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Augmenting RadioTherapy in REctal Cancer to Minimise Invasive Surgery

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ARTEMIS TRIAL SUMMARY

Title	**Augmenting RadioTherapy in REctal Cancer to Minimise Invasive Surgery**
Acronym	**ARTEMIS**
Background	Radiotherapy-based treatment for localised rectal cancer can result in long-term cure, enabling avoidance of surgery and 'organ preservation' (OP). Based on our own patient survey, this is one of the main priorities from a patient's perspective. However, this option is currently only achievable in a minority of patients receiving radiotherapy-based treatment. Improving the OP rate is an important research priority. Currently chemoradiation followed 8-12 weeks later by radical surgery is the standard of care (SoC) for locally advanced rectal cancer. However, radical surgery causes operative mortality, bowel, bladder and sexual dysfunction and stoma-related morbidity. In the UK, following chemoradiotherapy (CRT) approximately 15-20% of patients having radical surgery show a histopathologically confirmed pathological complete response (pCR). Emerging data supports considering active surveillance ('watch and wait') if a clinical complete response (cCR) is seen on post-CRT assessment. Over the last few years there have been a series of randomised controlled trials (RCTs) evaluating the use of chemotherapy before or after either short course radiotherapy (SCRT) or long course chemoradiotherapy (LCCRT) ("Total Neoadjuvant Therapy" or TNT). Many have been published although some have only been presented at American Society of Clinical Oncology (ASCO) in 2020. Collectively they have shown an improvement of pCR and other endpoints (including OP) at the expense of slightly increased toxicity. Because of the improvement in outcomes, TNT is now being more commonly used in good performance status (PS) patients with locally advanced rectal cancer. It is likely soon to become SoC in this cohort of patients. Immunotherapy is also rapidly changing the way we manage patients and its combination with radiotherapy (RT) has shown encouraging results. However further research is required because: There is a lack of prospective randomised clinical trials evaluating OP.

	There is a need to evaluate novel treatment regimens (such as immunotherapy) that may increase the OP rate. There is little information on health-related quality of life (HRQoL).
Population	Patients with moderate to high-risk rectal cancer as defined by the National Institute of Health and Care Excellence (NICE) 2011, where pre-operative chemoradiotherapy (CRT) or total neoadjuvant treatment (TNT) are standard treatment options, and who are interested in organ preservation will be approached to participate.
Design	Randomised phase II, multi-centre open-label study using the Sargent's comparative 3-outcome two-stage design, including an interim analysis for futility (Hong and Wang, 2007).
Objectives	To assess and compare the cCR rate at 6 months post-start of radiotherapy treatment between the control and intervention group.
Intervention	**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)** - 45Gy 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/m^2 twice daily (BID) throughout the radiotherapy course. 2) **Short-course radiotherapy (SCRT)** - 25Gy 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**). **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).
Sample size	140 patients (70 per arm)
Interim analysis	An interim assessment will be performed after 58 patients (29 per arm adjusted for loss, or 26 per arm response assessments) reach the 6-month post start of RT response assessment. If the proportion of participants with a cCR in the control arm is greater than the intervention arm the trial may close early for futility.
Follow Up	Patients will be followed-up at 4, 6 (Primary Endpoint – see section 11.1 Primary Endpoint), 9, 12, 18, 24 and 30 months from the start of radiotherapy.
Primary Endpoint	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).
Primary Endpoint*	P_C=proportion of participants with a cCR in the control arm; P_E= proportion of participants with a cCR in the experimental arm (intervention group). A cCR rate of approx. 0.25 (25%) is anticipated in the control arm based on previous data. A clinically relevant

3-outcome assessment	improvement in cCR rate to 0.45 (45%) is targeted with the addition of AN0025 to chemo-radiotherapy. Based on $P_C = 0.25$, $P_E = 0.45, \alpha = 0.1,\ \beta = 0.1$ the following cut values will be used for the final primary endpoint assessment: $P_E - P_C < 0.05$ Failure to reject the null hypothesis $0.05 < P_E - P_C < 0.113$ Neither reject nor accept null hypothesis $P_E - P_C \geq 0.113$ Reject the null hypothesis *** Please see Section 13.3 Primary Endpoint Analysis for further details on the primary objective analysis.**
Secondary Endpoints*	• Acute and late toxicity; • Treatment compliance; • Patient Reported Outcomes (PROs) and HRQoL – EORTC QLQ C30 and QLQ CR29 with additional items; LARS score; EQ-5D-5L); • Surgical outcomes (including procedures and morbidity); • Clinical, radiological and pathological response rates; • Stoma rates; • Locoregional regrowth following a cCR; • Organ preservation; • Organ preservation adapted disease-free survival; • Metastasis- free survival; • Overall survival. *** Please see Section 13.4 Secondary Endpoint Analysis for further details about the secondary endpoint analysis.**

Inclusion Criteria	• Patients age ≥18 years old;
	• Eastern Cooperative Oncology Group (ECOG) PS 0 or 1;
	• Capable of informed consent;
	• Able to fully understand trial treatment enough to provide informed consent;
	• Biopsy-proven rectal adenocarcinoma;
	• 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) OR ○ low tumours with involvement of the anal intersphincteric plane or with levator involvement. Within 14 days pre-randomisation the following must be met: • Estimated creatinine clearance ≥50 mls/min (using a validated creatinine clearance calculation e.g., Cockcroft-Gault or Wright formula); • Haemoglobin ≥9.0g/dL; • Neutrophils >1.5 x 10^9/L; • Platelets >100 x 10^9/L; • Adequate blood coagulation function as evidenced by a prothrombin time (PT) ≤1.5 x normal; • Alkaline phosphatase (ALP) ≤2.5 × upper limit of normal (ULN); serum transaminase (either alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) ≤2.5 × ULN; total bilirubin ≤1.5 × ULN except for unconjugated hyperbilirubinemia or Gilbert's syndrome.
Exclusion Criteria	• Unequivocal distant metastatic disease; • Previous pelvic radiotherapy; • MRI defined predominantly mucinous tumour i.e. more than one third of tumour volume assessed to consist of mucin; • Biopsy-proven neuroendocrine tumour; • Definite MRI pelvic side wall lymph node involvement, invasion of adjacent organ, ischio-rectal fossa involvement; • 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)); • Defunctioning colostomy or ileostomy; • Prior antineoplastic therapy for rectal cancer; • Pregnant or breast feeding; or of child bearing potential and unwilling to use highly effective contraceptive methods; • On-treatment participation in an interventional clinical study 30 days prior to randomisation; • Other concomitant antineoplastic therapy; • Inability to comply with taking oral capecitabine/AN0025 medication;

	• Active, uncontrolled infections; • Active, disseminated coagulation disorder; • Clinically significant cardiovascular disease ≤ 6 months before randomisation i.e. New York Heart Association (NYHA) Functional Capacity III or IV'; • Prior invasive malignancy unless disease free >3 years (excluding basal cell carcinoma of the skin or carcinoma in situ); • Known allergic reactions to either oxaliplatin or AN0025 or both capecitabine and 5-FU; • On medication with inhibitors of dihydropyrimidine dehydrogenase (DPD); • Known complete DPD deficiency; • Psychosocial issues which may affect treatment compliance; • Prolongation of corrected QT (QTc) interval to ≥480 msec when electrolyte balance is normal; • 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; • 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); • Presently receiving 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; • Presently receiving other investigational drugs. 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: • Non-steroidal anti-inflammatory drugs (NSAIDs); • Aspirin at doses of higher than 325 mg daily;

	• Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); • Uridine'5 diphospho-glucuronosyl transferase (UGT) inducers or inhibitors (atazanavir, probenecid, valproic acid, mefenamic acid, quinidine); • Anticoagulation with anti Xa agents (ie: 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. 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 FOLFOX 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.
Randomisation	Randomisation (1:1) Intervention to control arm.

TRIAL SCHEMA

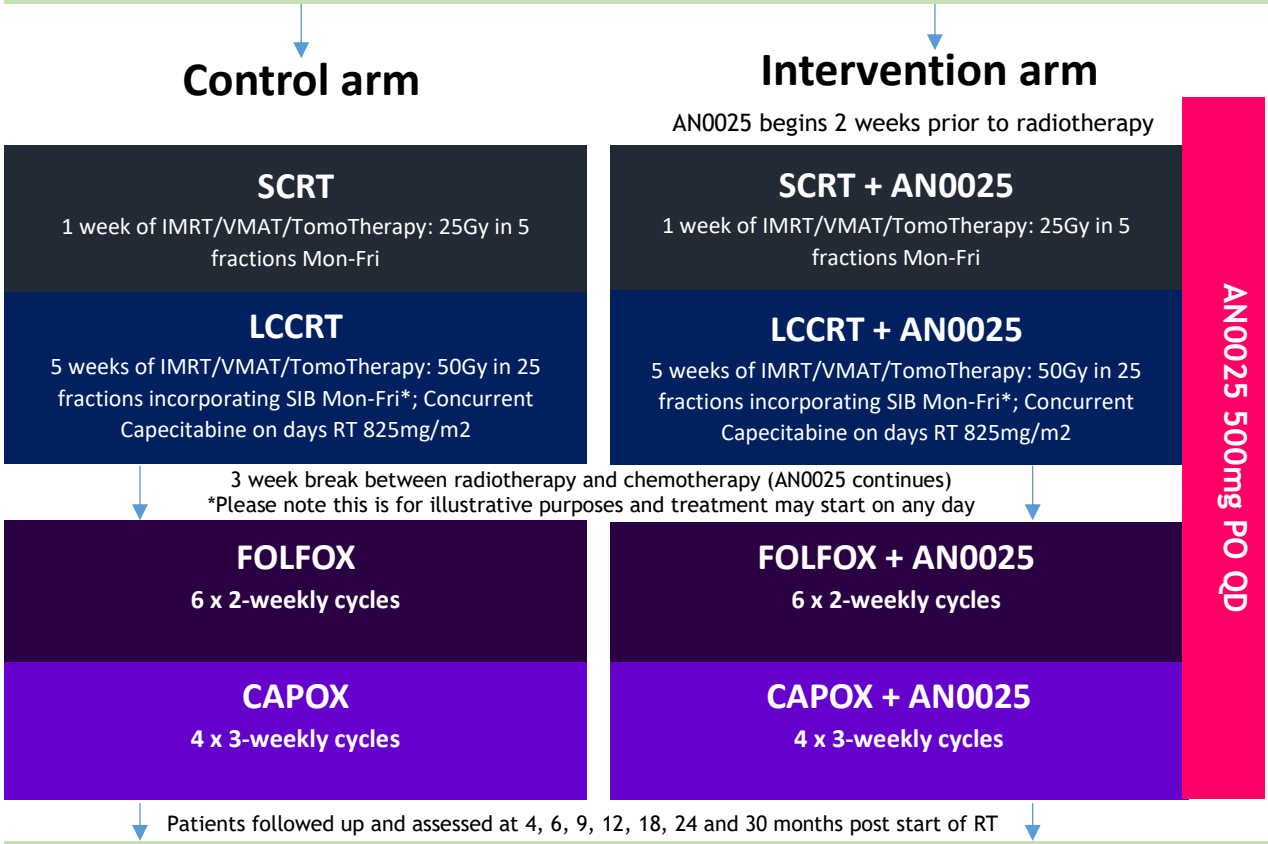
Patients with moderate to high-risk rectal cancer where pre-operative chemoradiotherapy (CRT) or total neoadjuvant treatment (TNT) are standard treatment options and who are interested in organ preservation.

Eligibility

Biopsy-proven rectal adenocarcinoma; ECOG PS 0-1;
Staged MRI: T3b-T4a or TanyN1-2 or TanyEMVI+ or with a threatened (<1mm) or involved mesorectal fascia resection margin, or 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 S1/2 junction on sagittal MRI.

Randomisation

1:1 (Control arm : Intervention arm)
Clinician choice between SCRT/LCCRT and CAPOX/FOLFOX
Stratified by: RT type (Short course/Long course) then minimised by T stage; EMVI status; CRM



Primary endpoint

Clinical Complete Response rate at 6 months post start of RT (interim futility analysis at ~58 patients)

Secondary endpoints

Acute and late toxicity, treatment compliance, HRQoL (patient reported - EORTC QLQ C30 and QLQ CR29 with additional items; LARS score; EQ-5D-5L), surgical outcomes, response assessment, stoma rates, locoregional regrowth, organ preservation, organ-preservation-adapted disease free survival, metastasis free survival and overall survival.

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ABBREVIATIONS

Abbreviation	Definition
5FU	5-Fluorouracil
ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine Aminotransferase
APL	Authorised personnel log
AE	Adverse event
AR	Adverse reaction
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BID	Twice a day
BSA	Body Surface Area
CAPOX	Capecitabine & Oxaliplatin
cCR	Clinical Complete Response
CEA	Carcinoembryonic antigen
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTRU	Clinical Trials Research Unit
CT	Computerised tomography
CTV	Nodal Clinical Target Volume
CV	Curriculum vitae
DFS	Disease-free survival
DMEC	Data Monitoring and Ethics Committee
DPD/DPYD	Dihydropyrimidine Dehydrogenase
DRE	Digital Rectal Examination
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMVI	Extramural vascular invasion
EORTC	The European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5 Dimension 5 Levels questionnaire
FBC	Full Blood Count
FOLFOX	Leucovorin calcium (folinic acid), fluorouracil and oxaliplatin

GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GTV	Gross tumour volume
Gy	Gray (unit of ionising radiation)
HR	Hazard ratio
HRA	Health Research Authority
HRQoL	Health-related quality of life
HUS	Haemolytic Uremic Syndrome
IB	Investigator Brochure
IMP	Investigational medicinal product
IMRT	Intensity modulated radiotherapy
INR	International Normalized Ratio
ISF	Investigator site file
IV	Intravenous
IWWD	International Watch and Wait Database
LA	Locally Advanced
LARC	Locally Advanced Rectal Cancer
LARS Score	Low Anterior Resection Syndrome Score
LCCRT	Long-course chemoradiotherapy
LFTs	Liver Function Tests
LMWH	Low-Molecular-Weight Heparin
MDT	Multidisciplinary team
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
mrTRG	MRI Tumour Regression Grade
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NICE	National Institute of Health and Care Excellence
NIHR	National Institute of Health Research
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
OP	Organ preservation
OP-DFS	Organ-preservation-adapted Disease free survival
OS	Overall survival
pCR	Pathological complete response
PET	Positron emission tomography

PGE2	Prostaglandin E2
PH	Proportional hazards
PI	Principal investigator
PIS	Patient information sheet
PISICF	Patient information sheet informed consent form
PO	To be taken orally
PPI	Patient and public involvement
PROs	Patient Reported Outcomes
PS	Performance Status
PT	Prothrombin Time
QA	Quality assurance
QD	Once a day
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
REC	Research ethics committee
REDCap	Research Electronic Data Capture
RGF	Research Governance Framework
RSI	Reference Safety Information
RT	Radiotherapy
RTQA	Radiotherapy Quality Assurance
RTTQA	Radiotherapy Trials Quality Assurance
SACT	Systemic anti-cancer treatment
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCRT	Short Course Radiotherapy
SFTS	Secure File Transfer Service
SoC	Standard of Care
SOP	Standard operating procedure
SSOP	Study Site Operating Procedures
SmPC	Summary of Product Characteristics
SR	Surgical resection
SUSAR	Suspected unexpected serious adverse reaction
TME	Total mesorectal excision
TMG	Trial management group
TNT	Total Neoadjuvant Therapy
TRAE	Treatment-related AEs
TRG	Tumour regression grade

TSC	Trial Steering Committee
U&Es	Urea and Electrolytes
ucCR	Uncertain Clinical Complete Response
ULN	Upper limit of normal
VMAT	Volumetric-modulated arc therapy
W&W	Watch-and-wait

1. BACKGROUND AND RATIONALE

1.1 RECTAL CANCER STANDARD OF CARE

Colorectal cancer is the third most common cancer in the UK, with almost 43,000 newly diagnosed cases per year, with over 8000 of these cancers arising in the rectum. For patients who present with localised rectal cancer, radical surgery combined with a selective use of pre-operative radiotherapy and adjuvant chemotherapy is the Standard of Care (SoC).

Radical surgery for rectal cancer consists of total mesorectal excision (TME), which is an oncologically effective treatment for early-stage rectal cancer; only 2% and 12% of patients will experience local or distant failure respectively (Bentrem et al., 2005; Endreseth et al., 2005; Peeters et al., 2007; Sebag-Montefiore et al., 2009). However, radical surgery is associated with significant risks of operative mortality, acute complications (such as anastomotic lead), acute and long-term morbidity, and the frequent need for a temporary or permanent stoma. Pelvic dissection causes autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and major sexual dysfunction (30-50%) (*National Bowel Cancer Audit Annual Report 2016*, 2016; Bakx et al., 2004; Hendren et al., 2005). More than half of all patients experience some form of faecal incontinence following primary TME surgery and 30-40% suffer daily symptoms of urgency, incomplete emptying and stool frequency (Wallner et al., 2008; Thyø et al., 2018). Prospective health-related quality of life (HRQoL) cohort studies show persistently poor social role, body image, and defaecation scores after rectal cancer surgery (Wallner et al., 2008; Temple et al., 2005; Sauer et al., 2004).

The commonest TME approaches include abdominoperineal excision (APER) (for low rectal tumours), Hartmann's procedure and Anterior Resection (AR). According to the National Bowel Cancer Audit (*National Bowel Cancer Audit Annual Report 2019*, 2019), 85% of rectal cancer patients who underwent a major resection had a stoma formed at the time of surgical resection (SR). Patients undergoing an APER or Hartmann's have a permanent stoma formed at the time of resection. Some 78% of patients undergoing an AR required a stoma at the time of initial resection, of which almost one third of patients had a stoma remaining at 18 months. Overall, 53% of all rectal cancer patients undergoing major resection had a stoma at 18 months.

1.2 NEOADJUVANT TREATMENT PRIOR TO RESECTION

Patients with rectal cancer undergo a staging magnetic resonance imaging (MRI) of the pelvis and this determines the need for pre-operative (neoadjuvant) treatment. Neoadjuvant treatment may be considered for locally advanced rectal cancers (LARC), which are usually defined by a combination of the following characteristics:

- T3c/d or T4 disease (disease extending > 5mm beyond the muscularis propria or adherent to adjacent structures/organs)

- N1 or N2 disease (nodal involvement)
- Disease within 1mm of the expected circumferential resection margin (CRM) (threatened) or extending to the CRM (involved)
- The presence of extra-mural venous invasion (EMVI)
- Tumour deposits (separate from the primary tumour and distinct from lymph nodes)

In LARCs, neoadjuvant treatment is required prior to surgery if the expected CRM is involved at presentation – either by the tumour, involved nodes or EMVI. The aim of neoadjuvant treatment is to downstage the disease and avoid an R1 resection (which is associated with an increased risk of pelvic recurrence). In selected cases, neoadjuvant treatment may also be considered if the CRM is not involved but a combination of other tumour characteristics, as listed above, are present.

Radiotherapy plays a pivotal role in the neoadjuvant landscape and several schedules are used in current clinical practice:

- LCCRT: Long Course ChemoRadioTherapy (45–50 Gy in 25#) with concurrent Capecitabine/5-Fluorouracil and restaging 6-8 weeks later
- SCRT: Short Course RadioTherapy (25Gy in 5#) and restaging 6-8 weeks later
- TNT: Total Neoadjuvant Therapy - the sequential use of both radiotherapy and chemotherapy. A TNT approach may include either SCRT or long course radiotherapy (LCRT) schedules, similarly, a variety of neoadjuvant chemotherapy schedules have been reported.

1.3 NEOADJUVANT RADIOTHERAPY

Pre-operative radiotherapy or chemoradiotherapy is recommended by the National Institute of Health and Care Excellence (NICE) as SoC for locally advanced rectal cancer (NICE, 2020). The use of both SCRT and LCCRT schedules are supported by this guidance, based on evidence showing similar outcomes relating to OS, R0 resection rates and quality of life (QoL). Local restaging using pelvic MRI is performed approximately 6-7 weeks from the end of treatment and surgery planned thereafter.

Until recently, LCCRT has been the mainstay of neoadjuvant radiotherapy to downstage disease. Delivered over 5 weeks, with concurrent Capecitabine (an oral fluoropyrimidine), peak toxicity is usually experienced during week 4 & 5 of chemoradiotherapy and takes several weeks to subside thereafter. A Simultaneous Integrated Boost (SIB) may be delivered to the gross tumour, to maximise treatment response. However, there may be comorbid or logistical considerations which make compliance with LCCRT challenging. Uncontrolled ischaemic heart disease is a contraindication to fluoropyrimidine use whilst dihydropyrimidine dehydrogenase (DPD) deficiency requires a dose reduction or avoidance of fluoropyrimidines. Geographical and transport restrictions may also make LCCRT challenging for the patient.

There is evolving data to support the downstaging effects of SCRT and delay as an alternative to LCCRT in rectal cancer. The Stockholm III trial – which included patients with early and locally advanced rectal cancers – indicated that rates of pathological complete response (pCR) in patients who received SCRT might be comparable to that in patients treated with LCRT without concurrent chemotherapy, with surgery 4-8 weeks post completion of radiotherapy (Erlandsson et al., 2019). Whilst there are some limitations of this study – the earlier tumour staging in the SCRT and delay group compared with LCRT and delay group, and lack of concurrent Capecitabine alongside LCRT, the trial nevertheless demonstrated a downstaging effect with SCRT. SCRT therefore may pose some advantages – most notably, a shorter treatment schedule for the patient and avoidance of concurrent chemotherapy. Peak toxicity is experienced 1-2 weeks following completion of treatment, when symptoms can be managed at home.

Currently, neoadjuvant XRT practice is varied in the UK, and both SCRT and LCCRT may be used to downstage locally advanced rectal cancers, as supported by NICE recommendations (NICE, 2020).

1.4 TOTAL NEOADJUVANT THERAPY (TNT)

Total Neoadjuvant Radiotherapy – TNT – encompasses both chemotherapy and (chemo)radiotherapy in the neoadjuvant treatment of LARCs. Delivering systemic treatment earlier in the treatment pathway may not only maximise primary tumour downstaging (and rates of clinical complete response (cCR) and stoma avoidance) but also enable improved compliance with the chemotherapy schedule and impact rates of distant failure (Bahadoer et al., 2021).

There remains uncertainty regarding the optimal TNT approach - trials have adopted varying TNT schedules utilising different radiotherapy courses, chemotherapy schedules (and duration) and treatment sequencing. In addition, various primary endpoints have been evaluated, including both clinical and pathological complete response rates, distant relapse and organ preservation (OP) rates. The following table demonstrates some of the varying TNT approaches and patient outcomes recently reported:

Table 1.1 TNT approaches and patient outcomes

Lead author	**Year**	**Pts total**	**Experimental Arm Neoadjuvant Treatment**		**Primary Endpoint**	**Result**
			Standard arm	Exp't arm		
Garcia-Aguilar et al (Garcia-Aguilar et al., 2020)	2020	292	LCCRT	LCCRT then FOLFOX Up to 6 cycles (0 / 2/ 4 / 6)	pCR	pCR rate increased from 18% (no FOLFOX) to 38% (6 cycles FOLFOX) (P=0.0036)

				Non-randomised (sequential groups)		
Garcia-Aguilar et al (Garcia-Aguilar et al., 2020) OPRA	2020	324	Two exp't arms: LCCRT then FOLFOX 8 cycles or CAPOX 5 cycles Vs. FOLFOX 8 cycles or CAPOX 5 cycles then LCCRT		Disease free survival (DFS)	3-year DFS was 76% in both arms. 3-yr TME-free survival improved from 41% with induction chemo to 53% with consolidation chemo (P=0.01)
Conroy et al (Conroy et al., 2020) PRODIGE23	2020	461	LCCRT	FOLFIRINOX 6 cycles then LCCRT	DFS	3-yr DFS sig improved from 68.5% to 75.7% (P=0.034)
Bahadoer et al (Bahadoer et al., 2021) RAPIDO	2021	920	LCCRT	SCRT then FOLFOX 9 cycles or CAPOX 6 cycles	Disease Related Treatment Failure (DrTF)	3-yr D-RTF sig improved from 30.4% to 23.7% (p=0.019)
Jin et al (Jin et al., 2021)	2021	591	LCCRT	SCRT then CAPOX 4 cycles	DFS	3-yr DFS 62.3% (control) vs. 64.5% Non-inferiority confirmed (p<0.001)

Whilst improved tumour outcomes have been reported, TNT is associated with higher rates of toxicity in comparison with conventional neoadjuvant (chemo)radiotherapy. Therefore, TNT may not be appropriate for all patients presenting with LARCs and careful patient selection, acknowledging patient and tumour factors, should be considered.

