.

This trial will compare two different regimens of radiotherapy which are both used currently in standard practice. The radiotherapy treatment in both arms will be combined with an immunotherapy drug called Durvalumab and followed by a combination of Durvalumab and chemotherapy. The chemotherapy being used is currently used in the standard treatment of colorectal cancer. The immunotherapy has been used in trials of colorectal cancer previously but is not currently a standard treatment for localised rectal cancer prior to surgery.

The aim of this trial is to understand which combination of treatment results in the highest rates of complete response to allow us to consider avoiding surgery. In addition, by using biopsies of tumours from the patients on the trial before, during, and after treatment we will learn about how the patient's own immune system is responding to the immunotherapy treatment. This

information will then be used to do a bigger trial using the combination of chemotherapy, radiotherapy, and immunotherapy treatments that have the highest rates of complete response with the least toxicity.

Who can participate?
Adult patients with non-metastatic, locally advanced rectal cancer.

What does the study involve?
Eligible participants will be randomly allocated to receive either durvalumab, short course radiotherapy, and FOLFOX chemotherapy, or durvalumab, long course chemoradiation (with capecitabine), and FOLFOX chemotherapy. Where appropriate participants may then proceed to surgery. Participants will be followed up for up to 36 months.

What are the possible benefits and risks of participating?
This trial will provide one of two treatment regimens to patients with rectal cancer that differ from the current standard of care. The differences compared to standard treatment mean that there is a definite increased risk of side effects from trial treatment however there is also the potential for it to be more effective than the standard. The trial treatments (radiotherapy, chemotherapy and immunotherapy) are known to be active and effective therapies against rectal cancer. By combining them there is the potential for additive benefits and a management strategy that is more effective than using radiotherapy or chemoradiotherapy alone which is the most likely treatment than patients would receive out with the trial currently in the UK. (NICE guidance) It is unlikely that the trial treatment will be less effective than standard providing that the patient is able to complete the management protocol.

This trial will involve a randomisation between an arm with short course radiotherapy or one with long course chemoradiation, both followed by a period of weeks during which chemotherapy and immunotherapy will be delivered. As previously mentioned, it is currently unclear which, if either of these treatments is superior and both are used in standard of care in the UK.

The potential increased side effects include those from using the immunotherapy drug Durvalumab. These side effects are generally related to the patient’s own immune system being activated and affecting normal tissues. There is also a risk of increased side effects because radiotherapy and Durvalumab immunotherapy are being combined and this is most likely to be manifested as diarrhoea. Finally, the combination of immunotherapy and chemotherapy may lead to increased side effects compared to if either of these treatments were used alone. The trial protocol contains specific guidelines for clinicians on how to manage overlapping toxicities from the trial treatment. If toxicities do occur, efforts will be made to continue standard of care treatment such as radiotherapy whilst additional trial treatments, such as immunotherapy, are withheld.

Where is the study run from?
NHS Greater Glasgow and Clyde (UK)

When is the study starting and how long is it expected to run for?
September 2020 to May 2026

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
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Type(s)
Scientific

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Additional identifiers

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Integrated Research Application System (IRAS)
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ClinicalTrials.gov (NCT)
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Protocol serial number
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Study information

Scientific Title
Priming the tumour microenvironment for effective treatment with immunotherapy in locally advanced rectal cancer: a phase II trial of durvulamab in combination with extended neoadjuvant regimens in rectal cancer

Acronym
PRIME-RT

Study objectives
1. Capecitabine and long-course radiotherapy followed by FOLFOX chemotherapy, with concurrent durvalumab and short-course radiotherapy, followed by FOLFOX chemotherapy with concurrent durvalumab, will result in rates of complete tumour response in excess of 30% at 6 months post start of treatment
2. Chemotherapy and radiotherapy will be effective at immune priming locally advanced rectal tumours. Subsequently, this immune priming can be exploited by adding immunotherapy to standard management to increase the effectiveness of neo-adjuvant treatment strategies.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/10/2020, East of Scotland Research Ethics Service (Tayside Medical Science Centre, George Pirie Way, Ninewells Hospital, Dundee, DD1 9SY, United Kingdom; +44 1382383848; eosres.tayside@nhs.net), ref: 20/ES/0083

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Patients will be randomised 1:1 to receive treatment in Arm A or Arm B. There will be a safety lead in for patients with metastatic rectal cancer or locally advanced rectal cancer not suitable for surgery. For the safety run-in cohort, Permuted block randomisation will be used to randomly allocate 3 patients to arm A and 3 patients to arm B for the initial safety cohort of 6 patients and for an additional 6 patients (3 per arm) if the safety cohort has to be expanded in both arms. If only one arm has to be expanded recruitment to that arm will be completed with all sequential patients.
For the main study, a minimisation algorithm incorporating a random component will be used to allocate patients (1:1) between the arms: Arm A and Arm B. Stratification will be whether the initial multi-disciplinary team review deemed the tumour to be resectable via abdominoperioneal resection or a sphincter-preserving resection (low anterior resection).

