Clinical Trials Summary for out of hours Important Reference

Lancashire Teaching Hospitals NHS Foundation Trust

Acronym study title	**ARTEMIS -** Augmenting RadioTherapy in REctal Cancer to Minimise Invasive Surgery
Study Details	Randomised phase II, multi-centre open-label study All patients will receive standard **radiotherapy**: 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. In addition, any other areas on staging MRI considered to represent definite macroscopic disease by the MDT will also receive an SIB to 50 Gy including extra-mural vascular invasion and involved lymph nodes (including involved pelvic side wall nodes). Concurrent capecitabine will be given on the days of radiotherapy orally at 825mg/m2 twice daily throughout the radiotherapy course. **OR** 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).
Principal Investigator PI Sub PI's	Dr Deborah Williamson
Research Nurse Team	Oncology - Rashmi Madden
Drug therapy	**AN0025 (Immunotherapy)** in addition to FOLFOX or CAPOX Chemo regimes
In the event that a patient calls this hotline for advice	ARTEMIS DRUG INTERRUPTION AND DOSE MODIFICATION FOR TOXICITY protocol section 7.4

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.

7.4.2. 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.

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*

7.4.2.

<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

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.

7.4.2.

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

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

7.4.2.

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)

Delay of cycle	Occurrence	Subsequent Dose reduction (DR)			
		Oxaliplatin	**5FU bolus**	**5FU infusion/ Capecitabine**	**AN0025**
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.					
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 80% starting dose	No change	No change	No change	100% dose
	2nd occurrence at 80% 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

Blood count on day 1	ANC<1.5x10^9/L	**o**					Platelets <100x10^9/L					

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ARTEMIS Protocol version 4.0, July 29th, 2024.

Table 7.19 Dose modificati ns for Febrile Neutropenia:

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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)

3 Muc sitis Toxicity
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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

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4 Neur sensory 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. e

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

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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.

6 R .nal impairment

Table 7.23 Dose modification for renal impairment during FOLFOX/CAPOX +/- 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%.

7.4.3. e

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.

7.4.3. e

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 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.

7.4.3. e

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

7.4.3.

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.

7.4.3. e

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.

7.4.3.e

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.