Garcia-Aguilar (Garcia-Aguilar et al., 2015) treated 292 patients with increasing duration of chemotherapy after LCCRT. With LCCRT alone, the pCR rate was 18% compared with 38% when patients received an additional 3 months of chemotherapy (p = 0.0036). The RAPIDO trial (Bahadoer et al., 2021) assessed whether the sequencing of treatment, and delivery of chemotherapy in the neoadjuvant period could impact rates of disease related treatment failure (DrTF). 920 patients were randomised to receive either standard treatment: LCCRT, surgery and adjuvant chemotherapy or experimental treatment: SCRT and neoadjuvant chemotherapy prior to surgery. An improvement in rates of DrTF was seen in the experimental arm – (30.4% vs 23.7%

DrTF at 3 years). In addition, a higher rate of pCR was achieved in the experimental arm compared with standard arm (27.7% vs 13.8%, p = 0.001). However, higher rates of toxicity were reported in the experimental arm although surgical complication rates e.g., infection and anastomotic leaks were similar.

A recent meta-analysis included eight phase II/III RCTs involving 2,196 patients with locally advanced rectal cancer (Liu et al., 2021). The primary analysis demonstrated a statistically significant improvement in the pCR rate for TNT compared to standard treatment (odds ratio, 1.77; 95% confidence interval [CI], 1.28–2.45; p = .0005). TNT also showed improvements in DFS compared with standard chemoradiotherapy and potential improvement in OS (hazard ratio [HR], 0.83; 95% CI, 0.72–0.96; p = .03 and HR, 0.88; 95% CI, 0.74–1.05; p = .15). In addition, TNT treatment showed significant efficacy in reducing the risk of distant metastasis (HR, 0.81; 95% CI, 0.68–0.95; p = .012).

1.5 ORGAN PRESERVATION (OP) IN RECTAL CANCER

Whilst organ-preservation (OP) in the form of non-surgical CRT has become SoC in a range of other Locally Advanced (LA) cancers (anal, head and neck, cervical and lung), there has been a lack of practice-defining RCTs in LARC addressing the question of OP. Habr-Gama initially reported this approach for rectal cancer in 2006 (Habr-Gama et al., 2006). This single centre experience, however, had limited impact. A later publication of a larger series reported 34% long-term OP in all treated patients (Habr-Gama et al., 2014). Nearly all (93%) local tumour re-growths were amenable to salvage surgery. For a long time, the lack of confirmatory and multicentre data inhibited the adoption of this approach. There is now a recent but growing body of published retrospective evidence that supports the oncological safety of this concept. This includes a large series of patients with cCR from Beets' group (Maas et al., 2011; Martens et al., 2016; Hupkens et al., 2018), with encouragingly low regrowth rates (14%), three-year OS (97%), and distant metastasis-free survival (97%). Of the 14% of patients who developed tumour regrowth, this occurred within 25 months of achieving cCR and was surgically salvageable with standard TME. The second report (Hupkens et al., 2018) included an additional 68 patients who had a 'near' cCR at 3 months, of whom 90% then proceeded to a full cCR on re-assessment 6–12 weeks later.

Within the North West UK OnCoRe (Oncological outcomes after clinical Complete Response in patients with rectal cancer) project, 259 patients with non-metastatic rectal cancer who completed pre-operative CRT were monitored in a W&W surveillance programme (Renehan et al., 2016). With a median follow-up of 33 months, there were 38 (31%) intraluminal re-growths (3-year actuarial rate: 35%). 86% of intra-luminal re-growths were salvaged. After propensity score matching, there were no deleterious effects on non-intraluminal disease-free survival (niDFS) for patients treated by W&W versus conventional SR (hazard ratio (HR), 95% confidence intervals: 0.516; 0.226 to 1.174). However, there was a significant improvement in 3-year colostomy-free

survival (CFS) rates for patients treated by W&W versus SR: 87% and 41% (HR: 0.299, 95% CI 0.163–0.548).

A systematic review of 575 patients from 15 studies (Sammour et al., 2017) of patients with cCR showed a pooled local regrowth rate of 21% at a mean of 16 months, of which 93% were surgically salvageable. The colostomy rate was 12%, disease-free survival (DFS) 83% and OS 92%. The International Watch and Wait Database (IWWD) international multicentre registry study was recently published in the Lancet (van der Valk et al., 2018). It comprised 880 registered patients with cCR. 25% exhibited local regrowth with 70% of the events occurring within 12 months and 30% >12-24 months measured from the time of cCR definition (i.e., up to 30 months from the start of CRT). 97% were located in the bowel wall and were surgically salvageable. A minority of patients (8%) developed distant metastases. 5-year disease specific survival was 94% and OS 85%.

These data support the oncological safety of an OP strategy in patients with cCR and a high rate of successful salvage surgery for the minority with intraluminal regrowth. In view of the morbidity associated with surgery and impact upon QoL it may be appropriate to offer cCR patients a surveillance programme and deferral of surgery. Although TME surgery remains the standard of care in the UK, offering an active surveillance programme to patients who achieve a cCR with neoadjuvant therapy, is becoming more commonplace in the UK. However, randomised data on efficacy and morbidity are lacking. It is important that this is policy is assessed through RCTs, including those that determine if OP rates can be increased by treatment intensification.

1.6 ASSESSMENT OF CLINICAL COMPLETE RESPONSE (CCR)

Following neoadjuvant treatment, a rectal cancer is reassessed clinically, radiologically and endoscopically to determine response to treatment. In some cases, an excellent response may be achieved with no evidence of residual disease. This is described as a Clinical Complete Response (cCR) and it has been suggested in a recent consensus statement that the following criteria should be fulfilled (Fokas et al., 2021):

- Digital rectal examination (DRE): no palpable tumour material present.
- Flexible sigmoidoscopy: No evidence of either mucosal tumour or submucosal swelling on white light endoscopy. A flat white scar remains with or without telangiectasia. A small residual erythematous mucosal ulcer is permitted. A biopsy is not required to confirm cCR and should not be performed if the other cCR parameters fulfilled.
- MRI: no tumour seen or residual fibrosis only (with limited signal on diffusion-weighted imaging), residual wall thickening due to oedema may be seen, no suspicious lymph nodes.

This approach has been standardised by Beets' group, with a sensitivity of detecting a cCR of 71% (Maas et al., 2015; Nahas et al., 2016). Repeat biopsy is not used due to the risks of infection, poor healing and necrosis. The sensitivity is improved using a 'two-step' assessment approach at 3 and

then 6 months from start of CRT. This approach is now increasingly used (international consensus at World Rectal Cancer Conference 2017). This 'two-step' approach allows full maturation of cCR; 90% of patients with a 'near' cCR at 3 months will evolve into full cCR at 6 months (Hupkens et al., 2018). This group and others have moved away from the use of biopsies. In anal cancer, it has been reported that when clinical and imaging assessment was performed, the optimal time to determine cCR is at 6 months (Glynne-Jones et al., 2017).

A recent consensus statement (Fokas et al., 2021) supports the use of cCR as an endpoint for early phase studies focused on OP. It also advises not carrying out repeat biopsies owing to the risks of a false negative result and a lack of added diagnostic value.

Subsequent active surveillance will involve regular clinical, radiological and endoscopic observation, with a view to planning radical surgery if locoregional regrowth is identified. Some patients may continue to demonstrate a sustained cCR and avoid surgery – and stoma formation – completely.

MRI re-staging reveals post-neoadjuvant therapy that there is a marked reduction in both number and size of benign and malignant lymph nodes (Koh et al., 2008; Heijnen et al., 2016). There is a correlation of nodal involvement with T stage response. Persistent nodal involvement after neoadjuvant therapy is associated with an increased risk of distant metastases and (Dinaux et al., 2018). It has been found that ypN+ patients have significantly larger nodes (than ypN0 patients) both pre- and post-CRT, and that diagnostic accuracy of nodal involvement may be increased post-CRT compared to pre-treatment (Heijnen et al., 2016). The definition of cCR and uncertain cCR (see section ARTEMIS trial design overview and section 11.1 Primary Endpoint) requires consideration of both lymph node regression 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 (Fokas et al., 2021).

1.7 SAFETY OF INCREASED INTERVAL UNTIL SURGERY

Recent retrospective data supports the safety of a relatively short extended interval from LCCRT until surgery both in terms of post-operative morbidity and cancer outcomes. A systematic review including 13 studies with a total of 19,652 patients concluded that an interval of ≥ 8 weeks from the end of LCCRT is safe and efficacious because of higher pCR rates, without increasing complication rates or affecting survival rates (Du et al., 2018). A recent large population-based cohort study in 6268 Dutch patients examined the effect of the time interval from completion of LCCRT to TME surgery. It was found that compared with 7–8 weeks, longer time intervals up to 13–20 weeks between chemoradiation and TME are not associated with more postoperative complications or more positive resection margins (Couwenberg et al., 2019).

A further Dutch study was carried out in in 475 rectal cancer patients from 71 centres who received pre-operative LCCRT (Detering et al., 2019). This 'real-life' data, reflecting routine daily

practice showed substantial variability in the time interval to surgery. Surgery before or after 14 weeks from the start of CRT resulted in similar short and long-term outcomes. CRM involvement (9.7% vs. 15.9%, p = 0.145) did not significantly differ, thirty-day surgical complications were similar (20.1% vs. 23.1%, p = 0.943), and no significant differences were found for local and distant recurrence rates, DFS, and OS.

A further recent Dutch study examined a total of 124 patients who received neoadjuvant treatment: 46 (37%) underwent surgery for persistent disease; 78 (63%) with cCR entered a watch and wait programme (Nasir et al., 2019). Twenty-three developed regrowth and all underwent salvage surgery, while 55 remained under surveillance. The regrowth-deferred surgery group had significantly smaller tumours than the non-deferred surgery group (2.3 cm ± 2 vs 4.5 cm ± 3, p=0.002). Anastomotic leaks, 30-day morbidity, re-intervention and readmission rates were similar between the non-deferred and deferred surgery groups. In addition, pathological features and 3-year oncological outcomes were identical between the groups.

Although the above data is reassuring, prospective clinical trial data is needed to confirm the safety of delayed surgery and where the outcome for all patients is reported (i.e. where the denominator is all patients treated with the initial aim of OP).

1.8 FOLLOW-UP SCHEDULE FOR PATIENTS ACHIEVING A CCR

A broad consensus is that follow-up assessments for patients achieving a cCR should include intensive surveillance with DRE, sigmoidoscopy, and MRI in the first 2 years, and decreasing intensity in subsequent years (van der Valk et al., 2018). The three highest contributors to the International Watch and Wait Database (IWAWD) (Northwest UK, Sao Paolo and Maastricht/ Amsterdam) used follow-up assessment schedules similar to one another, with the Northwest UK schedule being used in the current ARTEMIS protocol. A similar schedule is supported by the recent consensus statement (Fokas et al., 2021).

1.9 PATIENT PERSPECTIVE ON ORGAN PRESERVATION (OP)

There is currently little information concerning the patient perspective on rectal OP. A recent German study (Gani et al., 2019) reported on 49 patients with locally advanced rectal cancer who were assessed on their willingness to participate in an OP study and their acceptance of the associated aspects such as intensified CRT protocols and the subsequent need for close follow-up assessments.

A total of 83% of patients said they would consider the deferral of surgery in case of a cCR. Three monthly follow-up assessments and a 25% local regrowth rate were considered acceptable by 95% and 94% respectively, whilst 41% would be willing to exchange cure rates for a non-operative treatment strategy. This is reassuring for a prospective study on CRT intensification strategies

aiming at OP. However, there is a need for prospective data on HRQoL on which to objectively base future patient discussion.

We have widely consulted with, surveyed, and responded to feedback from consumers from the earliest stage of the ARTEMIS concept and throughout its development. This includes the two patient and public involvement (PPIs) members on the ARTEMIS Trial Management Group (TMG), consumer representatives on the National Cancer Research Institute (NCRI) Colorectal Clinical Studies Group (CSG), Anorectal and Surgical Subgroups and Clinical and Translational Radiotherapy Research Working Group (CTRad), the 'Dragon's Den' at the annual NCRI conference and representatives of Bowel Cancer UK. The current proposal has uniformly strong support amongst these groups, with similar themes to those expressed in the study above (Gani et al., 2019), i.e. patients are willing to tolerate an increased gap between CRT and surgery if there is a chance of OP. One patient replied 'The possibility to avoid surgery, particularly in rectal cancers where permanent stoma is a frequent outcome, is a big persuader!'. In addition, patients are willing to contemplate increased side effects in exchange for the chance of OP but want as accurate information as possible on which to base decisions.

1.10 PATIENT REPORTED OUTCOMES (PROS) AND HEALTH RELATED QUALITY OF LIFE (HRQOL)

Radical surgery (total mesorectal excision; TME) is the gold standard treatment for rectal cancer. While radical surgery provides effective local tumour control, patients risk appreciable short-term morbidity and long-term bowel (including a permanent stoma), bladder and sexual dysfunction that can impair quality of life (QoL) (Gilbert et al., 2015; Wiltink et al., 2014; Andreyev et al., 2011) Increasingly, clinicians and patients are keen to pursue curative treatment options that aim to avoid radical surgery and to improve QoL (Currie et al., 2015). Multiple RCTs and general population cohorts have also found relatively high rates of long-term patient-reported bowel and sexual dysfunction following TME surgery; although generally worse toxicity and overall HRQOL is reported by patients treated with both (chemo)radiotherapy and TME and in patients with a stoma (Gilbert et al., 2015; Downing et al., 2019). The impact of pre-operative radiotherapy in addition to TME surgery on bowel and sexual function is well-documented in the Dutch TME trial, with detailed reporting of patient-reported outcomes (PROs) up to 14-years (Wiltink et al., 2014). However, very few prospective studies have reported longer-term toxicity rates or patient-reported outcomes (PROs) including health-related QoL (HRQOL) both in the acute and long-term setting following organ-preservation. A few small studies reporting PRO data have been carried out, suggesting patients' who achieve organ preservation following CRT have better PRO and QoL than those who have TME following CRT (Maas et al., 2011; Appelt et al., 2015; Hupkens et al., 2017). For example, in one study patients managed by a watch and wait approach had better PRO incontinence and bowel frequency scores than those surgically managed with a complete pathological response (Maas et al., 2011). In addition, few studies have reported to the quality detailed in CONSORT-PRO guidance, limiting interpretation and clinical relevance (Calvert et al., 2013).

In the 'International consensus recommendations on key outcome measures of organ preservation in rectal cancer' 30 international clinical experts in organ preservation were involved in a Delphi process to establish key outcome measures for clinical trials (Fokas et al., 2021). For PRO and QoL outcomes it was agreed that as well as QoL and function scales (overall QoL, physical/role/social/emotional function); there were 10 symptomatic toxicity items (bowel urgency, faecal incontinence, bowel frequency, diarrhoea, tenesmus, toilet dependency, night time bowel opening, urinary urgency, impotence and pain) selected as highest priority for inclusion. The panel agreed that a new score was needed specifically validated for use in organ preservation, including bowel, urinary and sexual dysfunction issues, noting that existing questionnaires (C30, CR29, LARS) failed to include all key issues.

1.11 AN0025 AND PELVIC RADIOTHERAPY

AN0025, previously E7046, is a selective inhibitor of the EP4 receptor and targets macrophages and immunosuppressive cells of myeloid lineage in the tumour microenvironment. AN0025 reverses prostaglandin E2 (PGE2)-mediated tumour promotion and immune suppression preclinical studies have shown potent antitumor activity with AN0025 combined with RT and animal model data suggested antitumor memory T-cell response development by the combination (Bao et al., 2016).

A multicentre, open-label, Phase 1b study in patients with poor prognosis locally advanced rectal cancer as defined by standard MRI has been conducted (Wyrwicz et al., 2019). This study enrolled patients into two groups, AN0025 in combination with Long Course Chemoradiotherapy (LCCRT), or Short Course Radiotherapy (SCRT) followed by chemotherapy. It closed in 2019. The dose escalation design comprised 2 dose levels, 250mg and 500mg once a day (QD) for both SCRT and LCCRT. Treatment duration was 10 weeks followed by surgery at week 14-16. Pre-surgery MRI was done at week 11-13. Primary objective was safety and tolerability of AN0025 + CRT.

Interim results were presented at European Society for Medical Oncology (ESMO) in 2019 (Wyrwicz et al., 2019) and the full paper has been submitted. 28 patients were enrolled. Median age was 59, 71% were male, 57% were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 57% with T stage T3c-T4b, and 61% were EMVI+. Overall, 19 (68%) patients had treatment-related AEs (TRAE), most commonly fatigue (28.6%), diarrhoea (14.3%), nausea (10.7%), decreased appetite (10.7%), headache (10.7%), and paraesthesia (10.7%). Only 2 patients experienced grade 3 TRAEs (diarrhoea and fatigue) and 1 patient had serious TRAEs (abdominal pain, vomiting, and fatigue). MRI tumour regression grade (mrTRG) 1-2 rate was 29% (21% and 36% in LCCRT and SCRT respectively). Clinical responses led to 5/13 patients (38%) managed by a watch-and-wait (W&W) approach.

In conclusion, AN0025 was well tolerated in combination with chemoradiation, and preliminary efficacy results were encouraging.

1.12 THE ARTEMIS TRIAL (AUGMENTING RADIOTHERAPY IN RECTAL CANCER TO MINIMISE INVASIVE SURGERY)

One of the emerging aims of rectal cancer radiotherapy is to achieve cCR and OP, and there is increasing interest in treatment intensification to facilitate this. TNT has helped to improve this treatment and there is emerging evidence that this is also able to increase OP (Garcia-Aguilar et al., 2020). Immunotherapy is rapidly changing the way we manage patients and the PRAER trial has shown encouraging results of increased response and improved pCR rate. The rationale for ARTEMIS is therefore to combine both the TNT and immunotherapy strategies to try to increase both SCRT and LCCRT efficacy and in turn OP in a single trial.

ARTEMIS is designed primarily to determine whether the addition of AN0025 to SCRT/LCCRT followed by FOLFOX/CAPOX chemotherapy improves the 6-month cCR rate with acceptable toxicity, compared with standard SCRT/LCCRT + FOLXFOX/CAPOX treatment, for patients with moderate to high-risk rectal cancer where OP is deemed an appropriate option and pre-operative radiotherapy is a standard treatment option.

We have strong support from our investigator surveys for the use of Intensity modulated radiotherapy (IMRT) within ARTEMIS, which facilitates the use of a simultaneous integrated boost (SIB) technique when the pelvic elective clinical target volume (CTV) receives 45Gy in 25 fractions over 5 weeks, and the smaller gross tumour volume (GTV) receives 50Gy in 25 fractions over 5 weeks. This dose fractionation was used in the international phase III RAPIDO trial (ISRCTN14240288). Delivering the dose of 45Gy to the larger CTV reduces potential acute and late morbidity.

ARTEMIS will use IMRT in both standard CRT and standard CRT + AN0025 treatment arms. This minimises acute radiotherapy related toxicity. Members of the ARTEMIS team have been involved in establishing a UK-wide radiotherapy SoC using IMRT.

2. TRIAL AIMS AND OBJECTIVES

2.1 AIM

The primary aim of ARTEMIS is to determine whether the addition of AN0025 to SCRT/LCCRT + FOLFOX/CAPOX improves clinical outcomes, with acceptable toxicity, compared with standard SCRT/LCCRT + FOLXFOX/CAPOX treatment, for patients with moderate to high-risk rectal cancer who are interested in organ preservation and where pre-operative chemoradiotherapy (CRT) or total neoadjuvant treatment (TNT) are standard treatment options.

2.2 PRIMARY OBJECTIVE

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. Please see Section 13.3 Primary Endpoint Analysis for further details on the primary objective analysis.

2.3 SECONDARY OBJECTIVES

To evaluate the impact of the addition of AN0025 to SCRT/LCCRT + FOLFOX/CAPOX on the following outcomes:

- Acute and late toxicity;
- Treatment compliance;
- Patient Reported Outcomes (PROs) and HRQoL – EORTC QLQ C30 and QLQ CR29 with additional items; LARS score; EQ-5D-5L);
- Surgical outcomes (including procedures and morbidity);
- Clinical, radiological and pathological response rates;
- Stoma rates;
- Locoregional regrowth following a cCR;
- Organ preservation;
- Organ preservation adapted disease-free survival;
- Metastasis- free survival;
- Overall survival.

Please see Section 13.4 Secondary Endpoint Analysis for further details about the secondary endpoint analysis.

3. ARTEMIS TRIAL DESIGN OVERVIEW

ARTEMIS is a phase II, multi-centre, open-label, randomised controlled trial using IMRT/VMAT/TomoTherapy, comparing radiotherapy (SCRT/LCCRT) followed by chemotherapy (FOLFOX/CAPOX), with or without the addition of AN0025 throughout treatment. Eligible patients will have moderate to high-risk rectal cancer where pre-operative chemoradiotherapy (CRT) or total neoadjuvant treatment (TNT) are standard treatment options and who are interested in organ preservation.

ARTEMIS uses the Sargent's three-outcome two-stage comparative design, including an interim analysis for futility. The trial will randomise 140 patients, from 15-20 UK radiotherapy sites, with a 1:1 allocation ratio to receive either SCRT/LCCRT + FOLFOX/CAPOX or SCRT/LCCRT + FOLFOX/CAPOX +AN0025. To ensure balance between the randomised treatment arms and radiotherapy subgroups, the participants will be stratified by radiotherapy regimen (SCRT vs LCCRT) and then by the minimisation factors T-stage, EMVI status and CRM status. The number of patients in SCRT vs LCCRT is expected to be 50/50 split, providing up to 35 patients for each treatment type in each arm. These proportions will be actively monitored with the potential to adapt inclusion to specific RT regimens. Long term endpoints will be measured up to 30 months from the start of treatment.

In both the control arm and intervention arm, radiotherapy using IMRT/VMAT/Tomotherapy will start at the beginning of week 1 and consists of a total of 25Gy in 5 fractions given once daily Monday-Friday over 1 week (SCRT) or 45 Gy (with SIB to GTV of 50 Gy) in 25 fractions delivered once daily Monday to Friday over 5 weeks (LCCRT) (Figures 3.1 & 3.2). Patients receiving LCCRT will also receive capecitabine (825 mg/m2) twice daily on the days of radiotherapy only. Investigators can choose whether to use SCRT or LCCRT on a patient-by-patient basis, declaring this pre-randomisation, and this will be incorporated into the randomisation process. Three weeks after the end of SCRT/LCCRT, chemotherapy will start, delivering 12 weeks of either FOLFOX (six 2-weekly cycles) or CAPOX (four 3-weekly cycles). Investigators will choose whether to use FOLFOX or CAPOX on a patient-by-patient basis, declaring this pre-randomisation.

Patients assigned to the intervention arm will start AN0025 two weeks before treatment at 500mg QD (once daily) continuously, which will then continue throughout radiotherapy and chemotherapy.

Participants who do not undergo surgery will have a response assessment via an MRI at 4 months from the start of RT. As per standard practice, a flexible sigmoidoscopy and further assessments may be deemed appropriate. If patients demonstrate tumour progression, no response or poor response at 4 months (defined as <50% reduction in tumour size on rectal endoscopy) or mrTRG 4 (minimal response) or mrTRG5 (no response), radical TME surgery should be considered and discussed at the colorectal MDT.