Arm A will recieve:
1. Durvalumab 1500 mg IV over 60 min, starting in the week prior to day 1 of radiotherapy, and continuing every 4 weeks until completion of FOLFOX chemotherapy
2. Short course radiotherapy (25 Gy over 5 days) starting on day 1
3. FOLFOX chemotherapy will be given every 2 weeks, starting approximately 1-2 weeks after radiotherapy (RT) and continuing for 6 cycles in total

Assessment of response will be approximately 16-18 weeks after day 1 of RT. If the patient is proceeding to surgery, this will be performed at approximately 18-20 weeks after day 1 of RT where possible.

Arm B will recieve:
1. Durvalumab 1500 mg IV over 60 min, starting in the week prior to day 1 of RT, and continuing every 4 weeks until completion of FOLFOX chemotherapy
2. Long course radiotherapy (50G y over 5 weeks) starting on day 1
3. FOLFOX chemotherapy will be given every two weeks, starting approximately 1-2 weeks after RT for 4 cycles
Assessment of response at approximately 16-18 weeks after day 1 of RT. If the patient is proceeding to surgery, this will be performed at approximately 18-20 weeks after day 1 of RT where possible.

Trial Population
Safety Run-in
In the safety run-in, initially a cohort of six patients will be randomised to Arm A or Arm B; 3 patients to arm A and 3 patients to arm B. The Safety Review Committee will have frequent meetings (at least 2 weekly) to discuss reported toxicities during the safety run-in phase of the trial. The Safety Review Committee will review all adverse event data after each arm has recruited and completed treatment on three patients, including 30 day follow up. Continuing recruitment within the safety run-in cohort will not be postponed during this lead-in stage unless a safety signal is identified. The safety run-in is designed to identify if any significant overlapping toxicities could result in patients developing significant local symptoms that would potentially preclude surgery (e.g. procto-colitis) detected on sigmoidoscopy or MRI. If a safety signal is detected, a decision will be made on the appropriateness of de-escalating treatment. This will depend on the type of toxicity observed and an assessment of which part of the treatment is most likely to be responsible. Depending on the toxicity observed in the first 3 evaluable patients in each of the arms, an additional 3 patients may be added to that arm for the safety run-in cohort.

If at least 3 evaluable patients in each arm have safely completed treatment plus 30 day assessment post treatment and the Independent Data Monitoring Committee considers both treatment arms safe, the randomised phase II component will open.

Safety Run in Period
Patients will be assessed from the start of trial treatment until the end of neoadjuvant treatment visit (approximately week 15-18) by the principal investigator (PI) and Safety Review Committee.

Patients will be assessed against the following criteria:
1. Local toxicities that would be deemed by the treating MDT to result in a delay to potential rectal resection (e.g.significant proctitis identified on endoscopy
2. Mayo endoscopic colitis score >3 or significant oedema on rectal MRI
3. Any other toxicity that is greater than at baseline and is judged to be a DLT at the safety review meeting. In the safety run-in, the decision whether AEs should be considered as DLTs and /or that a specific treatment arm is considered intolerable will be made by the sponsor and investigators with a recommendation from an Independent Advisory Panel (safety review committee) based on, among others, incidence and severity of the AEs.

The period of evaluation for DLTs will be 30 days after the last dose of treatment.

DLTs will be study drug-related toxicities graded using NCI CTCAE 5.0 occurring during dose-limiting toxicity periods and include:
1. Non-haematologic toxicity, including immune-related adverse events, ≥ Grade 3 (except alopecia, diarrhoea, nausea and vomiting unless lasting >5 days despite optimal supportive care). Other non-haematological toxicity ≥ Grade 3 that is believed to be disease-related and not thought to be related to study treatment may not be deemed as a DLT. However, these events will be discussed, assessed, and documented by the Safety Review Committee, and the decision to record or not as a DLT approved
2. Haematologic toxicity: Grade 4 neutropenia ≥5 days, or Grade ≥ 4 febrile neutropenia, Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or lasting >7 days
3. Patient in Arm A does not complete SCRT within 14 day window
4. Patient in Arm B dose not complete LCRT within 42 day window
5. Any other toxicity assessed as related to study treatment, including increase of radiotherapy associated toxicity, and which, in the opinion of the study investigator(s) and the sponsor physician constitutes a dose-limiting toxicity

In a study arm, if 1 or more of the first 3 evaluable patients at the end of treatment have toxicity from treatment that would preclude surgical resection as assessed through multi-disciplinary discussion between the treating investigator/local surgeon and radiologist a further 3 patients would be recruited to that arm.

Hierarchy for alteration to trial treatment if expansion cohort required:
1. For patients experiencing toxicities, an initial review of radiotherapy plans, and in particular doses to organs at risk, in conjunction with RTTQA and the trial mandated dose constraints
2. Radiotherapy plan review as a first strategy will be followed by de-escalation of FOLFOX chemotherapy dose and/or number of cycles administered or a longer time period (>2 weeks) between finishing radiotherapy and starting FOLFOX chemotherapy
3. These above two strategies will be adopted in the first instance in preference to de-escalating the timing or number of doses of durvalumab. In the scenario where immune related toxicities during cycle 1 durvalumab are identified as a particular concern, it therefore may be necessary to delay dose 2 of durvalumab. The Safety Review Committee will make a judgement on the characteristics of the toxicity identified and make a judgement on the most appropriate alteration to treatment.