Patients will be assessed for response for the primary endpoint at 6 months from the start of radiotherapy, using trimodality assessment of DRE, pelvic MRI (if not undergone surgery) and rectal endoscopy. Those who have a clinical complete response (cCR) (see Section 11.1 Primary Endpoint) will undergo a programme of active surveillance, reserving surgery if disease subsequently progresses. Active surveillance will continue until 30 months post-start of radiotherapy. Patients with a definite incomplete response at 6 months will undergo salvage TME surgery.

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 in addition some small smooth mucosal nodules or minor mucosal abnormalities (Fokas et al., 2021). Such patients will be deemed to have an 'uncertain cCR' (ucCR). Patients with an ucCR at 6 months, will be considered for active surveillance. Those who are subsequently thought to have regrowth/residual disease in the opinion of the local MDT, will be considered for salvage TME surgery. Subsequent outcomes of these patients will be explored.

ARTEMIS secondary outcomes will be collected throughout trial treatment and during follow-up (at 4, 6, 9, 12, 24 and 30 months post-the start of radiotherapy).

Figure 3.1 ARTEMIS study flow chart short-course radiotherapy (SCRT) option

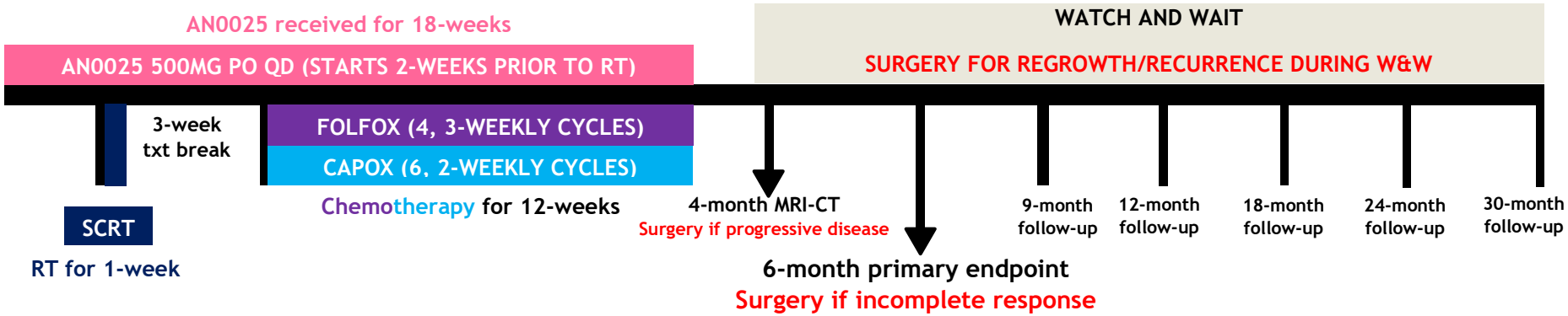
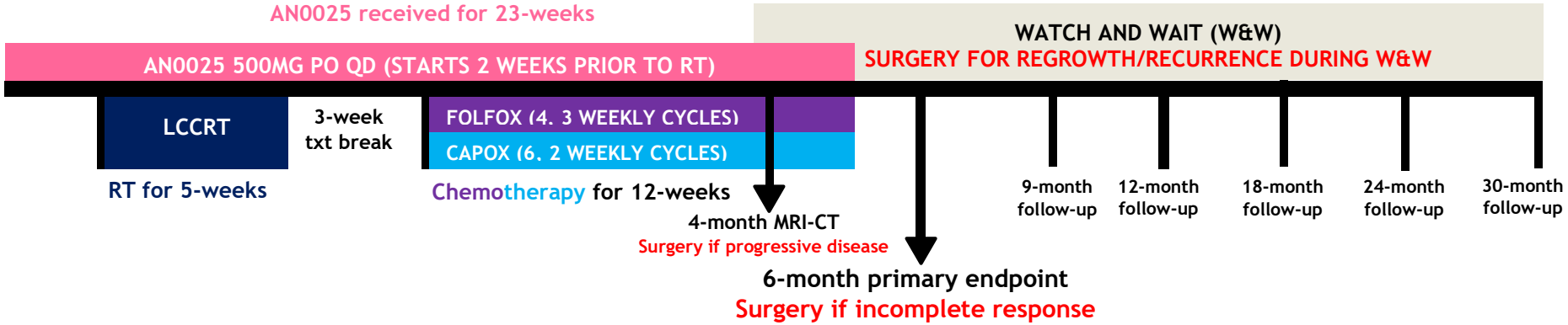


Figure 3.2 ARTEMIS study flow chart long-course chemoradiotherapy (LCCRT) option



AN0025: Administration starts 14 days before the first dose of radiotherapy. Subjects will be required to fast 2 hours before and 2 hours after the AN0025 dose. Treatment with AN0025 will be discontinued in case of disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or termination of the study programme. AN0025 is supplied as tablets in strengths of 125 mg.
SCRT: 25Gy in 5 daily fractions treating once per day on Monday-Friday over 1 week
LCCRT: 50Gy in 25 daily fractions treating once per day on Monday-Friday over 5 weeks; Concurrent Capecitabine 825 mg/m2 PO BID on days that RT is given.
FOLFOX: Oxaliplatin 85mg/m^2 IV over 2 hours, day 1; Folinic acid 350mg IV over 2 hours, day 1; 5-Fluorouracil 400mg/m^2 IV bolus over 10-15 minutes, day 1; 5-Fluorouracil 2400mg/m^2 IV infusion over 46-48 hours delivered either peripherally or via a central catheter, starting on day 1, two week cycle

4. ELIGIBILITY

Patients meeting all of the inclusion criteria and none of the exclusion criteria will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted. Further information related to patients with DPD deficiency can be found in section Patients with DPD Deficiency.

4.1 INCLUSION CRITERIA

- Patients age ≥18 years old;
- Eastern Cooperative Oncology Group (ECOG) PS 0 or 1;
- Capable of informed consent;
- Able to fully understand trial treatment enough to provide informed consent;
- Biopsy-proven rectal adenocarcinoma;
- 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) OR
    - low tumours with involvement of the anal intersphincteric plane or with levator involvement.

Within 14 days pre-randomisation the following must be met:

- Estimated creatinine clearance ≥50 mls/min (using a validated creatinine clearance calculation e.g. Cockcroft-Gault or Wright formula);
- Haemoglobin ≥9.0g/dL;
- Neutrophils >1.5 x 10^9/L;
- Platelets >100 x 10^9/L;
- Adequate blood coagulation function as evidenced by a prothrombin time (PT) ≤1.5 x normal;
- Alkaline phosphatase (ALP) ≤2.5 × upper limit of normal (ULN); Serum transaminase (either alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) ≤2.5 × ULN; total bilirubin ≤1.5 × ULN except for unconjugated hyperbilirubinemia or Gilbert's syndrome.

4.2 EXCLUSION CRITERIA

- Unequivocal distant metastatic disease;

- Previous pelvic radiotherapy;
- MRI defined predominantly mucinous tumour i.e. more than one third of tumour volume assessed to consist of mucin;
- Biopsy-proven neuroendocrine tumour;
- Definite MRI pelvic side wall lymph node involvement or, invasion of adjacent organ or, ischio-rectal fossa involvement;
- 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));
- Defunctioning colostomy or ileostomy;
- Prior antineoplastic therapy for rectal cancer;
- Pregnant or breast feeding; or of child bearing potential and unwilling to use highly effective contraceptive methods;
- On-treatment participation in an interventional clinical study 30 days prior to randomisation;
- Other concomitant antineoplastic therapy;
- Inability to comply with taking oral capecitabine/AN0025 medication;
- Active, uncontrolled infections;
- Active, disseminated coagulation disorder;
- Clinically significant cardiovascular disease ≤ 6 months before randomisation i.e. New York Heart Association (NYHA) Functional Capacity III or IV';
- Prior invasive malignancy unless disease free >3 years (excluding basal cell carcinoma of the skin or carcinoma in situ);
- Known allergic reactions to either oxaliplatin or AN0025 or both capecitabine and 5-FU;
- On medication with inhibitors of dihydropyrimidine dehydrogenase (DPD);
- Known complete DPD deficiency
- Psychosocial issues which may affect treatment compliance;
- Prolongation of corrected QT (QTc) interval to ≥480 msec when electrolyte balance is normal;
- 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;
- 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);

- Presently receiving 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;
- Presently receiving other investigational drugs.

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:

- Non-steroidal anti-inflammatory drugs (NSAIDs);
- Aspirin at doses of higher than 325 mg daily;
- Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs);
- Uridine'5 diphospho-glucuronosyl transferase (UGT) inducers or inhibitors (atazanavir, probenecid, valproic acid, mefenamic acid, quinidine);
- Anticoagulation with anti Xa agents (ie: 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.

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 FOLFOX 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.

4.3 BIRTH CONTROL

A person is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A person is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

For patients of child-bearing potential or for fertile patients with partners who are of child-bearing potential:

During LCCRT/SCRT, then through CAPX/FOLFOX, and then extending for six weeks after CAPOX/FOLFOX completion, a barrier method of contraception is required (i.e., **condoms or the cap**) to prevent transmission of chemotherapy contaminated bodily fluids and to prevent pregnancy. This may be used in conjunction with other highly effective methods of contraception.

Highly effective contraception is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Methods of contraception that are considered highly effective for the purposes of this trial include:

- Copper intra-uterine device (copper IUD)
- Levonorgestrel-releasing intrauterine system (LNG-IUS)
- Progestogen-only hormone contraception (oral, injectable or implantable) associated with inhibition of ovulation
- Combined hormonal contraception(pills, patches or vaginal ring) associated with inhibition of ovulation
- Bilateral tubal ligation (of patient or partner)
- Vasectomy (of patient or partner)
- Sexual abstinence

For patients receiving implants, combined hormonal contraceptives and progestogen-only pills, significant interactions with any concurrent medication should be determined. Alternative methods of contraception must be used if a significant interaction exists.

Sexual abstinence is a highly effective contraceptive method only when the patient refrains from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

For male participants, the duration of highly effective contraception must be during treatment and for 6 months following the last dose of oxaliplatin and fluorouracil, and during treatment and for 3 months after the last dose of capecitabine. Female participants are required to use a highly effective method of contraception during treatment and for 4 months following the last dose of oxaliplatin, and during treatment and for 6 months after the last dose of fluorouracil and capecitabine.

Participants must agree to use a highly effective contraceptive measure for the duration of the treatment period and for at least 5 half-lives after the last dose of the study drug (Pharmacokinetic data obtained from 27 subjects in the dose escalation part of FIH study, E7046-G000-101/monotherapy, showed that maximum plasma concentrations of AN0025 were achieved 2.00 to 4.00 hours following a single oral dose (C1D1), and 0.525 to 4.68 hours at steady state (C1D8) over the range of 125 to 750 mg. AN0025 exposure was dose proportional up to 500 mg dose, with no incremental increase at the 750 mg dose. Estimated geometric mean terminal half-life for AN0025 at steady state was approximately 6 to 11 hours, resulting in an approximately 3- to 7-fold (Cmax) and 2- to 3-fold (AUC) accumulation following multiple dosing. Overall, AN0025 presents a normal PK profile over the dose range tested). Participants of child-bearing potential or fertile

patients with partners who are of child-bearing potential, must therefore use an effective contraceptive for one week after the last dose of AN0025. Please see most recent approved version of AN0025 Investigator Brochure for further details.

For patients who are sexually active but who are not of child-bearing potential or for patients who are sexually active with persons who are not of child-bearing potential:

During chemoradiotherapy and for six weeks after, a barrier method of contraception is recommended (i.e., condoms or the cap) to prevent transmission of chemotherapy contaminated bodily fluids.

4.4 PREGNANCY TESTING

All persons of child-bearing potential must be pregnancy screened prior to entering the ARTEMIS trial and before signing the main informed consent form. They should provide informed consent on the eligibility pregnancy screening Patient Information Sheet Informed Consent Form (PISICF) to allow pregnancy screening. They should provide a negative pregnancy result and agree to continue to practice methods of contraception that are considered highly effective for the duration of the trial treatment and for the recommended time post-end of treatment. They must have a negative pregnancy test within 7 days prior to randomisation. A urine-based test is sufficient unless it is within 10 days of the patient's last menstrual period, when a urine-based test is unreliable. In this situation, a serum test should be performed.

4.5 PRIOR AND CONCURRENT PARTICIPATION IN OTHER CLINICAL TRIALS

Participation in therapeutic clinical trials is not permitted up to the 6-month primary endpoint assessment. However, participation in non-therapeutic registry studies or questionnaire-based studies is permitted. Questions about potential clinical trials can be addressed to the Chief Investigators (CIs) via Leeds Clinical Trials Research Unit (CTRU).

5. PARTICIPATING SITES AND INVESTIGATORS

5.1 PARTICIPATING SITES

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework (RGF) and amendments
- Data collection requirements, including adherence to paper (where applicable) and electronic case report form (eCRF) submission timelines as per section eCRFs
- Monitoring requirements as outlined in section 14 Trial Monitoring

5.2 PRINCIPAL INVESTIGATORS AND CO-INVESTIGATORS

Sites must have an appropriate Principal Investigator (PI) authorised by the site and ethics committee to lead and coordinate the work of the trial on behalf of the site.

Other investigators at a site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating rectal cancer.

5.3 TRAINING REQUIREMENTS FOR SITE STAFF

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site authorised personnel log (APL).

Curricula vitae (CVs) for all staff must be kept up-to-date, signed, dated and copies (or statement of their location) held in the Investigator Site File (ISF) or relevant Pharmacy Site File (PSF) held at site. An up-to-date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation.

Good Clinical Practice (GCP) training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation.

5.4 RADIOTHERAPY QUALITY ASSURANCE

The radiotherapy quality assurance (RTQA) programme will be implemented by the NCRI Radiotherapy Trials Quality Assurance (RTTQA) group to ensure treatment is planned and delivered according to the trial protocol. Full details of the RTTQA requirements are provided in the ARTEMIS Radiotherapy Guidelines.

5.5 SITE INITIATION

Before a site is activated, the CTRU trial team will arrange a site initiation. The site initiation will be an electronic process and an audio-visual recorded link with the initiation presentation will be sent to the site.

The audio-visual recorded link will come with the site initiation training log, which will need to be completed. Best practice would include other related trial specific staff who work on the trial, as a minimum the PI, pharmacist, radiotherapy physicist, research radiographer and research nurse must watch the site initiation video recorded link and slide presentation.

The site initiation audio-visual recorded link and presentation will act as the site initiation and will cover all areas of the trial and management at site.

The following areas will be covered:

- Trial overview and management
- Data collection and process
- Safety reporting
- Essential documentation required for trial

Trial specific staff are required to go through the recorded link and watch the site initiation presentations, then record on the site initiation training log that they have completed the site initiation training.

A site cannot open to ARTEMIS without the site initiation, the site staff assigned to work on the ARTEMIS trial must watch the site initiation video recorded presentation, complete the site initiation training log, and return this to the ARTEMIS team. The signed initiation training log must be returned to artemis@leeds.ac.uk. Once all documentation is returned, an email confirming that the site initiation has been successful will be issued.

Any questions or queries regarding the trial can also be sent via email to the artemis@leeds.ac.uk inbox or a meeting can be arranged to discuss any trial specific related queries before confirmation that the site initiation has been successfully completed.

The video recorded site initiation presentation slides can be used as a further training aid for new starters who will work on the study to ensure training standardisation. These staff will need to

confirm in the training log contained within the ISF that they have watched the audio-visual recorded site initiation presentation slides.

A copy of the site initiation presentations will also be provided for reference in the ISF.

5.6 ESSENTIAL DOCUMENTATION

The following documentation must be submitted by the site to the CTRU prior to site activation:

- All relevant institutional approvals (e.g., local NHS permission)
- A completed APL log for both trial and pharmacy that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed Site Contacts Form (with contact information for the PI, co-investigators, research/trial, pharmacy, radiography, and pathology staff)
- A copy of the PI's current CV that is signed and dated
- A copy of PI's current GCP training certificate
- Signed PI declaration
- Radiotherapy Quality Assurance approval
- A signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution
- Site Initiation Training Log

To minimise additional work in multiple sites opening, centres are asked wherever possible, to make every effort to manage patients for trial purposes on one central site (usually the radiotherapy site). Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites, which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

5.7 SITE ACTIVATION

Once the CTRU trial team has received all the required essential documentation, the site has received their ISF and the site has been initiated and the necessary documentation has been sent to the CTRU, a site activation email will be issued to the PI and other research staff by CTRU.

Sites must not approach any potential patients until they have received an activation email from CTRU.

6. CONSENT, RECRUITMENT AND RANDOMISATION

6.1 RECRUITMENT SETTING

Participants will be recruited to the trial from 15-20 UK sites. Research sites will be required to have obtained local management approval, completed and passed all the required quality assurance checks and undertaken a site initiation with the CTRU prior to the start of recruitment. Participants may be identified via referrals from local hospitals, MDTs or distant referrals for clinical trials not available locally.

Centres will be identified via a feasibility assessment to determine the most appropriate to participate in the trial. Research centres will be required to confirm capacity and capability and undertake site initiation training (see section Site initiation) prior to the start of recruitment into the trial.

6.2 RECRUITMENT AND INFORMED CONSENT

Patients will be approached for possible recruitment and decision to treat. Suitability for inclusion into ARTEMIS will be assessed according to the eligibility criteria for the trial.

A verbal explanation of the trial and the appropriate Patient Information Sheet (PIS) will be provided by the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial.

Following information provision, patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The formal assessment of eligibility and informed consent may only be obtained by the PI or an appropriate medically qualified doctor. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki. They must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial APL. The PI retains overall responsibility for the informed consent of participants at their research site.

Full informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the PIS and Consent Form are used
- Checking that information on the Consent Form is complete and eligible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e., information given, consent signed, etc.)

Following randomisation:

- Adding the patient trial number to the consent form and making sufficient copies and filing the original consent form in the ISF and a copy in the patient's medical notes
- Giving the patient a copy of their signed Consent Form, PIS and patient diary
- Sending a copy of the signed consent form to CTRU in line with the terms of the ethically approved consent form.
- The participant will be provided with a local contact point where he/she may obtain further information about the trial

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

The right of the patient to refuse consent without giving reasons will be respected. Consenting participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

The responsibility for prescription and treatment with radiotherapy ultimately remains with the PI.

After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated.

As MR imaging and sigmoidoscopy partly define the primary end point, MRI data may be collected retrospectively on all patients to confirm response reporting at local sites. This will be sent to the

CTRU via the Secure File Transfer Service (SFTS). Similarly sigmoidoscopic images may be collected on all patients retrospectively for confirmation of response reporting at local sites.

At trial entry patients will thus be consented for collection of these images in the future.

'Real time' central review of MRIs and sigmoidoscopic images will not be carried out within ARTEMIS.

6.3 LOSS OF CAPACITY FOLLOWING INFORMED CONSENT

Loss of mental capacity of a participant after giving informed consent for this trial is expected to be a rare occurrence. Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained may continue with protocol treatment and assessments in consultation with the PI and participant's carer / family if this is deemed in the participant's best interests. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

6.4 ELIGIBILITY SCREENING

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements, participating research sites will be required to complete a non-randomisation and screening log for all patients presenting with moderate to high risk rectal cancer and screened for eligibility for the ARTEMIS trial. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Anonymised information will be collected including:

- Date screened
- Patient demographics (e.g., age, sex, ethnicity)
- The reason for non-randomisation:
    - The reason not approached, or
    - The reason not eligible for trial participation, or
    - The reason declined if eligible.

However, the right of the patient to refuse consent without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU. Once eligibility has been confirmed, participants can then be randomised.

6.5 ELIGIBILITY PROCESS

The following assessments must be carried out prior to randomisation in order to establish eligibility (see section 4 Eligibility above for full eligibility criteria):

- Medical review (including medical history, physical examination, electrocardiogram (ECG) and date of biopsy proving rectal adenocarcinoma)
- Pre-treatment Imaging/Disease assessment (Pelvic MRI, computerised tomography (CT) scan of thorax, abdomen and pelvis, DRE and flexible sigmoidoscopy)
- Baseline assessments (Haematology, Biochemistry, carcinoembryonic antigen (CEA), DPD testing and baseline adverse events)
- Pregnancy test for patients of childbearing potential (those not post-menopausal or surgically sterile)

Informed consent must be obtained prior to undertaking any trial-specific procedures, including non-routine eligibility assessments.

6.6 RANDOMISATION

Written informed consent for entry into the trial must be obtained and eligibility must be confirmed prior to randomisation.

6.7 RANDOMISATION PROCESS

Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by Leeds CTRU. Patients will be randomised on a 1:1 basis to receive SCRT/LCCRT+FOLFOX/CAPOX either with or without AN0025.

The participant will first be stratified by planned radiotherapy regimen (SCRT vs LCCRT)

Within each of these strata, a computer-generated minimisation programme that incorporates a random element will be used to ensure the treatment groups are well-balanced for the following, details of which will be required at randomisation:

- T-stage (≤T3b vs ≥T3c)
- EMVI status (+/-)
- CRM (threatened/involved/breached vs clear)

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system, which can be accessed via the web. Authorisation codes and personal identification numbers (PINs), provided by the CTRU, will be required to access the randomisation system.

The following information will be required at randomisation:

- Site code (assigned by CTRU) of the research site
- Participant details, including initials and date of birth
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (as specified above)
- Confirmation that baseline HRQoL have been completed (for participants who provided consent for this)

Once randomisation is complete, the system will allocate participants a unique 5-digit trial number.

24hour Randomisation:

Web: https://lictr.leeds.ac.uk/webrand/

Please ensure that you have completed the following electronic case report forms (eCRFs) immediately after randomisation:

- **Consent Form**
- **Eligibility Checklist**
- **Baseline Assessment**
- **Randomisation**

A copy of the consent form should also be sent via CTRU's secure file transfer service and the paper based HRQoL baseline questionnaire must be sent to the CTRU immediately after randomisation

Confirmation of randomisation, including details of treatment allocation, will be emailed automatically to the PI, research team and pharmacy department.

Following randomisation, a paper F50 Contact Details CRF should be completed and sent to CTRU via the SFTS, to confirm the patient's preferred method of questionnaire administration and completion after randomisation. Applicable contact details, email address/mobile phone number will be collected on the F50 Contact Details CRF as appropriate.

7. TRIAL TREATMENTS

7.1 TREATMENT SCHEDULES

7.1.1 Treatment overview

Eligible patients will be randomised 1:1 to receive either:

Control: SCRT or LCCRT (investigator choice to be declared prior to randomisation on a patient-by-patient basis), then a 3 week gap, then 12 weeks FOLFOX or CAPOX (investigator choice to be declared prior to randomisation on an individual patient basis) (

Table 8.1 MRI **Tumour regression grading (mrTRG) scores on post-treatment MRI**

).

Or:

Intervention: SCRT or LCCRT (investigator choice to be declared prior to randomisation on a patient-by-patient basis), then a 3 week gap, then 12 weeks FOLFOX or CAPOX (investigator choice to be declared prior to randomisation on a patient by patient basis) plus AN0025 starting 2 weeks before RT and continuing daily throughout treatment including FOLFOX/CAPOX (Tables 8.3 & 8.4).

Further details of treatment schedules are given below (please see information at the end of this section for reduced dosing for patients with a partial DPD deficiency).

7.1.2 Radiotherapy options (control arm and intervention arm):

SCRT: IMRT/VMAT/TomoTherapy 25Gy over 5 days i.e., 5 fractions of 5Gy delivered once per day on consecutive weekdays (Monday to Friday).

Or:

LCCRT: IMRT/VMAT/TomoTherapy 45Gy 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.

7.1.3 Chemotherapy options (control arm and intervention arm):

FOLFOX chemotherapy details:

- Oxaliplatin: 85mg/m^2, IV over 2 hours, day 1.
- Folinic acid: 350mg flat dose, IV over 2 hours, day 1 (this can be given concurrently with the oxaliplatin).
- Fluorouracil bolus: 400mg/m^2 IV over 10-15 minutes, day 1
- Fluorouracil infusion: 2400mg/m^2, as a continuous IV infusion (via central line or peripheral line) over 46 hours or 48 hours (as per local practice) starting on day 1

Each cycle will be repeated every 2 weeks. Patients will receive a maximum of 6 cycles.

Or:

CAPOX chemotherapy details:

- Oxaliplatin: 130mg/m^2, IV over 2 hours, day 1.
- Capecitabine 1000 mg/m^2 BID to be taken daily days 1-14

Each cycle will be repeated every three weeks for a maximum of 4 cycles.

7.1.4 AN0025

Patients receiving the investigational medicinal product (IMP) AN0025 on the intervention ARM B will take oral AN0025 at 500mg once daily continuously (as four 125mg tablets) commencing 2 weeks prior to the start of SCRT/LCCRT for a total of 18 weeks (SCRT option) or 22 weeks (LCCRT option). If there is a delay of more than 3 weeks between completion of SCRT/LCCRT and starting CAPOX/FOLFOX then this can be extended by up to a week i.e., 19 weeks total and 23 weeks total respectively: see section General Management of Acute Toxicities.

Table 7.1 Control Arm short-course radiotherapy (SCRT) option

WEEK	**1**							**2-4**	**5**
Day*	1	2	3	4	5	6	7	3 week gap	
Radiotherapy	●	●	●	●	●				
FOLFOX or CAPOX									● Start day 1 week 5 and then repeat every 2 weeks for 6 cycles total (FOLFOX) or repeat every 3 weeks for 4 cycles total (CAPOX)

Table 7.2 Control Arm long-course chemoradiotherapy (LCCRT) option

WEEK	**1**							**2**						**3**						**4**						**5**						**6-8**	**9**
Day*	1							8						15						22						29						3 week gap	
Radio-therapy	●	●	●	●	●			●	●	●	●	●			●	●	●	●	●			●	●	●	●	●			●	●	●	●	●				
Capecita-bine	●	●	●	●	●			●	●	●	●	●			●	●	●	●	●			●	●	●	●	●			●	●	●	●	●				
FOLFOX or CAPOX																																		● Start day 1 week 9 and then repeat every 2 weeks for 6 cycles total (FOLFOX) or repeat every 3 weeks for 4 cycles total (CAPOX)

Table 7.3 Intervention Arm SCRT option

WEEK	**-2**	**-1**	**1**							**2-4**	**5**
Day*			1	2	3	4	5	6	7	3-week gap	
Radiotherapy			•	•	•	•	•				
FOLFOX or CAPOX											• Start day 1 week 4 and then repeat every 2 weeks for 6 cycles total (FOLFOX) or repeat every 3 weeks for 4 cycles total (CAPOX)
AN0025	• Start AN0025 14 days prior to SCRT and continue at 500mg orally once daily seven days per week for 18 weeks total										

Table 7.4 Intervention Arm LCCRT option

WEEK	**-2**	**-1**	**1**							**2**							**3**							**4**							**5**							**6-8**	**9**
Day*			1							8							15							22							29							3-week gap	
Radio-therapy			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•				
Capecita-bine			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•				
FOLFOX or CAPOX																																						• Start day 1 week 9 and then repeat every 2 weeks for 6 cycles total (FOLFOX) or repeat every 3 weeks for 4 cycles total (CAPOX)
AN0025	• Start AN0025 14 days prior to LCCRT and continue at 500mg orally once daily seven days per week for 22 weeks total																																						

*Treatment timelines are for illustration purposes only; RT can start any day of the week.

7.1.5 Supportive medications (capecitabine/FOLFOX/CAPOX/AN0025)

Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 7.5 mg/day of prednisolone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers should not be given concomitantly, or used for premedication. The following are allowed exceptions:

- Use prior to imaging procedures in patients with contrast allergies
- Short-term premedication for patients receiving combination chemotherapy agents, in which the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions
- Use for palliative treatment of oncologic emergencies
- Use of inhaled, topical, and intranasal corticosteroids
- A temporary period of steroids can be allowed if clinically indicated and considered to be essential for the management of adverse events experienced by the patient (e.g., chronic obstructive pulmonary disease, nausea, etc.).
- Pre and post-medication as prophylaxis for nausea and vomiting for FOLFOX and CAPOX chemotherapy is recommended as per local protocols except for the use of steroids as a post-chemotherapy anti-emetic treatment. Investigators should attempt to limit the use of steroids for prevention of chemotherapy induced nausea and vomiting after day 1 of each cycle. Dexamethasone IV as antiemetic prophylaxis, as per local protocols, prior to FOLFOX/CAPOX administration is permitted.

For individual patients, where local vein pain is a problem during infusion of FOLFOX, supportive interventions, such as increasing infusion times or “piggy-backing” chemotherapy with glucose infusions, can be instigated as per local protocols.

Supportive medications, such as anti-diarrhoeal therapy, treatment for mucositis, skin emollients and granulocyte-colony stimulating factors (G-CSFs) may be administered as per local protocols for managing radiotherapy and chemotherapy toxicities, including those for capecitabine toxicities.

The use of calcium and magnesium infusions during oxaliplatin administration is permitted if this is local practice to do so.

Patients should receive full supportive care during and after the administration of immunotherapy (AN0025) or chemotherapy. Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patients, including side effects from trial treatments or disease progression.

Anaphylaxis precautions should be taken during administration of study medication as per local practice.

7.1.6 Stock and funding for capecitabine, oxaliplatin, fluorouracil and folinic acid

Oxaliplatin, fluorouracil, capecitabine and folinic acid for use in this trial should be taken from usual pharmacy stock; there is no provision for funding, reimbursement or discounted stock.

7.1.7 Dispensing, Accountability and Administration: capecitabine, fluorouracil (5FU), folinic acid and oxaliplatin

Chemotherapy doses may be recalculated every cycle during treatment if it is local practice to do so e.g., automatic updates by electronic prescribing systems. Where it is not local practice to recalculate every cycle, the doses must be recalculated if the patient's weight changes by greater than or equal to 10% from baseline. It is recommended that weight is assessed within 72 hours of day 1 for each cycle.

Body Surface Area (BSA) capping is not recommended but is permitted as per standard practice. BSA may be calculated as per local standard practice.

Treatment on day 1 for FOLFOX chemotherapy may be administered up to 48 hours before or after the scheduled day 1 for administrative reasons. Likewise, treatment with AN0025, after the initial cycle, may be administered up to 48 hours before or after the scheduled treatment day for administrative reasons.

Dose banding (and use of pre-made infusion bags) is permitted for all drugs taken from hospital's own stock where it is local practice to do so and this must be notified to the sponsor at the time of initiation.

As FOLFOX is generally given over 2 days we would suggest that either all drugs (5-fluorouracil, folinic acid and oxaliplatin) be administered within a 3 day window, or that there is no more than 24 hours delay between drugs (with exceptions to this at the discretion of the PI). Toxicity management guidelines should be in place to manage toxicity related to either drug and dose modifications/discontinuation applied accordingly.

7.1.8 Trial treatment and compliance recording

During the planned visits, compliance checks of the subject's diary and tablet count and will be used to inform the completion of the CRFs and treatment compliance for capecitabine, FOLFOX, CAPOX and AN0025 will be performed. A subject diary will be issued to collect daily recording of the oral medications. Tablet counts of trial oral medications for patients receiving chemoradiotherapy will be performed and recorded for each trial visit to assess compliance. Patients should be advised to return empty, and part used packs to pharmacy at their next trial visit.

Reasons for any dose delays, dose reductions and dose omissions of trial drugs should be documented in the appropriate section of the eCRF and in the patient's medical records.

7.1.9 Concomitant therapy recording

All concomitant therapy taken at any point from 4 weeks before randomisation up to and including the end of treatment visit must be documented in the patient's medical records along with dose, frequency and therapeutic indication.

7.1.10 Prohibited therapy/medications

Use of the following concomitant therapy or medication is prohibited. Details of the administration of any prohibited therapies will be collected on the trial eCRFs and must be reported as a protocol violation.

Warfarin

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 FOLFOX 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.

Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Formal drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Allopurinol

Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

Clozapine

Clozapine prohibited due to the increased risk of agranulocytosis with fluorouracil.

Folic acid and folinic acid

Folic acid and folinic acid may increase toxicity and therefore should not be given (with the exception of folinic acid as part of the FOLFOX chemotherapy regimen).

Immunosuppressants

Immunosuppressants (including methotrexate, azathioprine, and tumor necrosis factor-α blockers) and steroids exceeding 7.5mg/day of prednisolone or equivalent. However, **there are exceptions to these**, please see section on 7.1.5 Supportive Medications above for further details.

Antivirals

Brivudine and **Sorivudine MUST NOT** be prescribed with capecitabine as they may produce a life-threatening interaction. These drugs are not licensed for use in the UK but may be prescribed in other countries.

Other anti-cancer therapies

No other anticancer therapies, with the exception of hormonal treatment, other than the study treatments (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is on trial treatment. Prior chemotherapy, biological therapy, radiation therapy, immunotherapy, other anticancer agents, with the exception of hormonal treatment, within 28 days of starting trial treatment are not permitted. Treatment with any other investigational agent within the preceding 4 weeks or within 5 half-lives of the investigational agent, whichever is longer, are also excluded. Pharmacokinetic data obtained from 27 subjects in the dose escalation part of FIH study, E7046-G000-101/monotherapy, showed that maximum plasma concentrations of AN0025 were achieved 2.00 to 4.00 hours following a single oral dose (C1D1), and 0.525 to 4.68 hours at steady state (C1D8) over the range of 125 to 750 mg. AN0025 exposure was dose proportional up to 500 mg dose, with no incremental increase at the 750 mg dose. Estimated geometric mean terminal half-life for AN0025 at steady state was approximately 6 to 11 hours, resulting in an approximately 3- to 7-fold (Cmax) and 2- to 3-fold (AUC) accumulation following multiple dosing. Overall, AN0025 presents a normal PK profile over the dose range tested. Please see most recently approved AN0025 Investigator Brochure, main trial inclusion and exclusion criteria for further details.

Herbal and complementary therapies

Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions. If a potential patient is currently taking or would like to start taking a herbal or complimentary therapy, please contact sponsor pharmacy first to discuss. These should be documented appropriately on the eCRF.

Concomitant medications

Concomitant medications except for supportive care for disease-related symptoms, analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Therapies considered necessary for

the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF.

Vaccinations

Vaccination with live attenuated vaccines, including yellow fever vaccine, is prohibited. In addition, patients should not receive live vaccines for 6 months after the end of study treatment. Vaccination with the COVID-19 vaccines is permitted as long as government guidelines are followed and a live attenuated vaccine is NOT given [Please note, although the AstraZeneca/ Oxford vaccine contains a live adenovirus vector, it is impossible for the vaccine to replicate or cause disease in humans and is therefore considered safe in immunosuppressed patients]. Please check with CTRU for clarification if needed, prior to the administration of any COVID-19 vaccine.

Additional information for patients receiving AN0025: please see AN0025: TRIAL INVESTIGATIONAL MEDICINAL PRODUCT (IMP) MANAGEMENT

7.1.11 Patients with DPD Deficiency

Reduced activity of DPD is one of the main causes of fluoropyrimidine-related toxicity, due to the lower capacity to degrade 5FU or capecitabine into the inactive metabolites, resulting in higher exposure of 5FU or capecitabine and cytotoxic metabolites. Most often, a DPD deficiency is the result of a deleterious single nucleotide polymorphism (SNP) in DPYD, altering the DPD enzyme activity. A DPD deficiency is classified as partial if there is remaining DPD activity. Patients with known complete DPD deficiency are excluded from this study.

Patients who are heterozygous carriers for any of the four variants below should have their starting dose of capecitabine and fluorouracil reduced by 50%. Specifically concurrent capecitabine in LCCRT should be reduced by 50% i.e., approx. 413mg/m^2 twice a day. For patients receiving FOLFOX the dose of 5FU should be reduced by 50% (both bolus and infusional) i.e. bolus 200mg/m^2 over 10-15 minutes and infusional 1200mg/m^2 over 46 or 48 hours. For patients receiving CAPOX the dose of capecitabine should be reduced to 500mg/m^2 BID days 1-14 of each cycle.

For patients established on treatment, who are experiencing no or clinically tolerable less than or equal to grade 2 toxicity with 6 weeks of FOLFOX or CAPOX, the dose of capecitabine or fluorouracil respectively may be cautiously escalated in subsequent cycles by 25% dose increments. Please contact the CTRU and CIs if further discussion on this issue is required. The dose of capecitabine during LCCRT should not be increased from 50%.

Table 7.5 DPYD variants and dose reduction for capecitabine/5FU

DPYD variant	% of 5FU or capecitabine starting dose

DPYD*2A (c.1905 + 1G>A; rs3918290)	50%
DPYD*13 (c.1679T>G; rs55886062)	50%
c.2846A>T (rs67376798)	50%
c.1236G>A/HapB3 (rs56038477)	50%

7.1.12 Capecitabine

Capecitabine concurrent with LCCRT administration

Capecitabine will be administered orally (PO) BID at a dose of 825 mg/m2 in equal doses (equivalent to a total daily dose of 1650 mg/m2) for 5 days per week (normally Monday – Friday), on the days of radiotherapy administration only (beginning on the morning prior to the first fraction of RT treatment), throughout the 25-day course of radiotherapy. If radiotherapy is not given (e.g., due to machine maintenance or bank holiday), then capecitabine should not be given that day either.

Capecitabine treatment can begin on any day of the week; however, **there is normally no capecitabine treatment on Saturday or Sunday,** unless radiotherapy is given on one of these days. Patients may receive a combination of tablet strengths to achieve the prescribed dose. Patients on capecitabine should be instructed to take their capecitabine within 30 minutes of a meal e.g., within 30 minutes of breakfast and within 30 minutes of the evening meal, and as close to 12 hours apart as possible. If a patient misses a dose and remembers within 2 hours of the missed dose, the dose can be taken then. Otherwise, the patient should wait until the next scheduled dose and should not double up missed doses. Delays of up to 7 days in radiotherapy are permitted once the patient has started radiotherapy. Capecitabine should only be taken on days that radiotherapy treatment is delivered. Therefore, if radiotherapy is not given for any reason, capecitabine should not be taken. Capecitabine may be stopped if toxicity is thought to be related to capecitabine. In this instance, radiotherapy may continue alone.

Please note that patients who have an inability to comply with oral medication are not eligible for this study. If the patient becomes unable to swallow their tablets whole during treatment within the study, it is permitted that the patient can dissolve the tablets in approximately 200mls of water. In this situation, the patient should wear a pair of non-sterile gloves and, ideally, a plastic apron before handling the tablets. The tablets should be left in the liquid to dissolve (they must not be crushed). This may take 15 minutes. The solution should be swallowed immediately and the contents that are left, rinsed and swallowed also. The container should be marked and used solely for the purpose of dissolving the capecitabine tablets.

Dose banding of capecitabine is permitted as per local practice.

Capecitabine prohibited medication/drug-drug interactions/toxicities

Information on prohibited concomitant therapies, and drug-drug interactions and the main expected toxicities and their management, is included elsewhere in this chapter. For comprehensive information please refer to Summary of Product Characteristics (SmPC) for capecitabine.

Specific Management of Patients taking Capecitabine

Multiple reports exist of patients failing to discontinue the oral capecitabine in the face of toxicity, which then becomes more severe and potentially irreversible.

Patients allocated capecitabine/CAPOX must be properly educated in the management of their home-based oral chemotherapy and need to be given rigorous advice with respect to contacting the hospital as soon as toxicities ensue.

Patients may often be prepared to experience toxicities and may not easily accept the idea of interrupting their treatment for fear this may decrease efficacy. Patients should be re-assured that protocol compliant dose modifications will not compromise the efficacy of their treatment and must be given clear instructions on when to discontinue capecitabine and who to contact (local Investigator/Research Nurse) at the onset of key toxicities such as nausea/vomiting and diarrhoea.

7.1.13 5-Fluorouracil

5-Fluorouracil prohibited medication/drug-drug interactions/toxicities

Information on prohibited concomitant therapies, and drug-drug interactions and the main expected toxicities and their management, is included elsewhere in this chapter. For comprehensive information please refer to Summary of Product Characteristics (SmPC) for fluorouracil.

In particular:

Increased phenytoin plasma concentrations have been reported during concomitant use with fluorouracil and capecitabine. Patients taking phenytoin concomitantly with fluorouracil or capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

There is a potential interaction for patients on fluorouracil or capecitabine taking warfarin therapy. Please note, within this study, treatment with warfarin is not permitted. Anticoagulation with low molecular weight heparin is allowed. An increase in INR can occur up to one month after stopping capecitabine therapy.

Antacids containing aluminium hydroxide or magnesium hydroxide may increase capecitabine concentrations and therefore should not be taken at the same time of day.

Photosensitivity

In patients treated with fluorouracil, prolonged exposure to sunlight is not recommended because of the risk of photosensitivity. Patients should be advised to follow sun protection strategies, including wearing sun protective clothing and wearing high-factor sun cream.

7.1.14 Oxaliplatin

Oxaliplatin toxicities/prohibited medication/drug-drug interactions

Information on prohibited concomitant therapies, and drug-drug interactions and the main expected toxicities and their management, is included elsewhere in this chapter. For comprehensive information please refer to Summary of Product Characteristics (SmPC) for oxaliplatin.

There are no known drug interactions but caution should be exercised in patients receiving coumarin-derived anticoagulants as there may be the potential for an increase in INR. Please note, within this study, treatment with warfarin is not permitted. Anticoagulation with low molecular weight heparin is allowed.

Caution is advised when oxaliplatin is co-administered with other medicinal products known to cause QT interval prolongation. In such cases, monitoring of the QT interval is advised.

Caution is also advised when oxaliplatin is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis.

7.1.15 Folinic acid

Following the use of methotrexate, overuse of folinic acid may lead to a loss of the effect of methotrexate therapy ("over-rescue"). However, methotrexate treatment is not permitted within this study.

Anti-epileptic drugs (phenobarbital, primidone, phenytoin and succinimides) may have their effect diminished by folinic acid and this may increase the frequency of seizures.

The efficacy of folic acid antagonists e.g., co-trimoxazole, pyrimethamine, may be reduced by folinic acid.

7.1.16 Radiotherapy

Patients will receive one of the two preoperative radiotherapy schedules (SCRT or LCCRT) as outlined above. For both schedules, IMRT should be used (though IMRT, VMAT and TomoTherapy are all acceptable treatment techniques). Treatment target includes the primary tumour, any involved lymph nodes, and elective pelvic nodal targets (as standard for pre-operative radiotherapy for locally advanced rectal cancer).

A detailed description of pre-treatment imaging requirements, radiotherapy target volume definition, dose constraints, on-treatment image guidance, and radiotherapy quality assurance is provided in the **ARTEMIS Radiotherapy Guideline** and should always be used during the radiotherapy planning and treatment process. This guideline has been closely aligned with the National Rectal Cancer IMRT Guidance from the Royal College of Radiologists (RCR) and should thus be easily implementable for most UK radiotherapy

centres. In particular, note that cone beam CT (CBCT), or other equivalent 3D imaging, is required for treatment image guidance for all patients, with a minimum imaging schedule in line with national guidance.

The radiotherapy quality assurance programme for ARTEMIS will be coordinated by the National RTTQA group. A pre-trial facility questionnaire will be sent to all participating sites. For centres where processes cannot be streamlined with previous RT QA activity for lower GI trials at that centre, they will be asked to submit a benchmark case to assess outlining and planning. For on-trial quality assurance, prospective review of the outlining and planning for at least the first case from all centres will be performed. Radiotherapy data (including diagnostic MRI) for all recruited cases will be collected by the RTTQA group, on behalf of the trial sponsor, via a secure data transfer system.

ARTEMIS patients will be treated as Royal College of Radiologists (RCR) category 2 patients. Unscheduled gaps in radiotherapy should be limited to no more than 2 consecutive planned fractions where possible.

7.2 AN0025: TRIAL INVESTIGATIONAL MEDICINAL PRODUCT (IMP) MANAGEMENT

Please refer to the ARTEMIS Pharmacy and Investigational Medicinal Product (IMP) Study Site Operating Procedures (SSOP) for full details of the trial IMP management requirements.

7.2.1 AN0025 Mechanisms of action

Within the ARTEMIS trial AN0025 is classed as the IMP in the intervention arm.

AN0025 is a selective inhibitor of the EP4 receptor. AN0025 inhibits PGE2-mediated differentiation and suppressive function of intratumoral monocytic myeloid cells by blocking EP4, one of the 4 known receptors for PGE2. Refer to AN0025 Investigator Brochure (IB) for information regarding the physical and chemical properties of AN0025 and a list of excipients.

7.2.2 AN0025 Composition

AN0025 is supplied as 125 mg or 250 mg tablets. Each 250 mg tablet is an orange oval film-coated tablet containing the off-white to white core, “250” on one side, “AN” on the other side. Each 125 mg tablet is an orange oval film-coated tablet containing the off-white to white core, “125” on one side, “AN” on the other side.

For details of the IMP composition please refer to the approved version of the IB.

7.2.3 AN0025 treatment compliance

A subject diary will be used to collect daily recording of the oral AN0025 compliance.

7.2.4 AN0025 drug supply, accountability, storage and destruction

In compliance with local regulatory requirements, drug supplies (including ancillary supplies) will not be sent to the investigator (or if regionally required, the head of the medical

institution or the designated pharmacist) until the obligatory documentation has been received by the sponsor.

Batch number, dose prescribed, quantity of tablets and expiry of AN0025 supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed. Full instructions regarding management, labelling and accountability of AN0025 is given in the IMP Management Document for the trial.

Refer to the respective approved version of the IBs and pharmacy manual for detailed information about preparation, handling and storage of AN0025. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study supplies (including dispensing, inventory, and record keeping) following the sponsor's instructions (please refer to: "Pharmacy Manual") and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study supplies to be used other than as directed by this protocol. Study supplies will not be dispensed to any individual who is not enrolled in the study. The site must maintain an accurate and timely record of the following: receipt of all study supplies, dispensing of study supplies to the subject, collection and reconciliation of unused study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and destruction of reconciled study supplies at the site. This includes but may not be limited to: (a) documentation of receipt of study supplies, (b) study supplies dispensing/return reconciliation log, (c) study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns, and (f) certificates of destruction for any destruction of study supplies that occurs at the site. All forms will be provided by the CTRU. Any comparable forms that the site wishes to use must be approved by the CTRU. The study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the CTRU or a representative of a health authority (e.g., FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). The site pharmacy should regularly check the supplies of AN0025 to ensure accountability of all product used. All used, partially used and unused AN0025 must be retained until the CTRU completes, reviews, and documents accountability.
Throughout the clinical study and following IMP accountability and supply reconciliation, sites are permitted to destroy IMP in compliance with all local regulations. Approval for destruction to occur at the site must be provided by the CTRU in advance and destruction certificates must be provided to the CTRU. At the end of the study, unused IMP can be destroyed on site in compliance with all local regulations.

Drug accountability will be reviewed during site visits and at the completion of the study.

7.2.5 AN0025 packaging

AN0025 is considered an IMP for the purposes of this trial (fluorouracil, capecitabine, oxaliplatin, folinic acid are considered off the shelf supplies). AN0025, will be supplied by ALMAC (the local distributor) in individually labelled containers containing 30 tablets. The dosage form is a 125 mg or 250 mg tablet. For more information on the packaging description please refer to the pharmacy manual.

7.2.6 AN0025 labelling

These will be labelled in English with text that is in full UK regulatory compliance.

7.2.7 AN0025 prescribing

The IMP AN0025 is administered orally continuously at 500 mg once daily (QD) starting 14 days before the first dose of radiotherapy then continuing through SCRT/LCCRT, through the 3 week gap before CAPOX/FOLFOX starts, then concurrently with the 12 weeks of CAPOX/FOLFOX chemotherapy. This therefore totals 18 weeks for the SCRT option or 22 weeks for LCCRT. Subjects will be required to fast 2 hours before and 2 hours after the AN0025 dose. Treatment with AN0025 will be discontinued in case of disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or termination of the study programme.

AN0025 is supplied as tablets in 30 count bottles in strengths of either 125 mg or 250 mg in each bottle.