For patients experiencing toxicities, ongoing assessments will be made and changes to regimens for those individual patients (e.g. dose reductions or expansion of time between last chemotherapy and assessment of surgery) will be discussed in a timely manner and decided upon on an ongoing basis via the Safety Review Committee who will be meeting regularly.

No adjustment to what is considered standard of care radiotherapy schedules will be made when adjusting treatment to improve tolerability.

Main Trial
42 patients will be recruited to the main trial across both arms. The main trial includes a population of patients with locally advanced rectal cancer as defined by MRI imaging or identified by the multi-disciplinary team as a low rectal tumour felt by the multi-disciplinary team to require abdomino-perineal resection. The MRI selection criteria are a rectal tumour with one of: cT3b+, or EMVI positive tumour, Primary tumour or morphologically malignant lymph node at 1mm or less from the mesorectal fascia or beyond the mesorectal fasica OR a low rectal tumour and the consensus of the multi-disciplinary meeting is that abdomino-perineal excision

would be required for sufficient surgical management. All patients will be ECOG performance status 0 or 1 and be medically fit to undergo surgery to remove their rectal tumour following neo-adjuvant treatment.

Potential patients will be identified at colorectal multi-disciplinary team meetings in participating centres. Eligibility to the trial will be assessed by histological diagnosis and suitability for neo-adjuvant (chemo)-radiotherapy, as defined by the inclusion criteria.

Identification of participants and consent
Potential patients will be identified at colorectal multi-disciplinary team meetings in participating centres. Eligibility to the trial will be assessed by histological diagnosis and suitability to undergo trial treatment, as defined by the inclusion criteria. Identification of participants and consent for the main trial are identical to the processes followed for the safety run-in, with the exception of different inclusion criteria for the safety run-in and main trial. Initially, 6 patients will be recruited to the safety run-in, with the potential to expand to twelve patients. In total, 42 patients will be recruited to the main trial; 21 in each arm.

The patient will be offered the option of standard treatment or participation in this trial. Patients will be given as much time as they require to decide whether or not they would like to take part in the trial (minimum of 24 h). Signed participant consent must be obtained and the consent forms should be signed by the person undertaking the consent procedure at site, who must be detailed on the delegation log as having this authorisation. The Principal Investigator is responsible for ensuring the designee is suitably qualified by training or experience to take informed consent, if consent is delegated to a designee. No screening activities related to the trial may be undertaken until informed consent has been obtained.

Patients cannot be screened or randomised to the trial until the site has been activated to begin recruitment.

Prior to starting treatment, when the patient’s eligibility has been confirmed by the Principal Investigator or designees, and consent forms and randomisation forms have been completed, site staff must contact the CRUK Clinical Trials Unit Glasgow using the contact details (telephone or fax) provided below for the main trial.

As there are only six patients to be included in the initial Safety Run-in Period, a Slot Allocation system will be in place to ensure this number of patients is not exceeded. Sites will be informed if the safety run-in period is to be extended to 12 patients. A Slot Allocation Form will be provided to sites and this should be completed and submitted to the CRUK CTU, Glasgow to ensure a slot is booked for the patient. Regular communication to sites regarding slots available will take place during the Safety Run-in Period.

Screening/Randomisation
Patients cannot be screened or randomised to the trial until the site has been activated to begin recruitment.

When the patient signs consent for the screening investigations to begin the site should complete a screening registration form and contact the CRUK Clinical Trials Unit in Glasgow to obtain a screening number.

Prior to starting treatment, when the patient's eligibility has been confirmed by the Principal Investigator or designees, and consent forms and randomisation forms have been completed, site staff must contact the CRUK Clinical Trials Unit Glasgow to randomise the patient to the study.

The patient's eligibility criteria will be checked and, if eligible, a trial number and trial arm will be allocated at this point. All patients must be randomised onto the trial prior to commencement of trial treatment. The patient's GP will be informed of their involvement in the trial.

Withdrawal
Patients have the right to withdraw from trial treatment at any point for any reason. Similarly, the Investigator may withdraw patients from the trial drug in the event of intra-current illness, AEs, SAEs, SUSARs, protocol violations or any other relevant reasons. Patients who become pregnant should also be withdrawn from the trial. If a patient withdraws from treatment early, they should be followed up as per trial schedule.