7.2.8 AN0025 Dispensing, Accountability and Administration

The investigator or a delegated individual (e.g., pharmacist) must ensure that the IMP AN0025 is dispensed in accordance with the protocol, local Standard Operating Procedures (SOPs) and applicable regulatory requirements. The batch number, dose prescribed, quantity of tablets and expiry of the drug supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed. Full instructions regarding management, labelling and accountability of AN0025 is given in the IMP Management Document for the trial.

7.2.9 AN0025 Interaction with other drugs

The medicines listed below should be used with caution due to their potential to interact with the AN0025.

Changes in exposure to AN0025 are not expected when it is co-administered with drugs which either induce or inhibit cytochrome P450 since the main metabolic pathway of AN0025 in human hepatocytes is acyl-glucuronidation to form ER-888188.

AN0025 showed no potential to induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in human cryopreserved hepatocytes at concentrations up to 50 µmol/L.

AN0025 and ER-888188 did not show reversible inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A at concentrations up to 100 µmol/L. AN0025 showed weak time-dependent inhibition (TDI) of CYP3A but no TDI of CYP2C9 or CYP2C8. ER-888188 showed no TDI for CYP3A, CYP2C9, and CYP2C8.

This data suggests clinically relevant changes in exposure of drugs metabolized via these CYPs, when co-administered with AN0025, are not expected (please also refer to current Global IB).

Based on the metabolism pathways, no drug-drug interactions are expected between AN0025 and capecitabine, CAPOX or FOLFOX.

7.2.10 AN0025: Contraindicated therapies and drugs

The following are **prohibited** during AN0025 therapy:

- NSAIDs
- Aspirin at doses of higher than 325 mg daily
- Anticoagulants including warfarin, anti-Xa agents (see below)
- ACE inhibitors and angiotensin II receptor blockers (ARBs): Subjects on these hypertensives at study entry should be switched to other hypertensives prior to study drug dosing
- Uridine'5 diphospho-glucuronosyl transferase (UGT) inducers or inhibitors (atazanavir, probenecid, valproic acid, mefenamic acid, quinidine)
- Other systemic and local antitumor therapies such as chemotherapy, antitumor interventions (SR, thoracocentesis, etc.), or antitumor immunotherapy
- Other investigational drugs

The following are **allowed** during AN0025 therapy:

- Aspirin at doses ≤325 mg daily
- LMWH
- Physiological replacement dosing of corticosteroids (for example, up to 7.5 mg/day of prednisolone) will be allowed.

If 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;

- Leeds CTRU is notified prior to screening/consent of the patient's requirement for anticoagulants and received approval by Leeds CTRU;
- Warfarin remains prohibited.

Sites should contact their PI or one of the Co-CIs if they have any questions prior to consenting a patient.

7.2.11 AN0025 Side Effects

Data in the current AN0025 IMP Brochure includes study E7046-G000-101 using AN0025 monotherapy. Within this study 16 of 30 patients (53%) experienced at least one adverse event. The most common (>5%) were diarrhoea in 6 (20%), fatigue in 6 (20%), decreased appetite in 5 (17%), nausea in 4 (13%) and weight decrease in 2 (7%). Sixteen subjects (53.3%) developed treatment-related AEs of any grade - most were grade 1 (7 subjects, 23.3%) or grade 2 (6 subjects, 20.0%). Grade 3 treatment related AEs were reported in 2 subjects (6.7%) and grade 4 treatment-related AEs were reported in 1 subject (3.3%). Please see summary Table710 Toxicity profile of AN0025.

The PRAER-1 trial combined 10 weeks of AN0025 with either concurrent SCRT followed by 6 weeks of FOLFOX, or LCCRT (including concurrent capecitabine). The above toxicities were confirmed, in addition to anaemia (3/28: 10.7%), proctitis (7/28: 25%), constipation (6/28: 21.4%), abdominal pain (3/28: 10.7%), vomiting (3/28: 10.7%), hypokalaemia (2/28: 10.7%), dizziness (4/28: 14.3%), headache (3/28: 10.7%), paraesthesia (3/28: 10.7%), urinary tract pain (3/28: 10.7%) and cough (3/28: 10.7%). Grade ≥3 toxicity was only encountered in 2 patients (7.1%: one fatigue and one diarrhoea) (Wyrwicz et al., 2019)(Wyrwicz et al. 2019 plus manuscript in preparation).

7.3 EXPECTED TOXICITY PROFILE OF RADIOTHERAPY, 5FU, CAPECITABINE, OXALIPLATIN AND AN0025

Toxicities of radiotherapy, 5FU, capecitabine, oxaliplatin and AN0025 are listed below. Note 'common' is >10% and 'uncommon' <10%. All toxicities are acute unless explicitly stated as 'long-term'.

Table 7.6 Toxicity profile of Radiotherapy

Toxicity of pelvic radiotherapy	
Common	**Less common**
Bleeding from rectum	A different cancer in the treatment area (rare)
Cystitis	Bowel/bladder damage which may require surgery (rare)
Diarrhoea including increased frequency and urgency	Long-term bleeding from rectum

Hair loss in treated area	Long-term bowel stricture/obstruction
Increased mucus/wind per rectum	Long-term more prone to bone fractures in treated area
Increased urinary frequency and urgency	Long-term urinary leak or incontinence, urgency, increased frequency, cystitis
Long-term bowel symptoms including increased frequency, urgency, incontinence	Men: Infertility Change in sexual experience including inability to ejaculate, dry ejaculate, erectile dysfunction,
Long-term skin changes in treatment area including colour change (darker/lighter) and telangectasia	Nausea and/or vomiting (rare)
Skin soreness, redness, itching	Women: Long-term vaginal narrowing/dryness causing pain and making sexual activity difficult Early menopause in premenopausal women
Tenesmus	
Tiredness	

Table 7.7 Toxicity profile of 5-FU

Toxicity of 5-FU	
Common	**Less common**
Anaemia	Angina or myocardial infarction
Anorexia	Cracking, peeling or excessively dry skin
Changes in taste	Discoloration of nails, loss of nails
Diarrhoea	Discoloration of the skin
Neutropenia	Hair loss
Stomatitis and mouth ulcers	Hand-foot syndrome
Thrombocytopenia	Rash or itching
Venous tracking	Skin sensitivity to sunlight
Watery eyes or sensitivity to sunlight	

Table 7.8 Toxicity profile of Capecitabine

Toxicity of Capecitabine	
Common	**Less common**
Abnormalities in liver function tests (LFTs).	Abdominal pain
Anaemia	Angina or myocardial infarction
Diarrhoea	Anorexia
Fatigue	Constipation
Hand -foot syndrome	Eye irritation
Lymphopenia	Fever
Nausea and vomiting	Headache
Skin reactions (increased pigmentation, itching, dry skin)	Joint and muscle pain
	Neutropenia
	Numbness or tingling of hands and/or feet (usually associated with hand-foot syndrome)
	Stomatitis and mouth ulcers
	Swelling of the ankles and/or feet
	Thrombocytopenia

Table 7.9 Toxicity profile of Oxaliplatin

Toxicity of Oxaliplatin	
Common	**Less common**
Anaemia	Abdominal pain
Changes in LFTs, liver damage	Abnormalities in renal function tests
Constipation	Anorexia
Diarrhoea	Back pain
Fatigue	Fever
Nausea and vomiting	Headache
Numbness or tingling of the hands or feet - this condition may be exacerbated by exposure to the cold (long term numbness of the hands or feet is less common)	Insomnia
Thrombocytopenia	Neutropenia
	Stomatitis and mouth ulcers

Table 7.10 Toxicity profile of AN0025

AN0025	
Common	**Less common**
Abdominal pain*	Weight loss
Constipation*	
Cough	
Decreased appetite	
Diarrhoea	
Dizziness	
Fatigue	
Headache	
Hypokalaemia	
Nausea	
Parasthesia	
Proctitis*	
Urinary tract pain*	

*Noted when combined with radiotherapy (Wyrwicz et al., 2019)(PRAER1 trial)

7.4 DRUG INTERRUPTION AND DOSE MODIFICATION FOR TOXICITY

7.4.1 General Management of Acute Toxicities and Dose Modifications

Toxicities will be graded using the NCI CTCAE v5.0. All dose adjustments to be made based upon the worst or most clinically significant preceding toxicity. When a dose reduction of chemotherapy is made for the development of Grade 2 or Grade 3 toxicity, this modification remains in place for the remainder of the planned treatment course i.e., no re-escalation of a dose is permitted.

For non-haematological AEs (excluding diarrhoea) which are considered by the investigator unlikely to develop into serious or life-threatening events (e.g., alopecia, altered taste, etc.), treatment may be continued at the same dose without interruption.

Due to the multi-drug and multi-modality treatment being used in this trial there is the potential for overlapping toxicity between the individual drugs and radiotherapy treatment.

If a patient experiences an acute toxicity, the clinician should make a clinical assessment to determine if the toxicity is related to the trial treatment. If the clinician judges the toxicity to be due to trial treatment, they should make a decision on the most likely cause(s) of the toxicity and follow management guidelines for each treatment given below. At times, there will be truly overlapping toxicity. If it is not clear which treatment is causing the toxicity, management should be according to the guideline for each treatment for the worst toxicity grade observed. In the case of overlapping toxicities, a combination of strategies from the tables relating to individual study treatment below can be followed. If, based on the grade of toxicity, there is differing advice regarding stopping treatment or permanently discontinuing treatment, the most cautious advice should be followed. Advice on stopping drugs or radiotherapy, or permanent discontinuation of either, is listed under the separate tables for each treatment. Please contact the CRUK CTU for further advice when required.

The local team should have a structure in place that ensures that subjects experiencing side effects can be seen on any day and that subjects can undergo daily review if required to monitor the severity of side effects and respective treatment.

The following guidance should be followed for the management of acute toxicity and dose modifications:

- AEs should be graded according to the National Cancer Institute Common Terminology Criteria for AEs version 5.0 (CTCAE v5.0).
- Dose modifications should be made according to the worst grade of AE (NCI-CTCAE v5.0). When a dose reduction is made for the development of Grade 2 or Grade 3 toxicity, this modification remains in place for the remainder of the planned treatment course.

For non-haematological AEs (excluding diarrhoea) which are considered by the investigator unlikely to develop into serious or life-threatening events (e.g. Alopecia, altered taste, etc.), treatment may be continued at the same dose without interruption.

- No dose reductions or interruptions are required for anaemia (non-hemolytic) if it can be satisfactorily managed by transfusions or erythropoietin
- In the event of overlapping toxicities, dose modification should be based on the worst toxicity grade observed.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken in the case report and in the medical notes.

ARTEMIS is to be conducted in multiple centres across the UK. The management of acute toxicity associated with standard CRT might vary on specific guidelines and experiences. The investigators are allowed to use their local practice for the medical management of toxicities including diarrhoea, with careful recording of the details of the severity and the medications and/or supportive measures being used. However, the investigators are expected to follow the recommendations for dose interruption and modification for specific toxicities as shown in Tables 7.11-7.24.

Toxicity due to chemotherapy administration may be managed by medication to control chemotherapy-related symptoms and/or modification of the chemotherapy doses (treatment interruption or dose reduction). In general, if any grade 1 toxicity occurs as a result of chemotherapy, then treatment will be continued, without interruption, at full dose. For all treatment-related toxicities ≥ grade 3, treatment should be withheld until recovery to ≤ grade 1 then restarted commencing as day one of the next cycle, if medically appropriate. Once a chemotherapy dose has been reduced, it should not be increased at a later time.

AN0025 is non-myelosuppressive and in general, when AN0025 is used concurrent with SCRT/LCCRT, it will not be dose reduced during RT for uncomplicated haematological toxicity. Similarly, during FOLFOX/CAPOX it will not be dose reduced for uncomplicated haematological toxicity unless FOLFOX/CAPOX are stopped completely (anticipated to be unlikely). However, for non-haematological toxicity, possible dose reductions will be carried out as appropriate as indicated below. The major elimination route of radioactivity in SD rats after oral administration of AN0025 was into faeces via bile and renal clearance of AN0025 was minor in rats and dogs (Adlai Nortye, 2020) (Global Investigator's Brochure, Sept 2020).

Dose modifications and toxicity management guidelines for chemotherapy during radiotherapy (capecitabine/5FU +/- AN0025) and after radiotherapy (FOLFOX/CAPOX +/- AN0025) are provided below. The dose of folinic acid is not modified for toxicity but should be omitted if both the bolus AND infusional 5-fluorouracil is omitted.

For further information related to dose modifications in patients with DPYD variants, please see: Table 7.5 DPYD variants and dose reduction for capecitabine/5FU

For those on intervention arm, if there is a delay of more than 2 weeks between commencement of AN0025 and starting SCRT/LCCRT, then AN0025 can be given for an extra week i.e., up to the end of week 3. However, if there is further delay before commencing SCRT/LCCRT, then AN0025 should be stopped, and the situation discussed with the ARTEMIS trials office. The AN0025 will then recommence once SCRT/LCCRT starts. It is anticipated that this will be uncommon.

The gap between completion of SCRT/LCCRT and commencing FOLFOX/CAPOX is 3 weeks. For those on intervention arm, during this time AN0025 should be continued. However, if this gap is extended beyond 4 weeks because of toxicities encountered, then AN0025 can be continued up until 4 weeks but beyond 4 weeks AN0025 should be discontinued. AN0025 treatment can then subsequently be recommenced once FOLFOX/CAPOX starts. Such a situation should be discussed with the ARTEMIS trial office. This will necessitate one extra week of AN0025 treatment i.e., a total of 19 weeks for the SCRT option (rather than 18) and 23 weeks for the LCCRT option (rather than 22).

The TMG are available to discuss the management of toxicity. If you would like to contact the TMG, please contact the ARTEMIS team at artemis@leeds.ac.uk.

7.4.2 Dose modifications during radiotherapy (SCRT or LCCRT +/- AN0025)

7.4.2.1 Diarrhoea management

Patients receiving LCCRT should be reviewed at least weekly, and it is expected that diarrhoea, fatigue and haematological toxicities will be most commonly observed toxicities during LCCRT.

It is particularly important to assess and monitor patients who experience diarrhoea during CRT. If admission is required, it is recommended that this is to the radiotherapy centre. If circumstances prevent this, then this guidance must be rapidly shared with the local treating team and regular contact maintained. The option of subsequent transfer to the centre should be discussed.

The site team should document a baseline assessment of stool frequency, and this should be repeated once weekly at the same time as toxicity assessment (distinguishing from tenesmus/mucous discharge/wet wind).

Loperamide is recommended as the initial anti-diarrhoeal medication. Codeine phosphate up to 30 mg four times a day can be added if diarrhoea is not controlled with 16 mg loperamide per day.

Table 7.11 Dose modifications for diarrhoea during radiotherapy (SCRT or LCCRT +/- AN0025)

CTCAE Grade	Description	Radiotherapy	Capecitabine	AN0025
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Continue	Full dose (100%)	Continue
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; Moderate cramping	Continue Manage as clinically indicated (eg. Loperamide, ensure oral hydration maintained)	Continue as long as patient considered fit for treatment. Needs monitoring with daily patient contact by clinic visit or phone	Continue
3	Increase of > 7 stools per day over baseline; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL); Severe cramping or peritonism (localised guarding on abdominal examination)	For incontinence - continue. Management as per clinically indicated (eg. loperamide, codeine, iv hydration, monitor renal function), consider inpatient management for treatment and support. Check that stoma is avoided from radiotherapy portals. Do not treat if localised peritonism	Interrupt until Grade 0 – 1, ≤6mg loperamide per 24 hours required, and patient considered fit on review, then recommence at 75% of starting dose.	Interrupt until Grade 0-1 Recommence at 75% dose (375mg/day)
4	Life threatening consequences; urgent intervention indicated	Interrupt until resolved to Grade 2. Reassess daily	Stop permanently.	Stop permanently

Grade 3 diarrhoea

The following guidance is recommended for patients who experience grade 3 diarrhoea during concurrent chemo-radiotherapy:

- Consider admission of the patient
- Commence loperamide
- Send stool for culture and C. difficile toxin
- Commence IV fluids with regular appropriate volumetric and electrolyte assessment
- Suspend chemotherapy
- If neutropenic, commence IV antibiotics and consider G-CSF

If grade 3 diarrhoea is not controlled to ≤ grade 1 by regular loperamide within 24 hours and patient not neutropenic:

- Commence IV broad spectrum antibiotics (including patients who are not pyrexial). The regimen used should be determined locally (an example option includes an intravenous second or third generation cephalosporin and metronidazole). The regimen used should cover likely enteric pathogens.

If grade 3 diarrhoea not controlled ≤ grade 1 by IV antibiotics and IV fluids and regular loperamide within 48 hours:

- Commence s/c octreotide – the recommended starting dose is 300µg per 24 hours by either s/c continuous infusion or s/c tds injections. The dose can be increased in accordance with British National Formulary (BNF) guidance and should be reviewed daily.
- Closely monitor serum C-reactive protein (CRP), renal function and albumin. The role of total parenteral nutrition should be discussed with the multi-disciplinary team who are responsible for this therapy and may play an important role for patients not responding well to the supportive treatments described above.

Grade 4 diarrhoea:

By definition grade 4 diarrhoea is life-threatening. Patients developing grade 4 diarrhoea at any stage must be admitted urgently and treated with full supportive measures including fluid replacement, IV antibiotics and IV octreotide in addition to any other immediate resuscitative measures that might be deemed necessary. Interrupt radiotherapy until resolved to Grade 2. Reassess daily.

7.4.2.2 Haematological toxicity during radiotherapy (SCRT or LCCRT +/- AN0025)

Haemoglobin must be maintained above 10g/dl throughout SCRT/LCCRT; if necessary maintain through blood transfusion. Please see Table 7.12 **Dose modifications for haematological toxicity during radiotherapy (SCRT or LCCRT +/- AN0025)** below for actions to be taken for capecitabine doses and radiotherapy treatment in the presence of haematological toxicity.

Table 7.12 Dose modifications for haematological toxicity during radiotherapy (SCRT or LCCRT +/- AN0025)

Blood count during any day of chemoradiotherapy:		**Action:**		
Neutrophils(x 10^9/L)	**Platelets (x 10^9/L)**	**Radiotherapy**	**Capecitabine**	**AN0025**
≥1.0	≥100	Continue	100% dose	100% dose
≥1.0	75-99	Continue	100% dose	100% dose
0.5-0.99	50-74	Continue	Omit dose for the week. Reduce dose by 25% on recovery	100% dose*
<0.5	<50	Discuss with ARTEMIS CIs	Omit dose until recovery to neutrophils ≥ 1, platelets ≥ 75, then re-start at 50% dose	Omit until RT resumed then restart at 100% dose*

*Uncomplicated neutropenia i.e., no evidence of infection

7.4.2.3 Mucositis Toxicity

Table 7.13 Dose modifications for mucositis toxicity during radiotherapy/chemoradiotherapy

Grade	Definition	Radiotherapy	Capecitabine	AN0025
Grade 1	Asymptomatic or mild symptoms; intervention not indicated	Continue	No change. Maintain starting dose level.	Continue at 100%
Grade 2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated.	Continue	1st appearance: Interrupt until resolved to grade 0-1 and maintain starting dose level. 2nd appearance: Interrupt until resolved to grade 0-1 and restart on 80% starting dose 3rd appearance: Interrupt until resolved to grade 0-1 and restart on 60% starting dose. 4th appearance: Discontinue capecitabine permanently.	Continue at 100% once resolved to grade 0-1. Continue at 100% once resolved to grade 0-1. Continue at 100% once resolved to grade 0-1. Continue at 100% once resolved to grade 0-1.
Grade 3	Severe pain; interfering with oral intake.	Continue	1st appearance: Interrupt until resolved to grade 0-1 and restart on 80% starting dose. 2nd appearance: Interrupt until resolved to grade 0-1 and restart on 60% starting dose 3rd appearance: Discontinue capecitabine permanently.	Continue at 100% once resolved to grade 0-1. Continue at 100% once resolved to grade 0-1. Continue at 100% once resolved to grade 0-1.
Grade 4	Life-threatening consequences; urgent intervention indicated.	Continue	Discontinue permanently Or If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1 after discussion with CI and reduce dose to 60% of starting dose.	Continue at 100% once resolved to grade 0-1.

*Supportive treatment (e.g., mouthwashes, analgesia etc.) as per local protocols should be considered throughout

7.4.2.4 Hepatic impairment

Transient increases in bilirubin and/or AST/ALT can be common with capecitabine.

Table 7.14 Dose modification for liver impairment during SCRT/LCCRT +/- AN0025

Grade	Definition	Capecitabine	Radiotherapy (either SCRT or LCCRT)	AN0025
Grade 1	ALT and/or AST increased: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal. And/or: Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal.	No change, 100% dose.	Continue.	No change, 100% dose
Grade 2	ALT and/or AST increased: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal. And/or: Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal.	Discontinue capecitabine. Treatment may be restarted at full dose when bilirubin <3 x ULN or AST/ALT <2.5 x ULN	Continue.	Discontinue AN0025. Treatment may be restarted at 75% dose i.e., 375 mg/day when bilirubin <3 x ULN or AST/ALT <2.5 x ULN
Grade 3	ALT and/or AST increased: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal. and/or: Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal.	Withhold capecitabine. Treatment should be restarted at 80% of starting dose when bilirubin <3 x ULN or AST/ALT <2.5 x ULN	Continue	Withhold AN0025. Treatment should be restarted at 50% of starting dose i.e., 250 mg/day when bilirubin <3 x ULN or AST/ALT <2.5 x ULN

Grade 4	ALT and/or AST increased: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. and/or: Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal.	Discontinue capecitabine.	Continue	Discontinue AN0025.

7.4.2.5 Renal impairment

Table 7.15 Dose modification for renal impairment during SCRT/LCCRT +/- AN0025

Grade	Definition	Radiotherapy	Capecitabine*	AN0025
Grade 1	Creatinine >ULN - 1.5 x ULN.	No change. Continue if the patient is considered by the investigator to be fit to undergo radiotherapy treatment.	No change. Please also see note below.*	No change
Grade 2	Creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN.	No change. Continue if the patient is considered by the investigator to be fit to undergo radiotherapy treatment.	Please also see note below.* As per non-haematological toxicity 1st appearance: Interrupt until resolved to grade 0-1 and maintain dose level 100%. 2nd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 25%. 3rd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 50%. 4th appearance: Discontinue capecitabine permanently.	Interrupt until resolved to grade 0-1 and maintain dose level 100%.
Grade 3	Creatinine >3.0 x baseline; >3.0 - 6.0 x ULN.	No change. Continue if the patient is considered by the investigator to be fit to undergo radiotherapy treatment.	Please also see note below.* As per non-haematological toxicity 1st appearance: Interrupt until resolved to grade 0-1 and reduce dose by 25%. 2nd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 50%. 3rd appearance: Discontinue capecitabine permanently.	Interrupt until resolved to grade 0-1 and resume on 75% dose i.e., 375 mg/day.
Grade 4	Creatinine >6.0 x ULN.	No change. Continue if the patient is considered by the investigator to be fit to undergo radiotherapy treatment.	Please also see note below.* Discontinue permanently Or If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1 after discussion with CI and reduce dose by 50%.	Discontinue permanently

***** If the creatinine clearance decreases during treatment to a value < 30 mL/min, capecitabine should be discontinued. If the creatinine clearance decreases to 30-49mL/min during treatment, then elimination of capecitabine may be impaired, therefore reduce dose to 75%. Patients should be closely monitored for increased toxicity and doses of therapy interrupted or modified for haematological or non-haematological toxicity.