A subject must be discontinued from the trial for any of the following reasons:
1. The subject or legal representative withdraws consent
2. Unacceptable adverse events
3. Intercurrent illness that prevents further administration of treatment
4. Investigator's decision to withdraw the subject
5. The subject has a confirmed positive serum pregnancy test
6. Noncompliance with trial treatment or procedure requirements
7. The subject is lost to follow-up
8. Administrative reasons

In many circumstances where a patient withdraws from trial treatment, it will nonetheless be desirable for the patient to remain on the trial (for example for follow-up purposes). If, however, the patient withdraws consent from the trial itself, it should be clearly documented in the patient's notes what they are withdrawing from. If a patient withdraws their consent from the trial, the site must contact the CTU with full details of the withdrawal. Where applicable, the CTU may ask the site to complete a Consent Withdrawal Form to record full details of the consent withdrawal.

For the safety of all trial participants, SAEs will continue to require to be reported and follow-up information for SAEs that have already been reported be provided, even once consent for trial participation has been withdrawn.

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 30 days after the end of treatment, or longer if treatment-related).

Trial Schedule
Eligibility evaluations (day -28 to randomisation):
1. Written informed consent
2. Discussion of the potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and given information about appropriate medically approved contraception
3. Demographic details
4. Medical history including confirmation of histological diagnosis, prior treatment, concomitant diseases, and concomitant treatment, including review of steroid use
5. Magnetic resonance imaging (MRI) scan of the rectum reported according to ESGAR primary rectal cancer reporting template

6. CT chest/abdomen/pelvis
7. Research biopsy of rectal tumour, MMR and CD3+ count will be performed on this biopsy specimen
8. DPD Testing (please note this can be outside the 28 day time frame prior to study entry)
9. CEA Levels

Baseline evaluations (day -7 to pre-dose day 1):
1. Review of eligibility criteria
2. Human chorionic gonadotrophin (HCG) test to rule out pregnancy at trial entry; results must be obtained and reviewed prior to study entry for people of childbearing potential
3. Physical examination
4. Height and weight (calculation of body surface area)
5. Urinalysis
6. Review of concomitant medications including steroid use
7. Toxicity assessment / adverse events (all toxicities must be graded according to NCI-CTCAE version 5)
8. Eastern Cooperative Oncology Group (ECOG) performance status
9. Baseline assessment of stool frequency/stoma output (number of times per day), distinguishing from tenesmus/mucus discharge/wet wind
10. Vital signs (temperature, oxygen saturation, seated blood pressure (BP) and pulse rate)
11. Electrocardiogram (ECG)
12. Blood sample for laboratory tests to confirm eligibility
13. Blood samples for translational research purposes (baseline)
14. QoL questionnaires (EQ5-D, EORTC QLQ-C30, EORTC QLQ-C29)

Assessments during the trial:
1. Flexible sigmoidoscopy and biopsy performed baseline, week 2, and 6 weeks after D1 of radiotherapy and at the end of treatment (see below for full details for End of Treatment visit). Flexible sigmoidoscopy and biopsy at week 6 is encouraged but not mandatory. If it is not possible to do a biopsy at week 6, flexible sigmoidoscopy alone is still encouraged.
2. Translational blood samples at baseline, week 2, and 6 weeks after Day 1 of radiotherapy and at the end of treatment. Flexibility of 7 days either side of week 2 and week 6 is permitted.
3. DLT Assessment (Safety Run-in Period only)
4. QoL questionnaires

Evaluations during immunotherapy (Durvalumab) treatment.
Patients will receive immunotherapy in the week prior to RT Day 1 and then every 4 weeks throughout the trial. The patient will be reviewed on Day 1 (or up to 48 h prior) and the following assessments will be performed:
1. Symptom directed physical examination if clinically indicated
2. ECOG performance status
3. Weight
4. Toxicity assessment / adverse events (all toxicities must be graded according to NCI-CTCAE version 5)
5. Review of concomitant medications including steroid use
6. Review of stool frequency/stoma output (number of times per day), distinguishing from tenesmus/mucus discharge/wet wind
7. Vital signs (as for screening visit), blood samples for haematology, biochemistry (including TFTs, cortisol, glucose). It is acceptable to use screening haematology/biochemistry samples if within 7 days of first durvalumab treatment for patients receiving treatment on Arm A
8. DLT Assessment (Safety Run-in Period only)

Evaluations during radiotherapy or chemoradiation treatment:
During radiotherapy/chemoradiotherapy treatment, all patients should be seen once a week. However, the local team should have a structure in place that ensures that patients experiencing side effects can be seen on any day and that patients can undergo daily review if required to monitor the severity of side effects and respective treatment. The following assessments /investigations/procedures should be performed at formal trial visits (please note these can be performed up to 48 h prior to each visit):
1. Symptom directed physical examination if clinically indicated
2. ECOG performance status
3. Weight and calculation of Body Surface Area
4. Vital signs (as for screening visit)
5. Blood tests (Biochemistry, haematology including coagulation), TFTS, cortisol and glucose only required on weeks when durvalumab being delivered
6. Review of stool frequency/stoma output (number of times per day), distinguishing from tenesmus/mucus discharge/wet wind
7. Toxicity assessment / adverse events (all toxicities must be graded according to NCI-CTCAE version 5)
8. Compliance with capecitabine tablets for those on Arm B
9. DLT Assessment (Safety Run-in Period only)