Table 7.16 Capecitabine and AN0025 dosing for other non-haematological toxicity during LCCRT

Toxicity		During course of chemoradiotherapy	Dose adjustment for next dose of capecitabine	Dose adjustment for next dose of AN0025
Grade 1	Any appearance	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0-1	Maintain dose level	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 20%	Reduce dose by 25% i.e., give 375 mg/day
	3rd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 40%	Reduce dose by 50% i.e., give 250 mg/day
	4th appearance	Discontinue capecitabine permanently		
Grade 3	1st appearance	Interrupt until resolved to grade 0-1	Reduce dose by 20%	Reduce dose by 25% i.e., give 375 mg/d
	2nd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 40%	Reduce dose by 50% i.e., give 250 mg/d
	3rd appearance	Discontinue capecitabine permanently		
Grade 4	1st appearance	Discontinue permanently Or If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1 after discussion with CI	Discontinue permanently Or Reduce dose by 40%	Discontinue permanently

7.4.3 Dose modifications during FOLFOX/CAPOX +/- AN0025 (post radiotherapy)*

7.4.3.1 Dose modification for diarrhoea

Table 7.16 Dose modifications for diarrhoea during FOLFOX/CAPOX +/- AN0025 (post radiotherapy)*

	Grade 2	Grade 3	Grade 4
1st occurrence	Withhold 5FU/capecitabine/Ox/AN0025 treatment until recovered to grade 0-1. Restart at full starting dose	Withhold 5FU/capecitabine/Ox/AN0025 treatment until recovered to grade 0-1. Restart 5FU/cape/Ox at 75% of starting dose. Restart AN0025 at 75% dose (375 mg/day)	Discontinue all chemotherapy or if rapid recovery, consider treating with 5FU/capecitabine/Ox at 50% of starting dose and AN0025 at 50% dose (250 mg/day).
2nd occurrence	Withhold 5FU/capecitabine/Ox/AN0025 treatment until recovered to grade 0-1. Restart 5FU/capecitabine at 75% dose of starting dose. Restart Ox at 100% of starting dose. Restart AN0025 at 75% of starting dose (375 mg/day).	Withhold 5FU/capecitabine treatment until recovered to grade 0-1. Restart 5FU/cape/Ox at 50% of starting dose. Restart AN0025 at 50% dose (250 mg/day).	
3rd occurrence	Withhold 5FU/capecitabine treatment until recovered to grade 0-1. Restart 5FU/capecitabine at 50% of starting dose. Restart Ox at 75% of starting dose. Restart AN0025 at 50% of starting dose (250 mg/day).	Discontinue	

*If dose reductions were necessary in 5FU/capecitabine during radiotherapy then these reductions should be considered with post-radiotherapy FOLFOX/CAPOX +/- AN0025.

7.4.3.2 Haematological Toxicity during FOLFOX/CAPOX +/- AN0025 (post radiotherapy)

Dose based upon full blood count (FBC) on day 1 of each cycle (see Table 7.18 Dose modifications for haematological toxicity during FOLFOX/CAPOX +/- AN0025 (post radiotherapy) below). Please note it is acceptable to take blood test up to 48 hours prior to treatment. If blood tests taken up to 48 hours prior to treatment are below the threshold to proceed with treatment, blood tests can be repeated on the day treatment is due.

Table 7.18 Dose modifications for haematological toxicity during FOLFOX/CAPOX +/- AN0025 (post radiotherapy)

Blood count on day 1	Delay of cycle	Occurrence	Subsequent Dose reduction (DR)			
			Oxaliplatin	5FU bolus	5FU infusion/ Capecitabine	AN0025
ANC<1.5x10^9/L	Hold all chemo until ANC ≥1.5x10^9/L	1st occurrence at starting dose level	No change	No change	No change	100% dose
		2nd occurrence at starting dose level or ANC <0.5x10^9/L lasting >7 days (1st occurrence)	Dose reduce to 80% of starting dose	Dose reduce to 80% of starting dose	Dose reduce to 80% of starting dose	100% dose
		1st occurrence at 80% dose	No change	No change	No change	100% dose
		2nd occurrence at 80% dose or ANC <0.5x10^9/L lasting >7 days (2nd occurrence)	Dose reduce to 60% of starting dose	Dose reduce to 60% of starting dose	Dose reduce to 60% of starting dose	100% dose
		1st occurrence at 60% dose	No change	No change	No change	100% dose
		2nd occurrence at 60% dose or ANC <0.5x10^9/L lasting >7 days (3rd occurrence)	Stop all FOLFOX/CAPOX/AN0025 study treatment			
If ANC have not recovered after 3 weeks delay, treatment of FOLFOX/CAPOX/AN0025 study drugs must be stopped.						
Platelets <100x10^9/L	Hold all chemo until platelets ≥100x10^9/L	1st occurrence at starting dose level	No change	No change	No change	100% dose
		2nd occurrence at starting dose level or platelets <25 x10^9/L (1st occurrence)	Dose reduce to 80% of starting dose	Dose reduce to 80% of starting dose	Dose reduce to 80% of starting dose	100% dose
		1st occurrence at 60% starting dose	No change	No change	No change	100% dose
		2nd occurrence at 60% starting dose or platelets <25 x10^9/L (2nd occurrence)	Dose reduce to 60% of starting dose	Dose reduce to 60% of starting dose	Dose reduce to 60% of starting dose	100% dose
		1st occurrence at dose level -2	No change	No change	No change	100% dose

Table 7.19 Dose modifications for Febrile Neutropenia:

Day:	Grade:	Action:
Febrile neutropenia on any day of CAPOX/FOLFOX +/- AN0025	3 – 1st occurrence	Defer all drug treatment until ANC ≥1.5 x 10^9/L and reduce capecitabine/5FU/oxaliplatin to 80% of starting dose. Keep AN0025 at 100% dose
Febrile neutropenia on any day of CAPOX/FOLFOX +/- AN0025	3 – 2nd occurrence	Defer all drug treatment until ANC ≥1.5 x 10^9/L and reduce capecitabine/5FU/oxaliplatin to 60% of starting dose. Keep AN0025 at 100% dose.
Febrile neutropenia on any day of CAPOX/FOLFOX +/- AN0025	4	Permanently discontinue all drug treatment (Capecitabine/CAPOX/FOLFOX/AN0025)

7.4.3.3 Mucositis Toxicity

Table 7.20 Dose modifications for mucositis during FOLFOX/CAPOX+/-AN0025 treatment (post radiotherapy or chemoradiotherapy)*

Grade	Definition	5-FU/capecitabine	Oxaliplatin	AN0025
Grade 1	Asymptomatic or mild symptoms; intervention not indicated	No change.	No change.	Continue 100% starting dose
Grade 2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated.	Withhold until resolution to less than or equal to Grade 1, then reinstitute at the same starting dose level. For a 2nd occurrence reinstitute at 80% of starting dose	Withhold until resolution to less than or equal to Grade 1, then reinstitute at the starting dose level. For a 2nd occurrence reinstitute at 80% of starting dose	Continue 100% starting dose once resolved to grade 0-1
Grade 3	Severe pain; interfering with oral intake.	Withhold until resolution to less than or equal to Grade 1, then reinstitute at 80% of starting dose For a 2nd occurrence then reinstitute at 60% of starting dose	Withhold until resolution to less than or equal to Grade 1, then reinstitute at 80% of starting dose For a 2nd occurrence then reinstitute at 60% of starting dose	Continue 100% starting dose once resolved to grade 0-1
Grade 4	Life-threatening consequences; urgent intervention indicated.	Permanently discontinue and commence supportive management.	Permanently discontinue and commence supportive management.	Discontinue and commence supportive management. Can resume at 100% once resolved to grade 0-1.

*Supportive treatment (e.g., mouthwashes, analgesia etc.) as per local protocols should be considered throughout

7.4.3.4 Neurosensory Toxicity

Neurosensory toxicity with FOLFOX/CAPOX is almost always due to the oxaliplatin. Therefore, reduction in this drug is the most important adjustment to make. The table below gives recommendations but is not meant to be prescriptive and dose adjustments according to local protocol may be followed as long as the dose given is carefully annotated in the CRF.

Table 7.21 Dose modifications for neurosensory toxicity

Regimen	Grade 1, or 2 (if Grade 2 persisting <7 days)	Grade 2 persisting >7 days	Grade 3	Grade 4
FOLFOX	Full dose oxaliplatin	75% dose oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin
CAPOX	Full dose oxaliplatin	75% dose oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin
AN0025	100%	100%	100%	100%

7.4.3.5 Hepatic impairment

Transient increases in bilirubin and/or AST/ALT can be common with capecitabine.

Table 7.22 Dose modification for liver impairment during FOLFOX/CAPOX +/- AN0025 (post SCRT/LCCRT)

Grade	Definition	5FU/Capecitabine	Oxaliplatin	AN0025
Grade 1	ALT and/or AST increased: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal. And/or: Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal.	No change, 100% dose	No change, 100% dose	No change, 100% dose
Grade 2	ALT and/or AST increased: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal. And/or: Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal.	Discontinue capecitabine/5FU. Treatment may be restarted at full dose when bilirubin <3 x ULN or AST/ALT <2.5 x ULN	No change, 100% dose	Discontinue AN0025. Treatment may be restarted at 75% of starting dose i.e., 375 mg/day when bilirubin <3 x ULN or AST/ALT <2.5 x ULN
Grade 3	ALT and/or AST increased: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal. and/or: Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal.	Withhold capecitabine/5FU. Treatment should be restarted at 80% of starting dose when bilirubin <3 x ULN or AST/ALT <2.5 x ULN	Stop. Treatment may be restarted at 80% of starting dose when bilirubin <3 x ULN or AST/ALT <2.5 x ULN	Stop. Treatment may be restarted at 50% of starting dose i.e., 250 mg/day when bilirubin <3 x ULN or AST/ALT <2.5 x ULN
Grade 4	ALT and/or AST increased: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. and/or: Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal.	Discontinue capecitabine/5FU	Discontinue oxaliplatin	Discontinue AN0025.

7.4.3.6 Renal impairment

Table 7.23 Dose modification for renal impairment during FOLFOX/+/- AN0025

Grade	Definition	5-fluorouracil	Capecitabine	Oxaliplatin	AN0025
Grade 1	Creatinine >ULN - 1.5 x ULN.	Treat at full dose.	No change. Please also see note below.*	Treat at full dose.	Continue
Grade 2	Creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN.	Treat at full dose.	Please also see note below.* As per non-haematological toxicity 1st appearance: Interrupt until resolved to grade 0-1 and maintain dose level. 2nd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 25%. 3rd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 50%. 4th appearance: Discontinue capecitabine permanently.	Treat at full dose.	Withhold until resolved to grade 0-1 then continue at full dose 100%.
Grade 3	Creatinine >3.0 x baseline; >3.0 - 6.0 x ULN.	Hold fluorouracil, until resolution to ≤grade 1, and then resume treatment at 80% of starting dose if, in the opinion of the investigator this is or may be the cause of toxicity. Otherwise, maintain fluorouracil at the current dose level.	Please also see note below.* As per non-haematological toxicity 1st appearance: Interrupt until resolved to grade 0-1 and reduce dose by 25%. 2nd appearance: Interrupt until resolved to grade 0-1 and reduce dose by 50%. 3rd appearance: Discontinue capecitabine permanently.	Hold oxaliplatin, until resolution to ≤ grade 1, and then resume treatment at 80% of starting dose if, in the opinion of the investigator this is or may be the cause of toxicity. Otherwise, maintain oxaliplatin at the current 100% dose level.	Interrupt until resolved to grade 0-1 and resume on 75% dose i.e. 375 mg/day.

Grade 4	Creatinine >6.0 x ULN.	Permanently discontinue.	Please also see note below.* Discontinue permanently Or If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1 after discussion with CI and reduce dose by 50%.	Permanently discontinue.	Stop permanently.

*****If the creatinine clearance decreases during treatment to a value < 30 mL/min, capecitabine should be discontinued. If the creatinine clearance decreases to 30-49mL/min during treatment, then elimination of capecitabine may be impaired, therefore reduce dose to 75%. Patients should be closely monitored for increased toxicity and doses of therapy interrupted or modified for haematological or non-haematological toxicity.

Table 7.24 Capecitabine and AN0025 dosing for other non-haematological toxicity during LCCRT

Toxicity		During course of chemoradiotherapy	Dose adjustment for next dose of capecitabine	Dose adjustment for next dose of AN0025
Grade 1	Any appearance	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0-1	Maintain dose level	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 20%	Reduce dose by 25% i.e., give 375 mg/day
	3rd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 40%	Reduce dose by 50% i.e. give 250 mg/day
	4th appearance	Discontinue capecitabine permanently		
Grade 3	1st appearance	Interrupt until resolved to grade 0-1	Reduce dose by 20%	Reduce dose by 25% i.e., give 375 mg/d
	2nd appearance	Interrupt until resolved to grade 0-1	Reduce dose by 40%	Reduce dose by 50% i.e., give 250 mg/d
	3rd appearance	Discontinue capecitabine permanently		
Grade 4	1st appearance	Discontinue permanently Or If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1 after discussion with CI	Discontinue permanently Or Reduce dose by 40%	Discontinue permanently

Table 7.25 FOLFOX/CAPOX/AN0025 dosing for other non-haematological toxicities during FOLFOX/CAPOX +/- AN0025

CTCAE grade	FOLFOX/CAPOX	AN0025
Grade 1	Full dose	Full dose
Grade 2 1st appearance or grade 3 nausea or vomiting.	Interrupt until resolved to grade 0-1 then treat at full dose. Nausea and vomiting: Escalate anti-emetics as per local practice.	Treat at full dose (100%)
Grade 2 2nd appearance	Interrupt until resolved to grade 0-1 then treat at 80% of starting dose.	Interrupt until resolved to grade 0-1 then treat at 75% dose i.e., 375 mg/day.
Grade 3 AE 1st appearance (except as above)	Hold either oxaliplatin and/or fluorouracil/Capecitabine as per investigator opinion regarding cause of toxicity, until resolution to ≤ grade 1, then resume treatment at 80% of starting dose. If the AE is clearly attributable to a single drug, the other drug may remain at the current dose level	Interrupt until resolved to grade 0-1 then treat at 75% dose i.e., 375 mg/day.
Grade 3 AE 2nd appearance (except as above)	Hold either oxaliplatin and/or fluorouracil/Capecitabine as per investigator opinion regarding cause of toxicity, until resolution to ≤ grade 1, then resume treatment at 60% of starting dose. If the AE is clearly attributable to a single drug, the other drug may remain at the current dose level	Interrupt until resolved to grade 0-1 then treat at 50% dose i.e., 250 mg/day.
Grade 4	Discontinue FOLFOX/CAPOX treatment	Discontinue permanently

7.4.4 Infusion reaction

Dose modification and toxicity management of infusion-reactions

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnoea, tachycardia, cyanosis, respiratory failure, urticarial and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and haemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to agents, but between can occur during subsequent treatments.

Treat as per local protocol for infusion related reactions but please see guidance below.

For Grade 1 symptoms: (Mild reaction)
The infusion rate may be decreased by 50% or temporarily interrupted until resolution. Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: antihistamine such as chlorphenamine 10mg IV or 4mg PO and/or paracetamol 500 to 1000 mg at least 30 minutes before additional SACT administration.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, NSAIDs, opiates, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the SACT infusion, begin an IV infusion of sodium chloride 0.9%, and treat the subject with antihistamine such as chlorphenamine 10mg IV or 4mg PO) and/or paracetamol 500 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further of that SACT will be administered at that visit. Administer antihistamine such as chlorphenamine 10mg IV or 4mg PO and remain at bedside and monitor the subject until resolution of symptoms. The amount of trial drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: antihistamine such as chlorphenamine 10mg IV or 4mg PO and/or paracetamol 500 to 1000 mg should be administered at least 30 minutes before additional SACT administrations. Subsequent infusions may be given at 50% of the initial infusion rate.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of

symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of SACT. Begin an IV infusion of sodium chloride 0.9% and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg (or equivalent e.g., adrenaline) of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or antihistamine such as chlorphenamine 10mg IV or 4mg PO, with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. The specific SACT will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

7.4.5 Laryngopharyngeal Dysaesthesia

Oxaliplatin is associated with a different type of neuropathy i.e., laryngopharyngeal dysaesthesia, at the time of administration or just after. This is generally cold-induced, of short duration and limiting with no evidence of bronchospasm although it may cause shortness of breath. Patients may respond well to reassurance, warm drinks and a prolongation of oxaliplatin infusion time. Local protocols and guidance should be followed.

7.4.6 Myocardial ischemia and angina

Cardiotoxicity is a serious complication during treatment with fluorouracil and capecitabine. Subjects, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil or capecitabine, should be carefully monitored during therapy.

7.4.7 Extravasation

Oxaliplatin is regarded as an exfoliant when extravasated and is capable of causing inflammation and shedding of skin but less likely to cause tissue death. Fluorouracil is regarded as an inflammitant if extravasated and has the potential to cause mild to moderate inflammation and flare in local tissues. Please local to your local policy on the treatment of extravasation for the trial drugs.

7.4.8 Venous occlusive disease

A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or oesophageal varices. Patients should be instructed to report any jaundice, ascites or haematemesis immediately.

7.4.9 Haemolytic Uremic Syndrome (HUS)

Oxaliplatin therapy should be interrupted if HUS is suspected: haematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 µmol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

7.4.10 Hand-foot Syndrome (HFS)

Treat symptomatically according to local protocol. A topical corticosteroid may help. If HFS is still a problem, dose reduce capecitabine or 5-FU as per Table 7.16 Dose modifications for diarrhoea during FOLFOX/CAPOX +/- AN0025 (post radiotherapy)*.

7.4.11 Respiratory Toxicity

As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with oxaliplatin. In the case of unexplained respiratory symptoms or signs, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

7.4.12 Unplanned breaks in radiotherapy

When an unplanned break in radiotherapy occurs (bank holiday, machine breakdown), the radiotherapy prescription remains unchanged and is delivered over a longer treatment time – **additional fractions should NOT be given on the same day.** If a break in treatment has occurred due to toxicity then treatment can be extended into week 6 and beyond (for chemoradiotherapy) or to week 2 (for short course RT), provided that the patient is considered fit for treatment and dose modifications have been applied as per protocol. When an unplanned break in chemoradiotherapy occurs (bank holiday, machine breakdown), capecitabine should be interrupted for that day and then resumed on the next planned day of radiotherapy. The specific reason(s) for any radiotherapy treatment interruption must be recorded.

8. TRIAL ASSESSMENTS AND DATA COLLECTION

Trial participant data will be collected electronically via the CTRU Remote Data Entry (RDE) database. Participants will be given the choice of completing the PROs either on paper or electronically, via the electronic patient reported outcome software 'REDCap' (Research Electronic Data Capture). REDCap is the CTRUs current solution for patient reported outcomes (PROs) and allows trial participants to directly enter data into REDCap as a replacement for paper-based forms and has been validated for use in all CTRU trials.

For participants wishing to complete the questionnaires electronically, they will be given the option of receiving an email or text message with a link to their questionnaire. Participants preferred method of questionnaire administration and completion will be collected during the consent process and applicable contact details, email address/mobile phone number collected on the paper F50 Contact Details CRF.

Non-responders will receive reminders by the pre-stated preferred method of communication, at the following time points where health-related quality of life (HRQoL) data is collected: 3 weeks post end of RT and then 4, 6, 9, 12, 24 and 30 months post start of RT. Reminders will be sent 2 weeks after the initial link to the questionnaire was sent and where records at CTRU show that it has not been completed. The CTRU will contact sites at intervals throughout the study to ensure that consenting participant's contact details and status have not changed.

The baseline questionnaires will remain paper based for all participants to ensure these are completed at the correct time point (after informed consent is obtained but before randomisation). Copies of any paper-based questionnaires will be provided within the ISF sent to sites and participant packs will also be provided in a pdf format for the appropriate time points.

Participants contact details, including names, date of birth and mobile phone number (if applicable), will be provided after randomisation to be used to facilitate the administration of PROs questionnaires during the trial.

This personal data will only be provided following the provision of informed consent by the participant as indicated on the informed consent form and will conform to the 2018 Data Protection Act and General Data Protection Regulation (GDPR).

8.1. GENERAL ECRF COMPLETION GUIDANCE

Assessments will be entered electronically via RDE onto eCRFs, using the MACRO programme which will be managed by the CTRU.

Access to the RDE system will be provided by the University of Leeds following site being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided. Participating sites will be expected to maintain a file of essential trial

documentation, ISF, which will be provided by the CTRU. Any paper CRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth and initials.

It is the responsibility of the site staff to ensure the ISF is properly maintained during the duration of the trial.

8.2 eCRFs

Data will be entered by site research staff on trial-specific eCRFs, which will be provided by CTRU on a trial-specific database, access to which will be provided by CTRU following sites authorisation to open to recruitment.

A number of (e)CRFs which require expedited reporting to the CTRU, will be collected within the time points specified below:

- A scanned copy of the consent form must be sent via the CTRU's SFTS at the time of consent
- A paper F50 Contact Details CRF should be sent to the CTRU via the SFTS immediately after randomisation
- All SAEs and SUSARs must be recorded on the appropriate eCRF to CTRU within 24 hours of becoming aware of the event. Please note: a paper SAE and SUSAR form will also be provided as a back-up in event any urgent reporting is required and the MACRO database cannot be accessed
- Protocol violations eCRFs must be entered within 24 hours of becoming aware of the event
- Notification of Pregnancy eCRFs must be entered within 24 hours of the site team becoming aware
- Any Notification of Death eCRFs must be entered within 7 days of the site team becoming aware
- Any Withdrawal Request eCRFs must be entered within 7 days of the date of withdrawal
- RT End of Treatment eCRFs must be entered within 14 days of completion of the end of radiotherapy treatment
- Surgery eCRFs must be entered within 14 days post-surgery

All other eCRFs must be completed within 28 days of the data collection time points detailed in Table 8.2 Schedule of Events.

Some paper records may be requested by CTRU during the course of the trial. It is the responsibility of staff at participating sites to obliterate all personal identifiable data, for example on any hospital reports, letters, etc., prior to sending to CTRU. Such records should only include the trial number, initials and date of birth to identify the participant. The

exception to this is the participant consent form where the participant's name and signature must not be obliterated.

Following receipt of the completed eCRFs, the CTRU will contact sites on a regular basis to resolve any missing or discrepant data.

RDE/ eCRFs must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific APL. Login details will be provided for these personnel only and should not be shared with others.

A paper copy of the Pathology CRF will be available for pathologists to complete to collect data on any post-surgery tissue samples for response assessment. The data can then be entered onto the corresponding eCRF at site on the trial database by an authorised member of the trial staff

8.3 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
- Completion of the baseline QoL questionnaires by the patient

8.4 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, weight and vital signs
- Haematology and biochemistry
- Planned start date of trial treatment
- 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.

8.5 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.

8.6 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

8.7 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.

8.8 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

8.9 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.

8.10 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, see section 11.1 Primary Endpoints. 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. The Surgery CRF should be completed within 14 days post-surgery . The pathology paper CRF is to be completed by the pathologist as part of local reporting and entered on to MACRO by a member of the research team at a later,. All times for follow-up assessments 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)
- Pathology paper CRF for reporting of response to be completed whenever salvage surgery occurs for local relapse or residual disease
- 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.

8.11 BASELINE AND FOLLOW-UP MRI

Imaging using MRI is of importance in ARTEMIS because it partly defines the primary endpoint. A separate document '**ARTEMIS Tri-modal Endoscopy DRE MRI Guidelines**' contains details of this aspect.

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 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 (see the document **'ARTEMIS Tri-Modal Endoscopy DRE MRI Guidelines'** for examples).

Table 8.1 MRI Tumour regression grading (mrTRG) scores on post-treatment MRI

Grade	Description
Grade 1	Complete radiological response (linear scar only), no evidence of treated tumour
Grade 2	Excellent response (dense low signal post treatment fibrotic change in the site of the previous tumour) and no obvious tumour signal
Grade 3	Moderate response (mixed fibrosis and indeterminate heterogeneous signal intensity) suspicious for residual tumour
Grade 4	Minimal response (mostly tumour, minimal fibrosis/mucinous degeneration)
Grade 5	No response in the primary tumour or frank tumour progression

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.

8.12 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 separate document '**ARTEMIS Flexible Sigmoidoscopy Guidelines**' contains details and guidelines with regard to this aspect.

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.

8.13 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 (see section 11.1 Primary Endpoint).

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 (Fokas et al., 2021).

8.14 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 (Fokas et al., 2021). 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) (Fokas et al., 2021).

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.

8.15 PARTICIPANT TRANSFERS

If a participant is being permanently transferred to a different site, the Participant Transfer eCRF should be entered on MACRO as soon as possible to enable tracking of the participant.

8.15.1 Transfer to another site participating in ARTEMIS

Copies of any paper CRFs, informed consent forms and any other relevant correspondence is sent to the new site, with originals kept at the original centre. Data from before the date of transfer is questioned with the original site, data after the transfer will be queried with the new site. Both sites must ensure that the participant transfer is recorded on the participant log in the Investigator Site File and the Pharmacy Site File.

8.15.2 Transfer to a site that is NOT participating in ARTEMIS

- All trial treatment will cease. Any further treatment for rectal cancer received by the participant will be off trial. If the participant is on observation only with no surgery, the new site must be made aware that the patient would, with the national standard of care, have had definitive surgery after initial radiotherapy and chemotherapy, and that the patient has not had the standard of care because of inclusion in the trial, which the patient has now withdrawn from, and may need closer observation to facilitate early intervention should local recurrence develop.
- If the participant agrees to be followed up at the new site, it is the responsibility of the original site to gather follow-up data from the new site in order to complete the eCRFs. The original site will keep all trial documentation and ensure that the participant transfer is recorded on the participant ID log in the Investigator Site File and the Pharmacy Site File.
- If the participant does not want to be followed up at the new site, a Participant Withdrawal eCRF must be entered by the original site on MACRO.

8.16 DEATHS

All deaths occurring from the date of randomisation to the end of follow-up must be recorded on the Notification of Death eCRF on the RDE system within 7 days of the site team becoming aware of the death. It is important that this is completed promptly so that any QoL questionnaire reminders sent by CTRU are stopped. Data collected will include (but may not be limited to):

- Date of death
- Cause of death

8.17 PREGNANCIES

All pregnancies and suspected pregnancies in a trial participant, or their partner, occurring from the date of randomisation and for the required length of time of contraception use (please refer to Section 4.3 Birth Control), must be reported to the CTRU within 24 hours of the site becoming aware. All protocol treatment must be stopped immediately if a pregnancy in a participant occurs or is suspected.

The CTRU will report all pregnancies occurring during treatment to the Sponsor along with any follow-up information.

8.18 PATIENT REPORTED OUTCOMES (PROS) DATA COLLECTION

HRQoL questionnaires will take place at baseline (after informed consent is obtained but before randomisation), 3 weeks post end of RT and then 4, 6, 9, 12, 24 and 30 months post start of RT. These are based on the key decision points within the patient pathway. The HRQoL questionnaires to be completed are described in further detail below.

All patients in the trial will complete these questionnaires whether they have surgery or not.

Participants will be given the choice of completing PROs either on paper or electronically. Participants wishing to complete the PROs on paper will be asked to do so on attendance at the scheduled outpatient appointments, prior to being seen in clinic. Copies of any paper-based PROs will be provided within the ISF and pdf copies of participant PRO booklet will be sent from CTRU to any sites once they are open to recruitment. Questionnaires should be completed independently by the participant. The completed questionnaires will then be sent promptly to Leeds CTRU.

Participants wishing to complete the PROs electronically will be sent a unique link sent out via email or text message at the time points specified above.

- European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 — This is a 30-item questionnaire developed by the EORTC to assess generic aspects of

QoL of cancer patients, such as physical, psychological and social functions. It is composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 toxicity related single items.

- EORTC QLQ-CR29 – The Colorectal Cancer Module developed by the EORTC QLQ-CR29 is used in conjunction with the EORTC QLQ-C30 to assess quality of life in patients with colorectal cancer. Additional items from the EORTC Item Library will be included to cover aspects of OP and novel agent toxicity expected.

- EuroQoL EQ-5D-5L – The EQ-5D-5L collects information about five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is the standard questionnaire used in health economic evaluation. The results can be combined into a 5-digit number that describes the patient's health state which in turn can be assigned a utility score. The questionnaire also includes a visual analogue scale to record the patient's self-rated health on a vertical visual scale (van Reenen and Janssen, 2015).

- LARS - The Low Anterior Resection Syndrome (LARS) is a questionnaire designed to assess bowel function (Emmertsen and Laurberg, 2012). The questionnaire is formed of five items to describe daily life on frequency of bowel movements, gas incontinence, faecal incontinence, fragmentation/clustering and urgency.

8.19 Sample Collection

If a patient has provided additional optional consent for the storage of their tissue for translational research, the standard of care pre-treatment biopsy FFPE tissue block containing tumour should be sent to the ARTEMIS bio-repository at the Leeds Institute of Medical Research, University of Leeds. If a patient undergoes radical surgical resection, an additional FFPE block containing tumour should be sent from the resection specimen. Please send these along with a copy of the local pathology report and ARTEMIS sample submission form. All direct patient identifiers should be removed e.g. patient name, date of birth and NHS number. If tissue blocks are required for urgent clinical testing at any time after sending, these can be requested back and will be returned at the earliest opportunity. Please send tissue blocks, pathology reports and sample submission forms to the **ARETMIS trial pathology laboratory, level 4 Wellcome Trust Brenner building, St. James's University Hospital, Leeds, LS9 7TF**. Queries should be directed to Dr Nick West (n.p.west@leeds.ac.uk) and pathologytrials@leeds.ac.uk.

8.20 End of Trial

The end of trial is defined as the date of collection of the last participant's last data item. Participants will be followed up for 30 months as outlined in Section 3 Trial Design Overview.

Table 8.2 SCHEDULE OF EVENTS: SCRT/CAPOX OPTION

(Applies to Control Arm and Intervention Arm - if Intervention Arm then AN0025 will start 14 days prior to the start of week 1)

SCRT/CAPOX	Eligibility	Pre-rand / Baseline	Pre-treatment	W -2	W -1	W1	W4	W5	W7	W10	W 13	W18 (4 months)	W26 (6 months)
				AN0025		SCRT	C1 CAP		C2 CAP	C3 CAP	C4 CAP		
Written Informed Consent		X											
Demographics		X											
Medical History[1]	X												
Treatment													
Radiotherapy SCRT[2]						X							
CAPOX[2]							X		X	X	X		
Investigations													
Pregnancy Test[3]	X												
ECOG PS	X		X			X	X		X	X	X	X	X
Height		X											
Weight		X	X			X	X		X	X	X	X	X
ECG[4]		X											
Vital Signs[5]		X	X				X		X	X	X	X	X
Haematology[6]	X		X[8]				X		X	X	X	X	X
Biochemistry[7]	X		X[8]				X		X	X	X	X	X
Biopsy histology adenocarcinoma	X												
CEA	X											X	X
DPD Testing[9]		X											
Toxicity assessment[10]		X	X			X	X		X	X	X	X	X
Con Meds	X	X	X			X	X		X	X	X	X	X
Imaging/Disease Assessment													
Pelvic MRI[11]	X											X[20]	X[20]
CT Scan Thorax, Abdomen and Pelvis[12]	X												X
DRE[13]	X											X	X
Flexible Sigmoidoscopy	X											X[14]	X
Patient Reported Outcomes													
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]		X					X					X	X
Optional Specimen Collection													
Archival Diagnostic Tissue		x											

Table 8.3 SCHEDULE OF EVENTS: SCRT/FOLFOX OPTION

(Applies to Control Arm and Intervention Arm - if Intervention Arm then AN0025 will start 14 days prior to the start of week 1)

SCRT/FOLFOX	Eligibility	Pre-rand / Baseline	Pre-treatment	W -2	W -1	W1	W4	W5	W6	W8	W10	W12	W14	W18 (4 months)	W26 (6 months)
				AN0025		SCRT	C1 FOL		C2 FOL	C3 FOL	C4 FOL	C5 FOL	C6 FOL		
Written Informed Consent		X													
Demographics		X													
Medical History[1]	X														
Treatment															
Radiotherapy SCRT[2]						X									
FOLFOX[2]							X		X	X	X	X	X		
Investigations															
Pregnancy Test[3]	X														
ECOG PS	X		X			X	X		X	X	X	X	X	X	X
Height		X													
Weight		X	X			X	X		X	X	X	X	X	X	X
ECG[4]		X													
Vital Signs[5]		X	X				X		X	X	X	X	X	X	X
Haematology[6]	X		X[8]				X		X	X	X	X	X	X	X
Biochemistry[7]	X		X[8]				X		X	X	X	X	X	X	X
Biopsy Histology Adenocarcinoma	X														
CEA	X													X	X
DPD Testing[9]		X													
Toxicity assessment[10]		X	X			X	X		X	X	X	X	X	X	X
Con Meds	X	X	X			X	x		X	X	X	X	X	X	X
Imaging/Disease Assessment															
Pelvic MRI[11]	X													X[20]	X[20]
CT Scan Thorax, Abdomen and Pelvis[12]	X														X
DRE[13]	X													X	X
Flexible sigmoidoscopy	X													X[14]	X
Patient Reported Outcomes															
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]		X					X							X	X
Optional Specimen Collection															
Archival Diagnostic Tissue		X													

Table 8.4 SCHEDULE OF EVENTS: LCCRT/CAPOX OPTION

(applies to Control Arm and Intervention Arm - if Intervention Arm then AN0025 will start 14 days prior to the start of week 1)

LCCRT/CAPOX	Eligibility	Pre-rand / Baseline	Pre-treatment	W -2	W -1	W1	W2	W3	W4	W5	W8	W11	W14	W 17	W18 (4 months)	W26 (6 months)
				AN0025		LCCRT					C1 CAP	C2 CAP	C3 CAP	C4 CAP		
Written Informed Consent		X														
Demographics		X														
Medical History[1]	X															
Treatment																
Radiotherapy LCCRT[2]						X	X	X	X	X						
CAPOX[2]											X	X	X	X		
Investigations																
Pregnancy Test[3]	X															
ECOG PS	X		X							X	X	X	X	X	X	X
Height		X														
Weight		X	X							X	X	X	X	X	X	X
ECG[4]		X														
Vital Signs[5]		X	X								X	X	X	X	X	X
Haematology[6]	X		X[8]						X[16]		X	X	X	X	X	X
Biochemistry[7]	X		X[8]						X[16]		X	X	X	X	X	X
Biopsy Histology Adenocarcinoma	X															
CEA	X														X	X
DPD Testing[9]		X[16]														
Toxicity assessment[10]		X	X			X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X							X	X	X	X	X	X	X
Imaging/Disease Assessment																
Pelvic MRI[11]	X														X[20]	X[20]
CT Scan Thorax, Abdomen and Pelvis[12]	X															X
DRE[13]	X														X	X
Flexible sigmoidoscopy	X														X[14]	X
Patient Reported Outcomes																
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]		X									X				X	X
Optional Specimen Collection																
Archival Diagnostic Tissue		X														

Table 8.5 SCHEDULE OF EVENTS: LCCRT/FOLFOX OPTION

(applies to Control Arm and Intervention Arm - if Intervention Arm then AN0025 will start 14 days prior to the start of week 1)

LCCRT/FOLFOX	Eligibility	Pre-rand / Baseline	Pre-treatment	W -2	W -1	W1	W2	W3	W4	W5	W8	W10	W12	W14	W16	W18 (4 months)	W26 (6 months)
				AN0025		LCCRT					C1 FOL	C2 FOL	C3 FOL	C4 FOL	C5 FOL	C6 FOL	
Written Informed Consent		X															
Demographics		X															
Medical History[1]	X																
Treatment																	
Radiotherapy LCCRT[2]						X	X	X	X	X							
FOLFOX[2]											X	X	X	X	X	X	
Investigations																	
Pregnancy Test[3]	X																
ECOG PS	X		X							X	X	X	X	X	X	X	X
Height		X															
Weight		X	X							X	X	X	X	X	X	X	X
ECG[4]		X															
Vital Signs[5]		X	X								X	X	X	X	X	X	X
Haematology[6]	X		X[8]						X[16]		X	X	X	X	X	X	X
Biochemistry[7]	X		X[8]						X[16]		X	X	X	X	X	X	X
Biopsy histology adenocarcinoma	X																
CEA	X															X	X
DPD Testing[9]		X															
Toxicity assessment[10]		X	X			X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X							X	X	X	X	X	X	X	X
Imaging/Disease Assessment																	
Pelvic MRI[11]	X															X[20]	X[20]
CT Scan Thorax, Abdomen and Pelvis[12]	X																X
DRE[13]	X															X	X
Flexible sigmoidoscopy	X															X[14]	X
Patient reported outcomes																	
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]		X									X					X	X
Optional Specimen collection																	
Archival Diagnostic Tissue		X															

Table 8.6 ACTIVE SURVEILLANCE POST 6 MONTHS[19]

Patients will continue on this assessment schedule unless they have salvage surgery for relapsed/residual disease, when they will then change to the schedule in Table 8.7

Time point post-start of RT	9 months	12 months	18 months	24 months	30 months
Investigations					
ECOG PS	X	X	X	X	X
Weight	X	X	X	X	X
CEA	X	X	X	X	X
Toxicity assessment[10]	X	X	X	X	X
Pelvic MRI	X	X	X	X	X
CT Scan Thorax, Abdomen and Pelvis			X		X
DRE	X	X	X	X	X
Flexible sigmoidoscopy	X	X	X	X	X
Patient reported outcomes					
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]	X	X		X	X

Table 8.7 POST-SURGERY FOLLOW-UP

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.

Time point post-start of RT	4 Months	6 Months	9 months	12 months	18 months	24 months	30 months
CEA	X	X	X	X	X	X	X
Post-surgery complications[18]	(X[18])	(X[18])	(X[18])	(X[18])	(X[18])	(X[18])	(X[18])
Pathology Reporting [19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]
CT Scan Thorax, Abdomen and Pelvis		X		X		X	
Patient reported outcomes							
EQ-5D-5L, QLQ-C30, QLQ-CR29, LARS Score[15]	X	X	X	X		X	X
Optional Specimen collection							
Tissue following surgery[21]	(X[21])	(X[21])	(X[21])	(X[21])	(X[21])	(X[21])	(X[21])

[1] Medical history including confirmation of histological diagnosis, concomitant disease and concomitant treatments, including review of steroid use and contraindicated medications. To be done within 14 days prior to randomisation.

[2] Either FOLFOX or CAPOX and either SCRT or LCCRT will be chosen at the discretion of the treating clinician.

[3] Pregnancy Test - Human chorionic gonadotrophic (HGC) results must be obtained and reviewed before the first dose of treatment () is administered for patients of childbearing potential. **To be done within 7 days prior to randomisation**. A patient is considered of childbearing potential (WOCBP), i.e.,+ fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[4] ECG to be done within 14 days prior to randomisation.

[5] Vital signs - including temperature, seated blood pressure and pulse rate. To be done within 14 days prior to randomisation.

[6] Haematology - FBC (including white blood cells (WBC) with differential count (neutrophils, platelets)). Note additional coagulation panel (Prothrombin Time (PT), aPTT, Fibrinogen) is required at baseline and at the end of AN0025 treatment, otherwise as clinically required. To be done within 14 days prior to randomisation.

[7] Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, calculated creatinine clearance, total protein, albumin, alkaline phosphatase (alk phos), bilirubin, ALT or AST, fasting glucose at baseline and as clinically indicated otherwise. To be done within 14 days prior to randomisation.

[8] For patients on the control arm, pre-treatment assessments, including biochemistry and haematology, should be done within 14 days of starting SCRT or LCCRT. For patients on the intervention arm, pre-treatment assessments including biochemistry and haematology will occur within 7 days of starting AN0025.

[9] There is no time limit on when DPD can be tested prior to study entry.

[10] Toxicity assessment including neurotoxicity (assessed using CTCAE v5.0). Please note that toxicities relating to trial procedures should be collected from consent. Baseline CTCAE assessment to be done within 14 days prior to randomisation. Please see section 9 Pharmacovigilance procedures for further information.

[11] Pelvic MRI to be done within 63 days prior to randomisation.

[12] 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). To be done within 63 days prior to randomisation.

[13] Digital Rectal Examination to be done within 63 days prior to randomisation.

[14] Flexible sigmoidoscopy to be carried out at 18 weeks (4 months) only if progressive disease seen on MRI and patient being considered for surgery.

[15] QoL questionnaires should be performed at baseline and then at 3-weeks post end of RT and 4, 6, 9, 12, 24 and 30 months post start of RT. QoL should be completed prior to the patient being reviewed by the PI/designee and any concerns raised discussed. **QoL assessments will be carried out according to this schedule in all patients including those undergoing active surveillance and those who have undergone surgery**.

[16] Patients receiving LCCRT should have haematology and biochemistry assessments following standard of care, including an assessment at the start of week 4 as a minimum.

[17] Patients with cCR at month 6 (26 weeks) by DRE, rectal endoscopy and high resolution pelvic MRI will enter the active surveillance protocol. Patients entering the deferral of surgery pathway at month 6 post-start of radiotherapy treatment (26 weeks) until 30 post-start of radiotherapy (unless they undergo surgery) will have CT scans of the thorax, abdomen and pelvis at 12 and 24 months post-start of radiotherapy. In the case of patients with an 'uncertain cCR' at 6 months, where the criteria for a cCR (primary endpoint) are not fulfilled due to additional superficial mucosal

ulceration, teams may decide to continue 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.

[18]Post surgery complications - Clavien-Dindo Classification to be completed once, at 90 days post-surgery

[19] Pathology reporting of response to be completed whenever salvage surgery occurs for local relapse or residual disease.

[20] 4 and 6 month MRIs not to be performed if participant has undergone surgery

[21] Whenever salvage surgery occurs for local relapse or residual disease, tissue samples are collected according to instructions in Section 8.19 Sample Collection

9 PHARMACOVIGILANCE PROCEDURES

9.1 GENERAL DEFINITION

9.1.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant which does not necessarily have a causal relationship with the treatment and can include:

- Any unintentional, unfavourable clinical sign or symptom.
- Any new illness or disease or the deterioration of existing disease or illness.
- Any clinically relevant deterioration in any laboratory assessments or clinical tests.

Perceived lack of efficacy of a trial intervention is not considered an adverse event.

Pre-existing symptoms that remain stable during the trial would not be considered as adverse events.

9.1.2 Adverse reactions (AR)

Adverse reactions (ARs) are all untoward and unintended responses to a trial treatment related to any dose administered. Trial treatment in ARTEMIS is defined as radiotherapy, chemotherapy and for those that receive it immunotherapy (AN0025).

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to a trial treatment qualify as adverse reactions. This definition implies a reasonable possibility of a causal relationship between the event and the trial treatment that is supported by facts, evidence or arguments to suggest a causal relationship.

This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error), including misuse and abuse of the product.

9.1.3 Serious adverse event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening *
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Jeopardised the subject or required intervention to prevent one of the above characteristics / consequences – herein referred to as ‘Other important medical events’ **

*The term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

**Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

Medical judgement should be exercised in deciding whether an event is "serious" in accordance with the criteria listed above. These characteristics / consequences must be considered at the time of the event.

9.1.4 Serious adverse reaction

A Serious Adverse Reaction (SAR) is an SAE deemed to have been related to the trial treatment. Reference is made to the criterion of 'Seriousness' above in relation to SAE and the definition of AR.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

9.1.5 Suspected unexpected serious adverse reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction, which also demonstrates the characteristics of being unexpected, the nature, seriousness, severity or outcome of which is not consistent with the information about the trial treatment in question. In determining whether an SAE is expected or not, information regarding expected AEs is set out in the approved reference safety information in section 4.8 of the Summary of Product Characteristics (SmPC) or in section 7.4.8 of the IB. For radiotherapy, please refer to section Expected toxicity profile of radiotherapy, 5FU, capecitabine, oxaliplatin and AN0025 for a list of expected radiotherapy related side effects.

Medical and scientific judgement must be exercised in deciding whether an event is related to chemotherapy, immunotherapy agent, re-irradiation, progressive disease or another cause.

9.1.6 Reference safety information

The Reference Safety Information (RSI) is the identified section of the SmPC or IB used for assessing the expectedness of an adverse reaction.

The RSI for chemotherapy and the immunotherapy agent is defined as:

- Section 4.8 of the current locally approved standard of care SmPC for capecitabine
- Section 4.8 of the current locally approved standard of care SmPC for calcium folinate
- Section 4.8 of the current locally approved standard of care SmPC for fluororacil
- Section 4.8 of the current locally approved standard of care SmPC for oxaliplatin
- Section 7.4.8 of the trial-supplied IB for immunotherapy agent

Expectedness of an adverse reaction will be routinely assessed by CTRU upon receipt (i.e. not by site). SAEs, SARs and SUSARs will be reviewed by the CI (or delegate) and expectedness will be

checked at this review. If CTRU is not able to perform the expectedness review it will be performed by site.

The version of the above SmPCs to be used for the purposes of pharmacovigilance reporting will be supplied to sites by CTRU and filed in the ISF.

Please note that where the RSI does not explicitly state that expected SARs may be life-threatening / result in death, then such SARs which are life-threatening / may result in death must be considered unexpected and reported as SUSARs.

9.2 RECORDING AND REPORTING AEs AND ARs

Information about all AEs and ARs whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant eCRF. AEs and ARs that are not serious will require no expedited reporting.

Information on all adverse events will be collected for all participants from consent, weekly during trial treatment and up to 30 days post end of treatment, the washout period for AN0025.

Information on all adverse reactions will be collected for all participants from consent, weekly during trial treatment and up to final follow-up at 30 months post start of RT.

Both AEs and ARs will be evaluated for duration and intensity according to the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), see Appendix A.

9.3 RECORDING AND REPORTING SAEs, SARs AND SUSARs

9.3.1 Events not to be classed as SAEs

The following events **will not** be classed as SAEs within the trial:

- Hospitalisation for routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Hospitalisation for treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition
- Admission to hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency or outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission
- Disease progression
- Deaths attributable to rectal cancer beyond 42 days of the last administration of the study treatment

9.3.2 Events classed as expected SAEs / SARs

Examples of events which will be classed as expected SAEs / SARs within this trial are given below. These will not be reportable as SUSARs on the trial, unless the severity of the event is considered to be unexpected.

This is not intended to be an exhaustive list, therefore when determining whether an SAE/SAR is expected or not, please always refer to the relevant approved SmPC.

All events should be reviewed and assessed (for seriousness and causality) by the site PI, or another clinically qualified member of the medical team, authorised on the ARTEMIS APL.

9.3.3 Expedited recording and reporting requirements for SAEs, SARs and SUSARs

All SAEs, SARs and SUSARs (any grade) related to radiotherapy and/or chemotherapy and AN0025 that occur after randomisation will be collected during the weeks of trial treatment and up to final follow-up at 30 months post start of RT. Beyond this period only, SARs and SUSARs related to the trial treatment should be reported if the investigator becomes aware of them. This should continue until the end of trial notification.

The washout period for chemotherapy and AN0025 is 30 days, therefore SARs and SUSARs related to either chemotherapy or AN0025 will only be collected up to 30 days post end of treatment.

All SAEs, SARs and SUSARs for all participants must be entered on the SAE/SAR or SUSAR eCRF within 24 hours of the trial site team becoming aware of the event, regardless of causality. Please note: a paper SAE and SUSAR form will also be provided as a back-up in the event any urgent reporting is required and the MACRO database cannot be accessed.

For each SAE/SAR and SUSAR the following information will be collected:

- Full details in medical terms with a diagnosis, if possible
- Case description
- Event duration (start and end dates, if applicable)
- Seriousness criteria
- Outcome
- Action taken
- Causality (i.e. relatedness to trial treatment/investigation), in the opinion of the investigator*
- Whether the event would be considered expected or unexpected

*Assessment of causality and expectedness must be made by an authorised medically qualified person. If such as person is unavailable, initial reports without causality and expectedness assessment should be submitted to CTRU within 24 hours but must be followed up by medical assessment as soon as possible thereafter.

Please ensure that only one event is reported on each SAE/SAR eForm (details of multiple symptoms should be listed if they relate to the same event).

Any change of condition or other follow-up information should be sent to the CTRU within 24 hours site becoming aware of the information. Events will be followed up until the event has resolved or a final outcome has been reached. A receipt will be sent by the CTRU to the participating site for all SAE/SUSAR reports. If a receipt is not received within 2 working days please contact the CTRU.

Once all resulting queries have been resolved, the CTRU will request the original form should be sent to the CTRU and a copy to be retained on site.

All SAEs assigned by the PI or delegate (or following CI review) as both suspected to be related to trial treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The CTRU will inform the MHRA, and the Sponsor of SUSARs within the required expedited reporting timescales.

10 RESPONSIBILITIES

10.1 TRIAL SPONSOR - UNIVERSITY OF LEEDS

The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

10.2 PRINCIPAL INVESTIGATOR (PI)

Checking for AE, ARs when participants attend for treatment. Using medical judgement in assigning seriousness and expectedness using the relevant SmPC used locally. Ensuring that all SAEs, (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting. Ensuring that AEs, ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

10.3 CHIEF INVESTIGATOR (CI) / DELEGATE OR INDEPENDENT CLINICAL REVIEWER

The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, and pharmacovigilance within the trial. Ensuring that Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit. Using medical judgement in assigning seriousness and expectedness of SAE where it has not been possible to obtain local medical assessment. Immediate review of all SUSARs. Review of specific SAEs in accordance with the trial risk assessment and protocol. Classify SAEs using the MedDRA (Medical Dictionary for Regulatory Activities) coding system to assign each SAE to a Primary System Organ Class.

10.4 CTRU

The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards and CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006, including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for: i) the day-to-day running of the trial including trial administration, database administrative functions, data management, safety

reporting and statistical analyses, ii) data collection verification of SAEs and SUSARs, according to the trial protocol onto a MACRO database, iii) reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan, iv) reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan, v) expedited reporting of SUSARs, to the MHRA, Adlai Nortye and Sponsor within required timelines, vi) notifying Investigators of all SUSARs that occur within the trial which compromise participant safety, vii) preparing annual safety reports for the Research Ethics Committee (REC), viii) providing Adlai Nortye and its vendors with summary line-listings of all SAEs and SUSARs on an annual basis and, ix) to perform annual RSI checks and to prepare tables/materials for the annual Data Safety Update Report, x) reporting events to collaborating pharmaceutical companies in accordance with the trial contracts.

10.5 TRIAL MANAGEMENT GROUP (TMG)

In accordance with the Trial Terms of Reference, the TMG will provide clinical and practical advice on trial related matters. The TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial and a PPI representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and Health Research Authority (HRA) and supporting applications for Site Specific Assessments, (iv) submitting a Clinical trial authorisation (CTA) application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development. The TMG is accountable to the TSC and DMEC and are responsible to escalate concerns to these committees.

10.6 TRIAL STEERING COMMITTEE (TSC)

The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a PPI representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. If appropriate, the Sponsor will be invited to TSC meetings. The Committee will meet annually as a minimum. In accordance with the Trial Terms of Reference for the TSC, periodically reviewing blinded safety data and liaising with the DMEC regarding safety issues.

10.7 DATA MONITORING & ETHICS COMMITTEE (DMEC)

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing un-blinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The DMEC will meet annually to review a full report and a 6 monthly safety report will be provided between meetings, or more/less frequently as deemed appropriate by the DMEC. An early assessment of safety will be conducted after 10 patients (approx. 5 patients on AN0025) have been recruited and treated or after 6 months of recruitment, whichever is sooner.

10.8 ADLAI NORTYE

Inform the CTRU/Chief Investigator of any new information that becomes available during the course of the trial, which may affect the overall safety profile of the study drug.

11. ENDPOINTS

11.1 PRIMARY ENDPOINT

11.1.1 Clinical complete response at 6 months from the start of RT

Participants will be assessed for their cCR at 6 months (+/- 5 weeks) post start of RT treatment, for the primary endpoint. Response to treatment will be assessed via a composite of digital rectal examination (DRE), high resolution pelvic Magnetic Resonance Imaging (MRI) and sigmoidoscopy.

Clinical complete response (cCR) will be defined as (Fokas et al., 2021):

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*.

(If the tumour is too proximal to reach with DRE then assessment will be via MRI and sigmoidoscopy alone).

*Complete response in primary tumour is defined as normal appearances on MR (can rarely happen with no evidence of any previous tumour) or a linear scar only or dense fibrosis with no obvious tumour signal (mrTRG 1 or 2). In cases where DWI is used there is no evidence of restriction on DWI at site of the primary. Complete response in nodes is when the Involved nodes on the baseline scan have either completely regressed or are now <5mm in size with no residual suspicious morphological features, that is lack of any heterogeneous signal on T2WI and no capsular irregularity.

Every effort should be made to ensure that trimodality assessment of response occurs at 6 months (endoscopy, DRE, MRI). However, in the unusual circumstance when this might not be possible for a specific patient, confirmation of a cCR should always include rectal endoscopy. If one of either DRE or MRI cannot be assessed for a specific patient, then confirmation of cCR may still occur based on the endoscopy plus either DRE (if tumour was originally palpable pre-treatment), or pelvic MRI.

Participants who do not undergo surgery will have a response assessment via an MRI at 4 months from the start of RT. As per standard practice, a flexible sigmoidoscopy and further assessments may be deemed appropriate. If patients demonstrate tumour progression, no response or poor response at 4 months (defined as <50% reduction in tumour size on rectal endoscopy or mrTRG 4 (minimal response) or mrTRG5 (no response)), radical surgery should be considered and discussed at the colorectal MDT. Patients who do not achieve cCR at 6 months post start of RT

should be considered for salvage radical TME surgery. Patients with a cCR will continue with active surveillance.

Participants who receive surgery prior to the primary endpoint at 6 months post start of RT cannot be assessed for a cCR. Where the ultimate treatment aim is organ preservation, surgery will be considered failure and therefore these participants will be included in the analysis classified as no cCR.

The current cCR definition is based on clinical experience with standard neoadjuvant (chemo)radiotherapy. It is unknown whether 'augmented' treatment, as in the ARTEMIS experimental arm, increases the chance of rectal mucosal abnormalities, even in the absence of any residual cancer. If this was the case, then the cCR decision and primary endpoint could be significantly affected. In order to help inform future research, within ARTEMIS the subsequent outcomes of patients who have an ucCR at 6 months will be assessed. 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 on rectal endoscopy** (Fokas et al., 2021) (Section 8.14).

11.2 Secondary Endpoints

11.2.1 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.

11.2.2 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.

11.2.3 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 (Calvert et al., 2013; Coens et al., 2020; Calvert et al., 2018). The data will capture early effects of treatment, and long term patient experience.

11.2.4 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.

11.2.5 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.

11.2.6 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.

11.2.7 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.

11.2.8 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.

11.2.9 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.

11.2.10 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.

11.2.11 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

12 STATISTICAL CONSIDERATIONS

12.1 SAMPLE SIZE

Sample size: 140 patients (70 per arm)

A Sargent's three-outcome, two-stage comparative two-arm design (Hong and Wang, 2007) will be used to determine whether AN0025 added to standard RT treatment demonstrates sufficient efficacy to warrant further evaluation. The trial is designed to test the null hypothesis (H_0) that the proportion of participants with a cCR at 6 month post start of treatment for the intervention or experimental arm (P_E) is no better than the proportion of participants with a cCR in the standard CRT control group (P_C).

A cCR rate of 0.25 (25%) is anticipated in the control arm based on previous data (Bahadoer et al., 2021). A clinically relevant improvement in cCR rate to 0.45 (45%) is targeted with the addition of AN0025 to RT – absolute difference 20%. Assuming a cCR rate of 0.25 in the standard RT control arm, and 0.45 cCR rate in the intervention or experimental arm, with a 1:1 randomisation, 62 patients are required per arm. The interim futility assessment requires 26 patients, with the following 36 recruited in stage 2. Allowing for a 10% loss to follow-up from any cause and providing an even number of patients in each of the SCRT/LCCRT radiotherapy regimens, 70 patients are required, 140 patients in total.

The current evidence suggests similar outcomes for both SCRT and LCCRT, therefore the trial is designed to assess the overall efficacy of the treatment and control arms. The participants will be stratified by SCRT vs LCCRT and then minimised within each strata. Though not specifically powered for comparison in the stratified sub-groups, outcomes will also be explored and reported by radiotherapy regimen.

The LC/SC radiotherapy regimen split is estimated to be 50/50, given preliminary site surveys and clinical input. Therefore, it is expected around 35 patients will be recruited to each RT type in each arm. However, the proportion of LC/SC choice will be monitored, with the consideration for any changes in best practices and wider clinician opinions. The final primary endpoint decision will remain between the control and treatment arms as a whole.

ARTEMIS uses the optimal design optimisation, minimising the expected sample size under H_0, incorporating the probability of early termination. This design allows for an early assessment of futility. Operating characteristics and cut-off values will be recalculated according to the number of patients included in the analysis. Using the optimal design, setting the constraints for each of the four error terms as 0.1 (allowing for a tolerance of 0.005), the following operating characteristics are produced: type I error (alpha) =0.098, type II error (beta) =0.104, gamma = 0.062, eta = 0.104. Gamma is the probability the difference in proportions lies in the statistical

inconclusive/amber region, when the alternative hypothesis is true. Eta is the probability the difference in proportions lies in the statistical inconclusive/amber regions, when the null hypothesis is true.

Based on this, the cut-off values and conclusions for the statistical test are defined as follows:

Stage 1 - Interim assessment

$P_E - P_C < 0$ Terminate for futility

$P_E - P_C \geq 0$ Continue to stage 2

If the difference in proportions of patients achieving a cCR between the experimental and control arm is less than zero, at the point of interim analysis, then the trial will be terminated for futility. Otherwise, the trial will continue to the stage 2 assessment. Recruitment will not be paused during follow up for the interim analysis patient population.

Stage 2 – Final assessment

$P_E - P_C \leq 0.05$	Red: Fail to reject the null
$0.05 < P_E - P_C < 0.113$	Amber: Neither reject nor accept either hypothesis
$P_E - P_C \geq 0.113$	Green: Reject the null hypothesis

Red: If the difference in proportions of patients achieving a CR between the experimental and control arm is less than or equal to 0.05 (5%) then intensified radiotherapy will not be considered worthy of further investigation.

Amber: If the difference in proportions is between 0.05 (5%) and 0.113 (11.3%) then the decision to take intensified radiotherapy forward will be uncertain and consider other factors. In particular, we will incorporate other local control data, including an uncertain cCR, and the pCR outcomes.

Green: A difference in proportions greater than or equal to 0.113 (11.3%) would demonstrate sufficient efficacy of intensified radiotherapy to warrant larger-scale evaluation.

12.2 PLANNED RECRUITMENT

Overall trial

ARTEMIS will recruit approximately 5-6 patients per month, over a 2-year recruiting period, from 15-20 UK radiotherapy sites.

Interim assessment

Allowing for a conservative recruitment ramp-up, the required 58 patients (29 patients per arm adjusted for loss/ 26 response assessments per arm) are expected to be recruited by the end of year 1 (month 12) of recruitment. After the 6-months for the response assessment follow-up, the

futility interim analysis will take place in months 19-20 of recruitment. Recruitment will continue during this period.

13 STATISTICAL ANALYSIS

13.1 GENERAL CONSIDERATIONS

The CTRU statisticians are responsible for all statistical analysis. The analysis detailed below provides an overview of the analyses to be performed for the ARTEMIS trial). A separate detailed statistical analysis plan (SAP) will be written in accordance with CTRU standard operating procedures, prior to conducting any analyses.

Analysis of the primary and secondary endpoints will be performed on a modified intention-to-treat (MITT) basis, unless specified otherwise within the SAP. The MITT population is defined as all participants randomised who received at least one dose of trial treatment on study (including any dose of AN0025, radiotherapy or chemotherapy).

13.2 FREQUENCY OF ANALYSIS

The interim analysis will take place once the first 58 patients (adjusted for assumed 10% loss to follow-up) have reached their primary endpoint, i.e., 6 months post start of RT treatment. The first 26 patients within each arm, where response data can be used, will be included in the interim assessment.

The primary endpoint assessment and analysis of early endpoint including treatment compliance and early toxicity, will take place once the final participant has reached their primary endpoint 6 months post start of RT, and all data have been received and cleaned.

Analysis of all other the secondary endpoints will take place once the final participant has reached their 30 month post start of RT followed-up time point.

13.3 PRIMARY ENDPOINT ANALYSIS

Summary statistics will be presented for the response assessments measured at 4 and 6 months post start of RT, overall and by treatment arm. The number and proportion of participants in each response category will be reported. Summary statistics will also be presented separated by radiotherapy regimen, presented by treatment arm.

The proportion of participants achieving a cCR at 6 months post start of RT treatment and the associated 80% confidence intervals (corresponding to 1-sided 10% alpha) and 95% confidence intervals will be presented overall and by treatment arm.

The assessment of treatment efficacy will focus on the absolute difference in the proportion of participants achieving a cCR between the experimental and control arms, according to the 3 levels specified in section 12 Statistical Considerations. Cut-off boundaries may be re-calculated in the event that the final sample size differs from the sample size required.

Logistic regression will be performed, adjusting for the stratification and minimisation factors. The odds ratio for the addition of AN0025 treatment will be presented with the associated 80% and 95% confidence interval. The final trial decision will be based on the cut values for the three outcome design.

A sensitivity analysis including participants with uncertain cCR at 6 months post start of RT treatment (defined in section 11.1 Primary Endpoint) as having a cCR will be conducted to explore the appropriateness of the current definition in this intensified treatment setting. Subset summaries will be presented for the outcomes of these patients, exploring response assessment data and opinions/decisions from the local MDT's, in addition to any surgical outcomes and local or metastatic disease data.

13.4 SECONDARY ENDPOINT ANALYSIS

13.4.1 Acute & Late toxicity

The proportion of participants experiencing each CTCAE grade of toxicities as their maximum grade will be summarised overall and by treatment arm for the acute and late toxicity period. Summaries of serious events will be presented by type using the MedDRA classification.

The number and proportion of participants experiencing any grade 3 and above acute toxicity and late toxicity will each be presented by radiotherapy regimen and treatment arm.

All summary statistics will also be explored by radiotherapy regimen.

13.4.2 Treatment compliance

Summary statistics for the total dose of radiotherapy received and the duration of treatment will be presented by radiotherapy regimen and by treatment arm. Time from randomisation to start of treatment will be reported and monitored. Reasons for interruption to radiotherapy schedule will be summarised.

Summary statistics will be presented for the chemotherapy type and number of cycles delivered. The number and proportion of participants who experienced dose modifications will be reported including the level of dose reduction along with reasons where available.

Summary statistics on the treatment compliance to AN0025 will be summarised for those in the intervention arm. The number and proportion of participants receiving a reduced dose or dose omission will be presented for the intervention arm by radiotherapy regimen. Details of the reductions and omissions and their associated reasons will also be presented.

The proportion of participants adhering to the radiotherapy and chemotherapy schedule will be reported and compared between the treatment arms.

13.4.3 Patient reported outcomes (PROs) and Health Related Quality of Life (HRQoL)

Summary statistics, including mean scores, will be calculated for all domains of the EORTC QLQ-C30 and EORTC QLQ-CR29, EORTC item library additional items, EQ-5D-5L and for the overall LARS questionnaire. Summaries will be presented overall and by treatment arm, at each follow-up time points. Summaries will also be explored by radiotherapy regimen.

Treatment groups will be compared using a repeated measures model, adjusted for the stratification and minimisation factors, identified relevant clinical characteristics and baseline QoL scores. Differences in scores between treatment arms will be presented with associated 95% confidence intervals for the follow-up time points. Further detail will be documented in the statistical analysis plan, following the estimand framework and SISAQOL updates (Coens et al., 2020).

13.4.4 Surgical outcomes

Summary statistics of the surgical approach and procedure will be presented. The number and proportion of participants undergoing each surgical type and the method used will be presented overall and by treatment arm. Details on outcomes of surgery including the tumour R classification will also be presented.

Summary statistics will be presented on outcomes after surgery, including length of stay, Clavien Dindo complications, and any reoperation details.

13.4.5 Response assessment

The number and proportion of participants with a cCR will be presented by radiotherapy regimen and treatment arm at each of the follow-up assessments for those on the active surveillance pathway. Summary statistics will include each grade of mrTRG for early assessments at 4, 6, 9 and 12 months post start of RT.

The proportion of participants with a pCR and each grade of TRG will be presented, these measures are only assessed once post-surgery for each patient.

The combined proportion of participants with either a cCR at 6 months or pCR after surgery (between 6-9 months) will be reported along with a 95% confidence interval overall and by treatment arm. The combined proportion of cCR and pCR will be compared between treatment arms using a chi squared test.

13.4.6 Stoma, Locoregional regrowth rates

Summary statistics for stoma rates, and locoregional regrowth will be calculated by the number and proportion of participants with each event type, presented overall and by treatment arm. The type of stoma and reasons for formation will also be summarised.

The proportion of participants that have had an event by 30 months post-randomisation will be reported along with 95% confidence intervals. Time from randomisation to fashioning of a stoma and time from randomisation to locoregional regrowth will each be assessed using cumulative incidence.

13.4.7 Organ preservation rates, Organ-preservation-adapted Disease-free, Metastasis Free Survival and Overall survival

Time-to-event endpoints including OP, OP-DFS, MFS and OS will be analysed in a similar manner. The number and proportion of participants experiencing each event type will be presented overall and by treatment arm.

Each time to event endpoint will be presented using Kaplan-Meier (KM) curves. The median time-to-event estimates and 95% confidence intervals will be presented along with the log-rank test statistic (and associated p-value) testing for a difference in the median OP, OP-DFS, MFS and OS.

OP, OP-DFS, MFS, and OS by 30 months post randomisation will be compared between the treatment arms using Cox's Proportional Hazards (PH) model, adjusting for the minimisation factors. The assumptions of the Cox PH model will be tested. The HR for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% confidence intervals and associated p-value testing for the difference between the arms.

Participants who are event-free at the time of analysis, or are lost to follow-up/withdrawn prior to observing an event, will be censored at the last date known to be event-free.

14 TRIAL MONITORING

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the PIS and are asked to consent to their medical notes being reviewed by appropriate individuals on the Consent Form.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1 THE TRIAL STEERING COMMITTEE AND THE DATA MONITORING AND ETHICS COMMITTEE

The trial will be overseen by an independent Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

The DMEC will monitor the trial data, safety including SAEs and SUSARs, treatment related mortalities and the associated ethics of the trial. Listings of SAEs, and SUSARs will be provided to the DMEC on a regular basis. The DMEC will be provided with detailed un-blinded reports containing the information agreed in the data monitoring analysis plan, by the CTRU, at approximately 12-monthly intervals, with a 6 monthly safety report provided between meetings. An early assessment of safety will be conducted after 10 patients (approx. 5 patients on AN0025) have been recruited and treated or after 6 months of recruitment, whichever is sooner. Reports may be provided more or less frequently as determined in discussion with the DMEC.

After each review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

14.2 DATA MONITORING

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment.

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

14.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC, Sponsor and, where applicable, to individual NHS Trusts.

15 QUALITY ASSURANCE PROCESSES

15.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and Scottish Executive Health Department RGF for Health and Social Care 2006, and through adherence to CTRU SOPs.

15.2 SERIOUS BREACHES

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

16 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 52nd World Medical Association General Assembly, Edinburgh, Scotland 1996. Informed written consent will be obtained from the participants prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

17 ETHICAL APPROVAL

The trial will be submitted to and approved by a REC and the appropriate Site-Specific Assessor for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

18 CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- Consent form from participants to take part in the trial.

- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.

- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.

- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.

- Copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is randomised into the trial. All other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.

- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.

- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final trial analysis.

19 ARCHIVING

19.1 TRIAL DATA AND DOCUMENTS HELD BY CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures for a minimum of 25 years.

19.2 TRIAL DATA AND DOCUMENTS HELD BY RESEARCH SITES

Site data and documents will be archived at the participating research sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

19.3 PARTICIPANT MEDICAL RECORDS HELD BY RESEARCH SITES

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

20 STATEMENT OF INDEMNITY

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

21 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment. A publication plan will be produced for review and discussion with the TMG to ensure all publications are planned and captured centrally, and appropriate external review is incorporated.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the CI(s), trial leads and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the final analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the DMEC and TSC. However, early safety data maybe published to inform the research community. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

An electronic copy of peer-reviewed, published papers arising from this research will be deposited in the Europe PubMed Central database.

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23 APPENDICES

APPENDIX A – NCI-CTCAE

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

A copy of NCI-CTCAE is provided in the ISF.

APPENDIX B – ECOG PS

Table B 1 ECOG PS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed of chair more that 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

APPENDIX C – COCKROFT & GAULT FORMULA

Males

Glomerular filtration rate (GFR)= 1.2 x [140-age] x wt (kg)

serum creatinine (µmol/l)

Females

GFR= 1.2 x [140-age] x wt (kg) x 0.85

serum creatinine (µmol/

APPENDIX D – UNION FOR INTERNATIONAL CANCER CONTROL (UICC), TNM CLASSIFICATION OF MALIGNANT TUMOURS, EIGHTH EDITION

Colon and Rectum (ICD-O-3 C18-20)

Rules for Classification

The classification applies only to carcinomas. There should be histological confirmation of the disease.

The following are procedures for assessing the T, N and M categories.

Table D1 Colon and Retum Classification

T categories	Physical examination, imaging, endoscopy and/or surgical exploration
N categories	Physical examination, imaging and/or surgical exploration
M categories	Physical examination, imaging and/or surgical exploration

Table D2 Anatomical Sites and Subsites Colon and Rectum

Rectum (C20)	
Regional Lymph Nodes For each anatomical site or subsite the following are regional lymph nodes:	
Rectum	Superior, middle and inferior rectal (haemorrhoidal), inferior mesenteric, internal iliac, mesorectal (paraproctal), lateral sacra, presacral, sacral promontary (Gerota)
Metastasis in nodes other than those listed here is classified as distant metastasis.	

Table D3 Clinical Classification of Primary Tumour

TNM Clinical Classification	
TX	Primary Tumour
TX	Primary tumour invades submucosa
T0	No evidence of primary tumour
Tis[a]	Tis - Carcinoma in situ: invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3*	Tumour invades subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures[b.c.d] and/or perforates visceral peritoneum
T4a	Tumour perforates visceral peritoneum
T4b	T4b Tumour directly invades other organs or structures

Notes

[a]Tis includes carrier cells confined within the mucosal lamia propria (intramucosal) with no extension through the muscularis mucosae into the submucosa. Tis is not used in standard UK practice.

[b]Invades through to visceral peritoneum to involve the surface.

[c]Direct invasion in T4b includes the invasion of other organs or segments of the colorectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal locations, direct invasion of other organs or structures by virture of extension beyond the muscularis propria.

[d]Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-3, depending on the anatomical depth of wall invasion.

*For ARTEMIS trial purposes outside of UICC TNM classification, T3 will be split into: T3a: <1 mm of tumour spread beyond muscularis propria, T3b: 1-5 mm of tumour spread beyond muscularis propria), T3c: >5-15 mm of tumour spread beyond muscularis propria; T3d: >15mm of tumour spread beyond muscularis propria.

Table D4 Regional Lymph Nodes

N	Regional Lymph Nodes
NX	Regional Lymph nodes cannot be asssessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2 to 3 regional lymph nodes
N1c	Tumour deposit(s), i.e. satellites,* in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	N2b Metastasis in 7 or more regional lymph nodes

Note

* Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination.

Table D5 Distant Metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node (s)) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement

APPENDIX E – TUMOUR REGRESSION SCORE (TRS) AND TUMOUR REGRESSION GRADE (TRG)

Table E1 Tumour regression score as assessed using the 'new' 4-point system described in AJCC TNM8 and adopted by the RCPath

Tumour regression score	Description
Complete response	No viable cancer cells remain
Near complete response	Only single cells or rare small groups of cancer cells remain
Partial response	Residual cancer showing evident tumour regression, but more than single cells or rare small groups of cancer cells
Poor/no response	Extensive residual cancer with no evidence of regression

Table E2 Tumour regression grading as assessed using the 'old' 5-point Dworak modification of Mandard grading

Tumour regression grade	Description
Complete response	No tumour cells remain
Marked response	Very few tumour cells (difficult to find microscopically) in fibrosis +/- mucin
Moderate response	Dominant fibrosis with few tumour cells or groups
Mild response	Dominant tumour mass with obvious fibrosis
No response	No evidence of regression