Evaluations during chemotherapy (FOLFOX) treatment:
Patients will receive chemotherapy (FOLFOX) every 2 weeks. Chemotherapy will commence 1-2 weeks after radiotherapy/chemoradiation has finished. For patients on Arm A who receive short course radiotherapy, they will receive a maximum of 6 cycles of chemotherapy. For patients on Arm B, who receive long course chemoradiation, they will receive a maximum of 4 cycles of chemotherapy. Immunotherapy is delivered every 4 weeks and chemotherapy every 2 weeks. Therefore, along with every second cycle of chemotherapy, the patient will also receive immunotherapy. Where possible, the weeks when immunotherapy is given should align with the weeks of chemotherapy delivery. For example, in Arm A, if durvalumab is given the week before RT, cycle 2 will be due 2 weeks after RT is finished. It would be appropriate to wait 2 weeks to deliver FOLFOX on the same week (or day if possible) as durvalumab. For Arm B, if cycle 1 is given the week before RT begins, cycle 2 will be during RT and cycle 3 will be approximately 2-3 weeks postRT. It would be appropriate to wait to start FOLFOX chemotherapy with cycle 3 of Durvalumab.

The patient will be reviewed on Day 1 (or up to 48 h prior) of each cycle and the following assessments will be performed:
1. ECOG performance status Symptom directed physical examination if clinically indicated
2. Weight and calculation of Body Surface Area
3. Review of concomitant medications including steroid use
4. Review of stool frequency/stoma output (number of times per day), distinguishing from tenesmus/mucus discharge/wet wind
5. Vital signs (as for screening visit)
6. Blood samples for haematology, biochemistry. TFTs, cortisol, and glucose only required on weeks when durvalumab is being delivered.
7. Toxicity assessment/adverse events (all toxicities must be graded according to NCI-CTCAE version 5)
8. DLT Assessment (Safety Run-in Period only)

Evaluations at “end of treatment” visit after neoadjvuant treatment completion:
1. ECOG performance status
2. Symptom directed physical examination if clinically indicated

3. Review of medications, including any steroid use
4. Vital signs (as for screening visit)
5. Review of stool frequency/stoma output (number of times per day), distinguishing from tenesmus/mucus discharge/wet wind
6. Blood samples for haematology and biochemistry
7. CEA Levels
8. MRI rectum (reported to ESGAR post treatment reporting guidelines template criteria)
9. CT chest/abdomen/pelvis
10. Digital rectal examination
11. Flexible sigmoidoscopy and biopsy
12. Translational blood samples

Following completion of FOLFOX chemotherapy, assessment with MRI, flexible sigmoidoscopy and digital rectal exam will be performed. Patients with cCR may enter a “deferred surgery” protocol. Patients with near-complete responses could be reassessed in 4-6 weeks by endoscopy and only if improving appearances (e.g. epithelialising ulcer or continued regression of nodularity), a “deferred surgery” path would be followed.

For the purposes of this trial, a deferral of surgery protocol (active surveillance) is included in Appendix 7 of the protocol for patients who meet the criteria defined in Table 4. Patients and clinicians may opt to proceed with a surgical procedure even if the criteria for cCR are met.

Evaluations during follow up (for patients who undergo surgery)
After radical surgery, patients will enter follow-up and should be assessed every 3 months for a total of 36 months.

At each follow-up visit, the following assessments should be performed:
1. Physical examination
2. Review of medications including steroid use
3. Toxicity assessment (assessed using CTCAEv5.0)
4. ECOG performance status

Evaluations during follow up (for patients who enter "Deferred surgery" protocol
Following the completion of FOLFOX chemotherapy, assessment with MRI, flexible sigmoidoscopy and digital rectal exam will be performed. Patients meeting the criteria for cCR may enter the “deferred surgery” protocol. Patients with near-complete responses could be reassessed in 4-6 weeks by endoscopy and only if improving appearances (e.g. epithelialising ulcer or continued regression of nodularity), a deferral of surgery path would be followed.

The specific protocol appendix includes an example follow up schedule of assessments in a “deferred surgery” protocol. Participating centres may use their own, local “deferred surgery” protocol where this exists. It is expected that whichever protocol is used, that patients will have MRI, DRE and flexible sigmoidoscopy assessment at least 3-4 monthly in year 1 of follow up.

Imaging requirements
MRI scans
MRI scans will be performed at baseline and at the end of treatment. For those patients following the deferred surgery follow up protocol will have further MRI scans as documented in the protocol

CT scans
CT scans will be performed at baseline and at the end of treatment.

Laboratory Tests
Routine blood tests
Routine blood tests will be collected at site and sent to local laboratories for processing. All laboratory tests will be conducted in participating centres according to local procedures.

Translational Research blood samples
Blood samples will be taken for translational research at the same time points as flexible sigmoidoscopy assessments.

Translational research blood tests will be collected at site and sent to the bio-repository in Glasgow for storage with the intention that these samples will be used for future research.

Flexible sigmoidoscopy and biopsy
Flexible sigmoidoscopy at baseline, 2 weeks, 6 weeks, and at completion of treatment will be performed to visualise and assess the tumour's response to treatment and perform targeted biopsies for assessment of the CD3+ biomarker (secondary endpoint) and for translational research purposes.

General advice on translational blood tests and biopsy or surgical material acquired for future research Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored to assist in any research scientific questions related to durvalumab or cancer and for potential diagnostic development.

For the purposes of this trial, the following are considered Investigational Medicinal Products (IMPs): Durvalumab, Oxaliplatin, Fluorouracil, Folinic acid, and Capecitabine (during chemoradiation).

Main Trial
Treatment Arms
Once the treatment in Arm A and Arm B is considered safe and the toxicity acceptable, patients will then be randomised 1:1 to receive either Arm A (Durvalumab- short course radiotherapy- FOLFOX) Or Arm B (Durvalumab- long course chemoradiation (with capecitabine)- FOLFOX).

Arm A will recieve:
1. Durvalumab 1500 mg IV over 60 min, starting in the week prior to day 1 of radiotherapy, and continuing every 4 weeks for a maximum of 4 cycles until completion of FOLFOX chemotherapy (whichever is longer).
2. Short course radiotherapy (25 Gy over 5 days) starting on day 1, 25 Gy over 5 days i.e. 5 Gy fraction each day from Monday to Friday (5 fractions in total)
3. FOLFOX chemotherapy will be given every 2 weeks, starting approximately 1-2 weeks after radiotherapy (RT) and continuing for 6 cycles in total
3.1. Oxaliplatin: 85 mg/m², IV over 2 h, day 1
3.2. Folinic acid: 350 mg flat dose, IV over 2 h, day 1 (this can be given concurrently with the oxaliplatin)
3.3. Fluorouracil bolus: 400 mg/m² IV over 10-15 min, day 1
3.4. Fluorouracil infusion: 2400 mg/m², as a continuous IV infusion (via central line or peripheral

line) over 46 h or 48 h (as per local practice) starting on day 1
3.5. Each cycle will be repeated every 2 weeks. Patients will receive a maximum of 6 cycles of FOLFOX.

In the post-radiotherapy stage, when durvalumab and FOLFOX are being administered, effort should be made to deliver durvalumab and FOLFOX on the same day. Durvalumab should be delivered prior to FOLFOX chemotherapy when they are delivered on the same day. A gap of at least 1 h for observation to monitor for significant infusion reactions should be left between durvalumab and FOLFOX the first time these treatments are given on the same day. If there is no reaction, this period can be reduced to 30 min for subsequent cycles.

Arm B will recieve:
1. Durvalumab 1500 mg IV over 60 min, starting in the week prior to day 1 of RT, and continuing every 4 weeks until completion of FOLFOX chemotherapy
2. Long course radiotherapy (50 G y over 5 weeks) starting on day 1
2.1. 50 Gy over 5 weeks i.e. 1.8 Gy fraction each day from Monday to Friday for 5 weeks (25 fractions in total). A simultaneous integrated boost as per the Radiotherapy Planning Manual is acceptable
2.2. Capecitabine 825 mg/m² orally twice a day, to be given on the same days of radiotherapy (Monday to Friday), along with radiation treatment over 5 weeks, starting on day 1 of radiotherapy
3. FOLFOX chemotherapy will be given every two weeks, starting approximately 1-2 weeks after RT for 4 cycles
3.1. Oxaliplatin: 85 mg/m², IV over 2 h, day 1
3.2. Folinic acid: 350 mg flat dose, IV over 2 h, day 1 (this can be given concurrently with the oxaliplatin).
3.3. Fluououracil bolus: 400 mg/m² IV over 10-15 min, day 1
3.4. Fluououracil infusion: 2400 mg/m², as a continuous IV infusion (via central line or peripheral line) over 46 h or 48 h (as per local practice) starting on day 1
3.5. Each cycle will be repeated every 2 weeks. Patients will receive a maximum of 4 cycles of FOLFOX.

In the post radiotherapy stage, when durvalumab and FOLFOX are being administered, effort should be made to deliver durvalumab and FOLFOX on the same day. Durvalumab should be delivered prior to FOLFOX chemotherapy when they are delivered on the same day. A gap of at least 1 h for observation to monitor for significant infusion reactions should be left between durvalumab and FOLFOX the first time these treatments are given on the same day. If there is no reaction, this period can be reduced to 30 min for subsequent cycles.

Radiotherapy
Subjects will receive one of the two preoperative radiotherapy schedules (SCRT or long course chemoradiation). For both schedules, radiotherapy will be delivered with CT-based 3D-conformal treatment planning with a definition of target volumes. Intensity modulated radiation therapy (IMRT) should be used.

There is considerable debate about target volume definition in rectal cancer. Reasons for this include the limited number of studies of patterns of failure, the lack of QA in the delivery of radiation therapy. There are also widespread differences in views amongst radiation oncologists regarding their preferred volume of elective nodal irradiation. A direct comparison of different target volumes within the context of clinical trials has never been performed.

It is recognised that during the conduct of Prime-RT study, it may be necessary to modify the defined protocol either because of the publication of convincing new data regarding target volume definition or consensus views derived from the radiotherapy planning workshops.

A detailed description of radiotherapy target volume definition, verification and quality assurance is provided in the PRIME-RT Radiotherapy Manual and should always be used during the radiotherapy planning and treatment process. A brief summary is provided here in the main section of the protocol. Patients should be planned using the details provided in the Radiotherapy Manual

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Proportion of patients achieving a clinical complete response (cCR) or a pathological complete response (pCR) at 6 months, in each arm, treatment would be considered to be effective if >30% of patients exhibit a complete clinical or pathological response at 6 months

Key secondary outcome(s))
1. Occurrence of Grade 3-5 treatment-emergent adverse events and treatment-related adverse events during neo-adjuvant treatment and for up to at least 90 days after the last dose of CTIMP
2. Presence of a moderate-high grade CD3+ T cell infiltrate on rectal tumour biopsy during treatment as measured on biopsy samples taken during neoadjuvant treatment and at the end of treatment at 2 and 6 weeks. In each arm, treatment would be considered to be effective if a mod-high grade CD3+ infiltrates are seen at any time point after commencing treatment in 40% of patients.
3. In patients who do not achieve a cCR, the proportion of patients with a neoadjuvant rectal (NAR) score <8 post-surgery
4. Proportion of patients achieving MRI-confirmed complete tumour regression using the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) template at post treatment MRI
5. Proportion of patients achieving MRI-confirmed near complete tumour regression using the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) template at post treatment MRI
6. Proportion of patients achieving MRI-confirmed downstaging in T stage at post treatment MRI
7. Proportion of patients with local regrowth after a cCR at any time during follow up
8. Overall survival at 36 months
9. Recurrence free survival at 36 months
10. Proportion of patients who have a permanent colostomy after surgery until the end of follow up
11. Proportion of patients who proceed to surgery (or who have a complete clinical response and go onto the deferred surgery pathway) at the end of treatment (15-18 weeks)
12. Proportion of patients receiving at least 4 fractions of short course RT or 20 fractions of long course RT at the end of treatment (15-18 weeks). For those patients having long course chemoradiotherapy the proportion of patients receiving 80% or greater of the planned capecitabine dose will also be evaluated.
13. Proportion of patients undergoing surgical resection with Clavien-Dindo grade 3-5 complications post-surgery
14. Patient Reported Outcome Measures (PROMS) using the European Organization for

Research and Treatment of Cancer quality of life questionnaires EORTC QLQ30 and EORTC CR29, and the EuroQol 5-dimension quality of life questionnaire (EQ5D) at baseline and months 3, 6, 12, 18, 24 and 30

Exploratory outcomes:
1. Proportion of MMR proficient and MMR deficient patients with mod-high grade CD3+ infiltrates measured using biopsy samples taken during neoadjuvant treatment and at the end of treatment at 2 and 6 weeks
2. Proportion of MMR proficient and MMR deficient patients with a cCR/ pCR at 6 months
3. Molecular and immunological biomarkers of response to immunotherapy-radiotherapy combination measured using pancancer next generation sequencing panel, multiplex immunohistochemistry for immune cell counts, checkpoint expression, RNA-seq, transcriptional analysis, and circulating cytokine/chemokine profiles at baseline, 2, and 6 weeks and the end of treatment
4. Biomarkers of treatment resistance to immunotherapy-radiotherapy combination measured using pancancer next generation sequencing panel, multiplex immunohistochemistry for immune cell counts, checkpoint expression, RNA-seq, transcriptional analysis, and circulating cytokine/chemokine profiles at baseline, 2, and 6 weeks and the end of treatment
5. Molecular characteristics of rectal cancers in which an immune priming response is seen with radiotherapy measured using pancancer next generation sequencing panel, multiplex immunohistochemistry for immune cell counts, checkpoint expression, RNA-seq, transcriptional analysis, and circulating cytokine/chemokine profiles at baseline, 2, and 6 weeks and the end of treatment

Completion date
31/05/2026

Eligibility

Key inclusion criteria
1. Willing and able to provide written informed consent for the trial
2. Willing to comply with scheduled visits, treatment plans and laboratory tests and other trial procedures including a willingness to provide repeated biopsy samples of the tumour via flexible sigmoidoscopy
3. Aged ≥18 years on the day of signing informed consent
4. Histologically confirmed non-metastatic, locally advanced rectal adenocarcinoma deemed appropriate for radical treatment.
5. Non-metastatic disease confirmed with CT of chest/abdomen and pelvis. Suspicious extramesorectal lymph nodes identified on initial staging investigations are not considered exclusion criteria if the local MDT deem these
resectable at and would treat patients with curative intent.
6.The rectal tumour must have at least one of the following high-risk criteria on MRI scan:
6.1. cT3b+
6.2. EMVI positive
6.3. Primary tumour or morphologically malignant lymph node at 1mm or less from the mesorectal fascia or beyond the mesorectal fascia
6.4. Low rectal tumour and the consensus of the multi-disciplinary meeting is that abdomino-perineal excision would be required for sufficient surgical management
7. ECOG performance status 0-1
8. No contra-indication to treatment with pelvic radiotherapy. For example, no pre-existing condition which would deter radiotherapy such as fistulas, severe ulcerative colitis (particularly

subjects currently taking sulphasalazine), Crohn’s disease, prior adhesions.
9. Primary disease which can be encompassed within a radical radiotherapy treatment volume
10. Adequate haematological and biochemical function as indicated below. These measurements should be performed within 7 days prior to randomisation:
10.1. Absolute neutrophil count >1.5 x10^9/l
10.2. Platelets ≥100 x10^9/l.
10.3. Haemoglobin ≥90 g/l. Transfusion is acceptable if necessary to increase haemoglobin levels.
10.4. Coagulation International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 xULN unless the subject is receiving
anticoagulant therapy as long as PT or PTT is within the therapeutic range of intended use of anticoagulants
10.5. Activated Partial Thromboplastin Time (aPTT) ≤1.5 xULN unless the subject is receiving anticoagulant therapy as long
as PT or PTT is within therapeutic range of intended use of anticoagulants
10.6. Renal Creatinine or measured or calculated creatinine clearance (calculated per institutional standard) ≤1.5 X upper limit of normal (ULN) OR ≥660 ml/min for subject with creatinine levels >1.5 x institutional ULN. GFR can also be used in place of creatinine or CrCl.
10.7. Bilirubin <1.5 x upper limit of normal (ULN) except for unconjugated hyperbilirubinemia in patients who have Gilbert’s
syndrome. In this case, direct bilirubin must be ≤ULN for subjects with total bilirubin levels >1.5 ULN.
10.8. AST and ALT ≤2.5 xULN.
10.9. Albumin ≥2.5 g/dl

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
46

Key exclusion criteria
1. Patients with dihydropyrimidine dehydrogenase (DPD) deficiency (any degree).
2. Unable to have MRI assessment
3. Patient weight less than or equal to 30 kg
4. Previous pelvic radiotherapy
5. Metastatic disease defined by computerized tomography (CT) including resectable metastases
6. Previous treatment with immunotherapy including but not limited to anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA4
agents, interferon or anti-IL2 for the treatment of malignancy

7. Previous treatment with chemotherapy for the treatment of current malignancy or treatment with chemotherapy within the last 5 years for a separate malignancy (unless that malignancy was treated squamous/basal cell skin cancer, treated early stage cervical cancer or treated /biochemically stable, organ confined prostate cancer)
8. History of a separate malignancy in the last 5 years (other than treated squamous/basal cell skin cancer, treated early stage cervical cancer or treated/biochemically stable, organ confined prostate cancer)
9. Pregnant or lactating participants. Participants who are of childbearing potential, or with partners of childbearing potential, must agree to use adequate contraceptive measures for the duration of the study and for 6 months after the completion of study treatment.
10. Major surgery within 28 days prior to trial entry
11. Prolongation of corrected QT (QTc) interval to >470 msec when electrolyte balance is normal
12. Recent occurrence (within 3-6 months) of a major thromboembolic event, such as pulmonary embolism or proximal deep vein thrombosis, unless stable on (2 weeks) 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 to participate in the study.
13. Active inflammatory bowel disease affecting the colon and rectum based on a previous endoscopy and defined by ongoing drug treatment
14. Has an active autoimmune disease that has required systemic treatment in past 2 years (such as the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
15. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease requiring immunosuppressive treatment
16. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisolone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of the trial drug
17. Has a history of (non-infectious) interstitial pneumonia or pneumonitis that required steroids or current pneumonitis.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject’s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial
20. Has received a live vaccine within 30 days prior to the first dose of trial drug
21. Any patients receiving treatment with brivudine, sorivudine and analogues or patients who have not stopped these drugs at least 4 weeks prior to start of study treatment
22. Any patient with severe diarrhoea (defined as ≥grade 3 diarrhoea despite maximum supportive measures and exclusion of underlying infection)
23. Known hypersensitivity for any component of any study drug
24. Administration of any investigational drug within 28 days or 5 half-lives, whichever is longer, prior to receiving the first dose of trial treatment
25. Uncontrolled congestive heart failure (CHF), or history of myocardial infarction (MI), unstable angina, stroke, or transient ischemia within the previous 6 months
26. Patients with known malabsorption or inability to comply with oral medication
27. Patients with known human immunodeficiency virus (HIV1/2)
28. Patients with known Hepatitis B or Hepatitis C
29. Receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Includes prior organ transplantation including

allogenic stem-cell transplant.
30. Known history of active TB

Date of first enrolment
07/01/2021

Date of final enrolment
25/05/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
NHS Grampian
Summerfield House
2 Eday Road
Aberdeen
United Kingdom
AB15 6RE

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
NHS Ayrshire and Arran
PO Box 13
Boswell House
10 Arthur Street
Ayr
United Kingdom
KA7 1QJ

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

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes