PelvEx II

Multicentre, open-label, randomised, controlled, parallel arms clinical trial of induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer.



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CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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1. ABBREVIATIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
BSA	Body surface area
CA	Competent Authority
CAPOX	Capecitabine, oxaliplatin
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CT	Computed Tomography
CTCAE	Common terminology criteria for adverse events
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FOLFOX	5-fluorouracil, leucovorin, oxaliplatin
FOLFIRI	Irinotecan, leucovorin, 5-fluorouracil
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HDR-IOBT	High-dose-rate intra-operative brachytherapy
IB	Investigator's Brochure
IC	Informed Consent
IKNL	Integraal Kankercentrum Nederland (Netherlands Comprehensive Cancer Organisation)
IOERT	Intra-operative external beam radiotherapy
IORT	Intra-operative radiotherapy
IV	Intravenously
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LARC	Locally advanced rectal cancer
LRRC	Locally recurrent rectal cancer
MDT	Multidisciplinary team
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MRI	Magnetic resonance imaging
pCR	Pathologic complete response
R0 resection	Resection with clear resection margins
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TME	Total mesorectal excision
PME	Partial mesorectal excision

UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WHO	World health organisation
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

2. SYNOPSIS

2024-512526-28-00

'Multicentre, open-label, randomised, controlled, parallel arms clinical trial of induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer.'

Rationale

The overall survival of patients undergoing curative multimodality treatment for locally recurrent rectal cancer (LRRC) remains poor, with a 5-year overall survival of approximately 30%. The most important prognostic factor for survival is a clear resection margin (R0 resection). Neoadjuvant chemoradiotherapy aims at downstaging local disease, thus facilitating radical resection. However, even with neoadjuvant chemoradiotherapy, radical resections are achieved in only ±60% of patients. The addition of induction chemotherapy prior to neoadjuvant chemoradiotherapy may improve downstaging of the tumour and thereby result in more R0 resections. Subsequently, increasing the rate of R0 resections should decrease local re-recurrence and thereby improve quality of life and overall survival in patients with LRRC.

Objective

The primary objective of this study is to determine the rate of resections with clear resection margins after treatment with induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery compared to treatment with neoadjuvant chemoradiotherapy and surgery alone. The secondary objectives are to determine the local re-recurrence free survival, progression free survival, metastasis free survival, disease free survival, overall survival, radiological response, pathologic response, toxicity, surgical complications, quality of life and costs for both arms.

Main trial endpoints

The primary endpoint of the study is the rate of clear resection margins after surgery.

Secondary trial endpoints

Secondary endpoints are local re-recurrence free survival, progression free survival, distant metastasis free survival, disease free survival, overall survival, pathologic response, radiological response, systemic therapy related toxicity (NCI-CTCAE v5.0 grade ≥3), the number of patients completing neoadjuvant treatment, surgical characteristics, major postoperative complications (Clavien-Dindo ≥3) up to 90-days postoperatively, quality of life and cost-effectiveness.

Trial design

This is a multicentre, open-label, phase III, parallel arms, randomised controlled trial that randomises eligible patients in a 1:1 ratio to receive induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm).

Trial population

Patients diagnosed with locally recurrent rectal cancer who previously underwent a partial or total mesorectal excision for rectal cancer or for distal sigmoidal cancer, with or without (chemo)radiation, without distant metastases or contraindications for the planned intervention are eligible for inclusion.

Interventions

Patients allocated to the experimental arm will receive induction chemotherapy which consists of three 3-weekly courses CAPOX or four 2-weekly courses FOLFOX/FOLFIRI, followed by restaging with pelvic MRI and thoracoabdominal CT-scan. In case of distant metastases or progressive unresectable local disease, palliative treatment will be offered. In case of progressive but resectable local disease, patients will start chemoradiotherapy within 3-5 weeks. In case of responsive or stable disease, one additional 3-weekly course CAPOX or two additional 2-weekly courses FOLFOX/FOLFIRI will be administered. Subsequently, but not earlier than 3 weeks after the first day of the last cycle of induction chemotherapy, chemoradiotherapy will be administered. Chemoradiotherapy will be administered according to standard of care. The radiotherapy dose will be either 30 or 50 Gy, depending on whether the patient received previous radiotherapy. After restaging with MRI and CT-scan, surgery will be performed 10-14 weeks after the last day of chemoradiotherapy. If deemed necessary and feasible, intra-operative radiotherapy will be administered. Patients allocated to the control arm receive chemoradiotherapy alone followed by surgery.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

The potential benefit from adding induction chemotherapy to the neoadjuvant treatment regimen of patients with LRRC has to be weighed against the burden and risks of adding chemotherapy in the experimental arm. The risks of this study primarily consist of treatment-related toxicity and morbidity. There is extensive experience with the investigational chemotherapy agents in human beings with colorectal cancer and they are proven to be feasible and safe. Toxicity caused by these chemotherapy agents when administered prior to chemoradiotherapy and surgery will be investigated in this study and will also be a part of the interim analysis in order to ensure safety. The other potential risks/burdens are: additional visits to the outpatient department during the administration of induction chemotherapy, preoperative disease progression and secondary unresectability, repeated withdrawal of an additional 20ml blood during standard scheduled blood collection moments if patients have signed informed consent for participation in blood collection for translational research, and quality of life questionnaires. The investigators feel that the potential benefit of the experimental arm outweighs the burden and risks of participation.

3. INTRODUCTION AND RATIONALE

3.1 Current status and treatment approach

As a result of several developments in the treatment of rectal cancer, the overall survival of patients with rectal cancer improved significantly and the rate of locally recurrent rectal cancer (LRRC) has declined from 20-30% to 6-10%.[1–3] However, patients who develop a local recurrence still have a poor prognosis with a 5-year overall survival of approximately 30% in those patients treated with curative intent.[4–7]

The most important prognostic factor influencing survival after surgery is a clear resection margin (R0 resection).[1,2,8–11] After achieving an R0 resection, 5-year overall survival rates vary between 48% and 58%, whereas a resection without clear resection margins (R1/2 resection) results in a 5-year survival of 10-18%.[5,9,10,12–14] Moreover, incomplete resections result in 5-year local re-recurrence rates of 70-80% [5,9,10] and local re-recurrence is associated with severe morbidity and a poor quality of life.[15] A recent study by our group showed that patients who underwent a gross incomplete resection have a prognosis as poor as patients who were offered palliative treatment, despite the obvious bias that only patients in good condition who were deemed to have a chance of cure were selected for surgery.[12]
Unfortunately, achieving an R0 resection in these patients is challenging because of a distorted anatomy due to prior TME or PME surgery, the difficult distinction between fibrosis and malignant tissue after previous radiotherapy and the ingrowth of the recurrent disease in other structures such as the adjacent organs, pelvic side wall and sacrum. Therefore, in the Netherlands, preoperative treatment with chemoradiotherapy is standard of care in accordance with the ESMO guidelines.[16] However, a proportion of the patients with locally recurrent rectal cancer has already received (chemo)radiotherapy for their primary tumour. In those patients treatment consisting of reirradiation with a dose of 30 Gray combined with capecitabine has been proven safe and effective.[1,17] Despite neoadjuvant treatment with chemo(re)irradiation, R0 resections are achieved in only 60% of patients.[7,18]

3.2 Potential benefit and disadvantages of induction chemotherapy

A possible way to increase the number of R0 resections, and hereby eventually decrease the local re-recurrence rate, is the addition of induction chemotherapy. The addition of induction chemotherapy to the neoadjuvant treatment of patients with LRRC may lead to more R0 resections by inducing more local tumour downstaging than what can be achieved with chemoradiotherapy alone. In addition, induction chemotherapy may also potentially improve tumour vascularity, which may enhance tumour sensitivity to chemoradiotherapy.[19]

Besides the achievement of more R0 resections, improved local downstaging could also lead to a higher proportion of patients with a pathologic complete response (pCR). A pCR proved to be a predictive variable in LRRC patients.[20] Alongside the local effect, induction chemotherapy may also have the potential to eradicate micrometastases which may decrease the occurrence of distant metastases.
The addition of induction chemotherapy may also have drawbacks. Induction chemotherapy induces toxicity itself, and could therefore delay subsequent treatment due to chemotherapy induced morbidity or reduce compliance. Moreover, a prolonged and more intensified neoadjuvant course may influence the patients' performance state and hereby have a negative impact on the surgical morbidity.

Furthermore, the prolonged neoadjuvant treatment may increase the risk for disease progression and secondary unresectablity. However, it is unlikely that patients with disease progression under induction chemotherapy would have benefited from surgery as this progression reflects an unfavourable tumour biology. In these patients induction chemotherapy offers the opportunity to avoid potentially harmful surgery.

3.3 Current evidence regarding induction chemotherapy

Induction chemotherapy in addition to neoadjuvant chemoradiotherapy is increasingly being used although robust evidence is lacking.[21] Several retrospective studies and phase 2 clinical trials have been performed to investigate the role of induction chemotherapy in patients with primary locally advanced rectal cancer, showing high R0 resection rates.[22–25] However, other studies did not demonstrate superior R0 resection rates after the addition of induction chemotherapy.[26–28] Several others studies investigating this treatment regimen used pCR as their primary endpoint. As with the studies focussing on R0 resection rate, the results were mixed. Some studies described promising pCR rates, whereas others found no effect of adding induction chemotherapy with regard to the pCR rate.[29–33]

Regardless of the effect of this treatment regarding the R0 resection or pCR rate, induction chemotherapy seemed feasible with high compliance rates to the treatment as well as the subsequent chemoradiotherapy and with acceptable toxicity as well as postoperative morbidity.[27,32,34]

The available literature regarding induction chemotherapy in addition to chemoradiotherapy for patients with LRRC is limited; up to this moment only three retrospective studies, performed by the group of one the principal investigators of this study, have been published.[20,35,36] The first study focused on patients with a lateral local recurrence.[35] In this cohort, a subgroup of thirteen patients were treated with induction chemotherapy followed by chemoradiotherapy resulting in a drastically improved R0 resection rate of 85%. In the second study, 58 patients with locally recurrent rectal cancer who underwent previous radiotherapy for the primary tumour received induction chemotherapy followed by chemoreirradiation. This group was compared to a historical cohort of 71 similar patients who received neoadjuvant reirradiation alone. Patients who received induction chemotherapy had a high pathological complete response rate of 17%, whereas the pCR rate was only 4% in patients who received chemoradiotherapy alone. Despite the improved pCR rate in the induction chemotherapy group, R0 resection rates were comparable between both groups.[36] Certainly, the induction chemotherapy group consisted of surgically unfavourable cases which hampers comparison. The most recently published study evaluated 132 patients who received induction chemotherapy prior to neoadjuvant chemoradiotherapy and surgery. In accordance with results from the previous publication a pCR of 17% was observed, implying superior downstaging by induction chemotherapy in addition to neoadjuvant chemoradiotherapy.[36] However, although this was not a comparative study, the R0 resection rates did not appear to have increased (63%). This may be explained by the fact that in this cohort study induction chemotherapy was initially administered to patients with unresectable disease or prognostic unfavourable characteristics specifically, thereby negatively affecting the R0 resection rate.

To further evaluate these results, we studied the R0 resection rate in all patients who underwent a resection for LRRC in the Catharina Hospital Eindhoven regardless of type of neoadjuvant treatment (unpublished). Between 2010-2014 we found a 54% R0 resection rate (80/141). During 2015-2016 this

increased to 65% (56/86) and during 2017-2018, the R0 resection rate increased to 75% (67/90). In a CUSUM analysis, this was identified as a trend. Since the addition of induction chemotherapy was the only variable that changed over this time period, from 26.5% between 2010-2014 to 58.1% in 2015-2016 to 75.6% in 2017-2018, it is likely that induction chemotherapy is responsible for this increasing R0 resection rate.

3.4 Rationale for the study

In conclusion, the additional value of the prolonged and intensified treatment with induction chemotherapy to chemoradiotherapy and surgery in LRRC is currently not established. Nonetheless, induction chemotherapy in addition to chemoradiotherapy and surgery for patients with LRRC is increasingly being applied.[21] Therefore, there is a strong need for a randomised controlled trial to determine the value of induction chemotherapy.

This study randomises patients with locally recurrent rectal cancer to receive either induction chemotherapy followed by chemoradiotherapy and surgery (experimental arm) or chemoradiotherapy and surgery (control arm). As mentioned before, an R0 resection is the single most important prognostic factor in patients with LRRC, as patients without clear resections margins are at higher risk for developing a local re-recurrence, which is associated with high morbidity and a significant impact on the quality of life, as well as a higher risk of developing distant metastases.[6,10,11,15] Therefore, the aim of this study is to improve the R0 resection rate.

The investigators hypothesize that treatment with induction chemotherapy will lead to a 15% increase of the R0 resection rate compared to treatment with neoadjuvant chemoradiotherapy and surgery alone.

4. STRUCTURED RISK ANALYSIS

4.1 Potential issues of concern

Not applicable, as all investigational medical products will be used in their authorised form for their authorised indication; see Chapter 4.2.

4.2 Overall synthesis of the direct risks for the research subjects

The most important potential risks and burden in the experimental arm are: additional hospital visits for the induction chemotherapy, toxicity of induction chemotherapy, preoperative disease progression and secondary unresectability, increased toxicity of chemoradiotherapy, increased postoperative complications and decreased quality of life due to an intensified and prolonged neoadjuvant treatment course.

With regard to toxicity of treatment, all investigational products (capecitabine, oxaliplatin, 5-fluorouracil, leucovorin, irinotecan) have a marketing authorisation and are used in the authorised form for the authorised indication (colorectal cancer). Therefore, the mechanism of action for these chemotherapy agents is well-understood, its side-effects can be managed well and the potential effect has been proven. We thus expect the risk of toxicity to be outweighed against the potential benefit. With regard to the potential increased toxicity of chemoradiotherapy and postoperative complications, several phase 2 trials in patients with locally advanced rectal cancer showed high compliance rates to the subsequent chemoradiotherapy and with acceptable toxicity as well as postoperative morbidity.[27,32,34] In addition, patients will be operated 10-14 weeks after completing chemoradiotherapy. This should give the patient enough time recover from the neoadjuvant treatment.

With regard to the preoperative disease progression and secondary unresectability, it is unlikely that patients with disease progression under induction chemotherapy would have benefited from surgery as this progression reflects an unfavourable tumour biology. In these patients induction chemotherapy offers the opportunity to avoid potentially harmful surgery.

In both arms, the questionnaires and additional blood collection could be an additional burden for the participating patients. However, patients are given the opportunity to give separate permission for participation in blood collection.

Furthermore, all above mentioned potential risks will be actively monitored by the DSMB. In conclusion, the principal investigators consider the extra potential risk for patients in the experimental arm to be acceptable, hypothesizing that a significant improvement in radical resections may be obtained.

4.2.1 Risks and unknowns

Although capecitabine, oxaliplatin, leucovorin, 5-fluorouracil, irinotecan and S1 (Teysuno) are routinely used in clinical practice, they carry inherent risks, particularly in relation to chemotherapy-induced toxicity. While induction chemotherapy, consisting of CAPOX or FOLFOX/FOLFIRI, is generally considered a well-tolerated regimen, it is not without risks. Common adverse effects include fatigue, myelosuppression, hand-foot syndrome, nausea, diarrhea, sensory neuropathy, dysesthesia and rarely cardiac arrythmias and ischemia. While the majority of side-effects are manageable and transient, they

still require close monitoring and appropriate management. All patients will receive neoadjuvant radiotherapy with concurrent oral chemotherapy, according to standard operating procedures. Concomitant chemotherapy consists of capecitabine, or alternatively Teysuno in case of unacceptable toxicity to capecitabine. Common adverse effects include hand-foot skin reactions, fatigue, nausea, diarrhea, proctitis, sensory neuropathy and leukopenia. Overall, majority of chemotherapy-related toxicity observed are generally manageable and resolve without long-term consequences. Timely identification and appropriate clinical management of these events are critical to ensuring participant safety. Lastly, to allow patients sufficient time to recover from neoadjuvant treatment, surgery will be performed 10-14 weeks after completing chemoradiotherapy.

Beyond chemotherapy-related toxicity, there are additional risks associated with neoadjuvant therapy and subsequent surgery. Patients undergoing neoadjuvant chemotherapy and radiotherapy may experience delayed wound healing, increased risk of anastomotic leakage and a higher incidence of post-operative infections. These risks are well-documented in standard treatment and are inherent to the multimodal approach used in this study. Furthermore, while neoadjuvant therapy is expected to improve local tumor control, there remains a possibility of disease progression despite treatment, which could ultimately necessitate more extensive surgical interventions or systemic therapy adjustments.

All abovementioned potential risks will be actively monitored by a data safety monitoring board (DSMB), consisting of a medical oncologist and a surgical oncologist as well as a statistician who are not involved in the study and have no competing interests. The DSMB will review the safety data after 100 patients have undergone surgery. Premature cessation of the study is warranted if the percentage of patients not able to complete neoadjuvant chemoradiotherapy due to treatment related toxicity in the experimental arm is 20% higher compared to patients in the control arm, or if the percentage of patients with major post-operative morbidities (Clavien Dindo ≥3) is 25% higher in the experimental arm compared to the control arm.

In summary, the principal investigators deem the additional potential risk for patients in the study to be justifiable, as they hypothesize that it could lead to a significant improvement in radical resection rates.

4.2.2 Risk mitigation strategies

The study is designed to ensure that patients receive optimal supportive care to minimize adverse effects and treatment-related complications. To manage chemotherapy-induced toxicities, dose adjustments will be implemented as necessary in accordance with standard clinical guidelines. Patients will be monitored for early signs of toxicity, and treatment modifications will be made in cases of severe adverse events. Supportive measures, such as laboratory results and vital functions are taken into account.

A DSMB will be established to oversee trial progress and ensure patient safety throughout the study. This independent body will periodically review safety data, monitor adverse events, recommend modifications if needed to maintain an acceptable risk-benefit ratio and to decide whether recruitment should be terminated early because of safety reasons. Additionally, all patients will undergo regular evaluations by multidisciplinary teams (MDTs), including surgical oncologists, medical oncologists, radiation oncologists, gastroenterologists and radiologists, to optimize treatment decisions and ensure that any emerging risks are promptly addressed. Standardized imaging protocols will be employed for

restaging after neoadjuvant therapy, allowing for precise evaluation of tumour response and resectability, further facilitating informed decisions regarding surgery.

4.2.3 Justification of risk acceptance

Given that the investigational medical products in this study are authorized and widely used in clinical practice, the study does not introduce additional risks beyond those already inherent to standard treatment for locally recurrent rectal cancer. The expected benefit of the study—a potential increase in radical resection rates and — outweighs the manageable toxicities associated with each treatment regimen. As aforementioned, a radical resection is the single most important prognostic factor in patients with LRRC, as patients without clear resections margins are at higher risk for developing a local re-recurrence, which is associated with high morbidity and a significant impact on the quality of life, as well as a higher risk of developing distant metastases.[6,10,11,15] Thus, the potential benefits of this study justify the risks involved, making it an ethically and clinically sound investigation.

Furthermore, patients enrolled in this trial will undergo close monitoring, with frequent safety assessments and access to dose modifications, ensuring that any severe adverse events are addressed promptly without compromising treatment efficacy. The presence of the multidisciplinary teams (MDTs) and an independent DSMB ensures that patient safety remains the highest priority.

A comprehensive overview of the most relevant potential risks and safety measures is available in the Summary of Product Characteristics (SmPCs) for each treatment regimen.

5. OBJECTIVES AND ENDPOINTS

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint for the primary objective(s)**
To compare the proportion of patients with a clear (R0) resection margin between both arms.	Clear resection margin rates, as determined by a pathologist working in one of the *expert centres.* A resection margin is considered clear if there are no tumour cells in any of the resection surfaces as determined by microscopy (resection margin >0 mm). An R1 resection is considered a resection with the presence of tumour cells in any of the resection surfaces as determined by microscopy (resection margin = 0 mm). An R2 resection is considered a gross incomplete resection with clinically overt tumour remaining in the patient, with involved margins confirmed by the pathologist. In case of a clear resection margin, the margin in millimetre is recorded in the pathology report as well. The criteria for histopathological evaluation and recording will be defined in a standard operating procedure. A standardized evaluation form will be provided; all pathologists involved will use this form for all patients included in the trial.
Secondary objective(s), if applicable	**Endpoint(s) for secondary objective(s), if applicable**
To compare long term oncological outcomes at 3- and 5-years between both arms.	• 3-year and 5-year local re-recurrence free survival. Re-recurrence is defined as a local re-recurrence confirmed by either radiology or histopathology. Re-recurrence is registered by the treating physician in the patient file during follow-up. • 3-year and 5-year progression free survival. Progression is defined as progression of the local recurrence, a local re-recurrence confirmed by either radiology or histopathology, distant metastases confirmed by radiology or histopathology or death. Data regarding disease progression are registered by the treating physician in the patient file during follow-up. • 3-year and 5-year metastasis free survival. Distant metastases may be confirmed by either radiology or histopathology. Data on distant metastases are registered by the treating physician in the patient file during treatment course and follow-up. • 3-year and 5-year disease free survival. Disease free survival is defined as no confirmed re-recurrence, distant metastases or death. Disease recurrence is registered by the treating physician in the patient file during follow-up.

	• 3-year and 5-year overall survival. Mortality is registered in the patient file which is linked to municipal personal records database.
To determine the pathologic response and compare this between both arms.	The pathologic response is graded according to the Mandard grading system.[43] The Mandard grading is registered by the pathologist in the pathology report.
To determine the toxicity related to the administration of induction chemotherapy in the experimental arm.	Systemic related toxicity is graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Toxicity caused by induction chemotherapy will be scored from day one of the first cycle of induction chemotherapy until one month after the last administration of the chemotherapy and is registered in the patient file by the treating medical oncologist. Only all non-hematologic NCI-CTCAE grade 3 and all NCI-CTCAE ≥4 are registered.
To determine the compliance to induction chemotherapy in the experimental arm.	Information on completion of induction chemotherapy is registered by the treating medical oncologist. In all patients in whom a dose reduction is required the reason for dose reduction will be recorded.
To compare the toxicity related to the administration of chemoradiotherapy between both arms.	Chemoradiotherapy related toxicity is graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Toxicity caused by chemoradiotherapy will be scored from start of radiotherapy until 3 months after the last administration of the radiotherapy and is registered in the patient file by the treating radiation oncologist. Only all non-hematologic NCI-CTCAE grade 3 and all NCI-CTCAE ≥4 are registered.
To compare the compliance to chemoradiotherapy between both arms.	Information on completion of chemoradiotherapy is registered by the treating radiation oncologist. In all patients in whom a dose reduction is required the reason for dose reduction will be recorded.
To compare the number of patients undergoing surgery between both arms.	This is calculated as a percentage from the total number of patients that were randomised.
To compare surgical characteristics between both arms.	Directly after surgery information with respect to procedure related characteristics is registered in the surgical report in the patient file by the operating surgeon. Data on intra-operative radiotherapy, if administered, are registered in the patient file by the treating radiation oncologist.
To compare the rate of major surgical complications between both arms.	Surgical complications are graded according to Clavien-Dindo.[44] Complications will be scored from date of surgery up to 3 months after surgery and are registered in the patient file by the treating physician.

To assess the objective radiological response to the neoadjuvant treatment.	Assessment and reporting of all MRI scans is performed according to a standard operating procedure and is registered in the patient file by the radiologist.
To compare the quality of life between both arms.	Generic and cancer-specific quality of life assessments are assessed with EQ-5D-5L, QLQ-C30 and QLQ-CR29 at inclusion and at 3-, 12- and 24-months post-operative. The questionnaires will be sent either by mail or digitally, according to the patient's preference.
To determine the cost-effectiveness and –utility.	For the purpose of economic evaluation, the EQ-5D-5L questionnaire is used at inclusion and at 3, 12 and 24 months post-operatively. The questionnaires will be sent either by mail or digitally, according to the patient's preference.
To systematically collect blood and tissue samples from enrolled patients for future translational research.	In two 10 mL evacuated blood draw tubes a total of 20 ml of blood will be drawn at baseline, before induction chemotherapy (only in experimental arm), before chemoradiotherapy, before surgery, 3 months after surgery, and once per year during 3 years of follow up. Blood draws will be combined with routine blood draws for standard care. Blood draw tubes are maintained at room temperature and sent to the Department of Medical Oncology of the Erasmus Medical Centre where they will be processed within 96 hours after drawing the blood.
Exploratory objective(s), if applicable	**Endpoint(s) for exploratory objective(s), if applicable**
Not applicable.	Not applicable.

6. STUDY PLAN AND DESIGN

6.1 Trial Design

This is a multicentre, open-label, phase III, parallel arms, randomised controlled trial. The study randomises eligible patients in a 1:1 ratio to receive either induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm), the latter being the current standard of care in the Netherlands.

This study is conducted by the Catharina Hospital Eindhoven, Erasmus Medical Centre, Antoni van Leeuwenhoek, University Medical Centre Groningen, Amsterdam University Medical Centres, Maastricht Medical Centre, Haaglanden Medical Centre, Leiden University Medical Centre and Noordwest Clinics. All these hospitals performed a minimum of 10 resections of LRRC per year during the past three years and thus qualify as an expert centre. These expert centres are responsible for inclusion, administering neoadjuvant treatment, surgery, and follow-up of patients. Once the expert centres have commenced with the study, additional hospitals and radiotherapy institutes will be included in the trial with the purpose of administering neoadjuvant treatment and performing follow-up. These centres are, in contrast to the expert centres, not involved in inclusion or surgery of patients.

After successful implementation of this study protocol in the Netherlands it is intended to extend this trial to several centres within Europe. These centres all qualify as expert centre as defined above. This international collaboration will greatly contribute to patient accrual.

After complete work-up is performed patients will be discussed in the multidisciplinary tumour board (MDT) in one of the expert centres. The MDT consists of at least one surgical oncologist, one medical oncologist, one radiation oncologist and one radiologist who are experienced in the diagnosis and treatment of LRRC. Only if there is consensus in the MDT about whether or not a patient meets the inclusion and exclusion criteria, the patient will be randomised.

Patients allocated to the experimental arm start treatment with induction chemotherapy. Patients are referred to the medical oncologists within 2 weeks after randomisation, and induction chemotherapy starts within 4 weeks after randomisation. The treating medical oncologist is responsible for the counselling, administration and follow-up with regard to the neoadjuvant treatment. Before starting the treatment, the patient will be checked for a possible homozygous DPD deficiency (if this was not performed before). If so, patient will be excluded from the study. Induction chemotherapy consists of either three three-weekly cycles of CAPOX or four two-weekly cycles of FOLFOX. It is left to the discretion of the treating medical oncologist which of the two will be administered. In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFIRI may be prescribed. FOLFIRI consists of four two-weekly cycles. After three cycles of CAPOX or four cycles of FOLFOX/FOLFIRI, a pelvic MRI is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT-scan is optional. Assessment and reporting of the MRI will be done according to a standard operating procedure. All restaging imaging will be assessed during one of the multidisciplinary tumour board meetings in one of the before mentioned expert centres. If a patient developed distant metastases or local disease became unresectable, best palliative treatment is offered according to standard of care. If a patient has progressive local disease, but surgery is still considered feasible, no further systemic therapy will be administered and patients will start treatment with chemoradiotherapy. If a patient has stable or responsive disease, induction chemotherapy will be continued with either one three-weekly cycle of

CAPOX or two two-weekly cycles of FOLFOX/FOLFIRI. The timing of the restaging MRI must be in such way that a potential continuation of the induction chemotherapy will not be delayed.

All patients receive chemoradiotherapy. In the control arm, patients are referred to the radiation oncologist within 2 weeks after randomisation, and chemoradiotherapy starts within 4 weeks after randomisation. Patients in the experimental group will start chemoradiotherapy within 3-6 weeks after the first day of the last cycle of chemotherapy. Concurrent chemoradiotherapy will be delivered according to standard operating procedures. The radiotherapy dose depends on whether the patient previously received radiotherapy. In radiotherapy-naïve patients, full course radiotherapy will consist of 25x2.0 or 28x1.8 Gy radiotherapy. In case of previous radiotherapy, the radiotherapy dose will consist of 15x2.0 Gy. Concomitant chemotherapy will be capecitabine, administered orally with a dose of 825 mg/m2 twice daily on radiotherapy days. In case of unacceptable toxicity to capecitabine during chemoradiotherapy, concomitant Teysuno administered orally with a dose of 25mg/m2 twice daily on radiotherapy days may be prescribed (physician's discretion). Delineation of the clinical target volume will be done according to the delineation guidelines that are described in a Standard Operating Procedure. To ensure uniform delivery of radiotherapy a quality-assurance (QA) procedure with central assessment of individual cases will be performed. The QA procedure is described in more detail in a Standard Operating Procedure. The treating radiation oncologist is responsible for the counselling, administration and follow-up with regard to the neoadjuvant treatment.

Between 4-6 weeks after the last day of the radiotherapy course an MRI of the pelvis is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT scan is optional. Assessment and reporting of the MRI will be done according to a standard operating procedure. Restaging imaging will be discussed during a specialised MDT including surgeons, radiologist, radiation oncologists and medical oncologists in one of the aforementioned expert centres. In case of distant metastases or unresectable local disease, best palliative treatment is offered. In case of resectable disease, patient will undergo surgery.

Surgery is performed according to the national standard of care by experienced surgical oncologists within 10-14 weeks after completing chemoradiotherapy. Type of surgery depends on the location of the recurrence and involvement of adjacent structures and is left to the discretion of the operating surgeon. In case of the need for reconstructive surgery (e.g., after complete cystectomy), the required specialist is consulted and will attend the surgical procedure. When deemed necessarily, e.g., when there is tumour adherence or no adequate soft tissue margin for a clear resection, and feasible by the surgeon and radiation oncologist intra-operative radiotherapy will be administered. Intra-operative radiotherapy (IORT) is delivered by either intra-operative external beam radiotherapy (IOERT) or high-dose-rate intra-operative brachytherapy (HDR-IOBT), and dose is left to the discretion of the treating radiation oncologist.[40,41]

A flowchart of the study is presented in Figure 1:

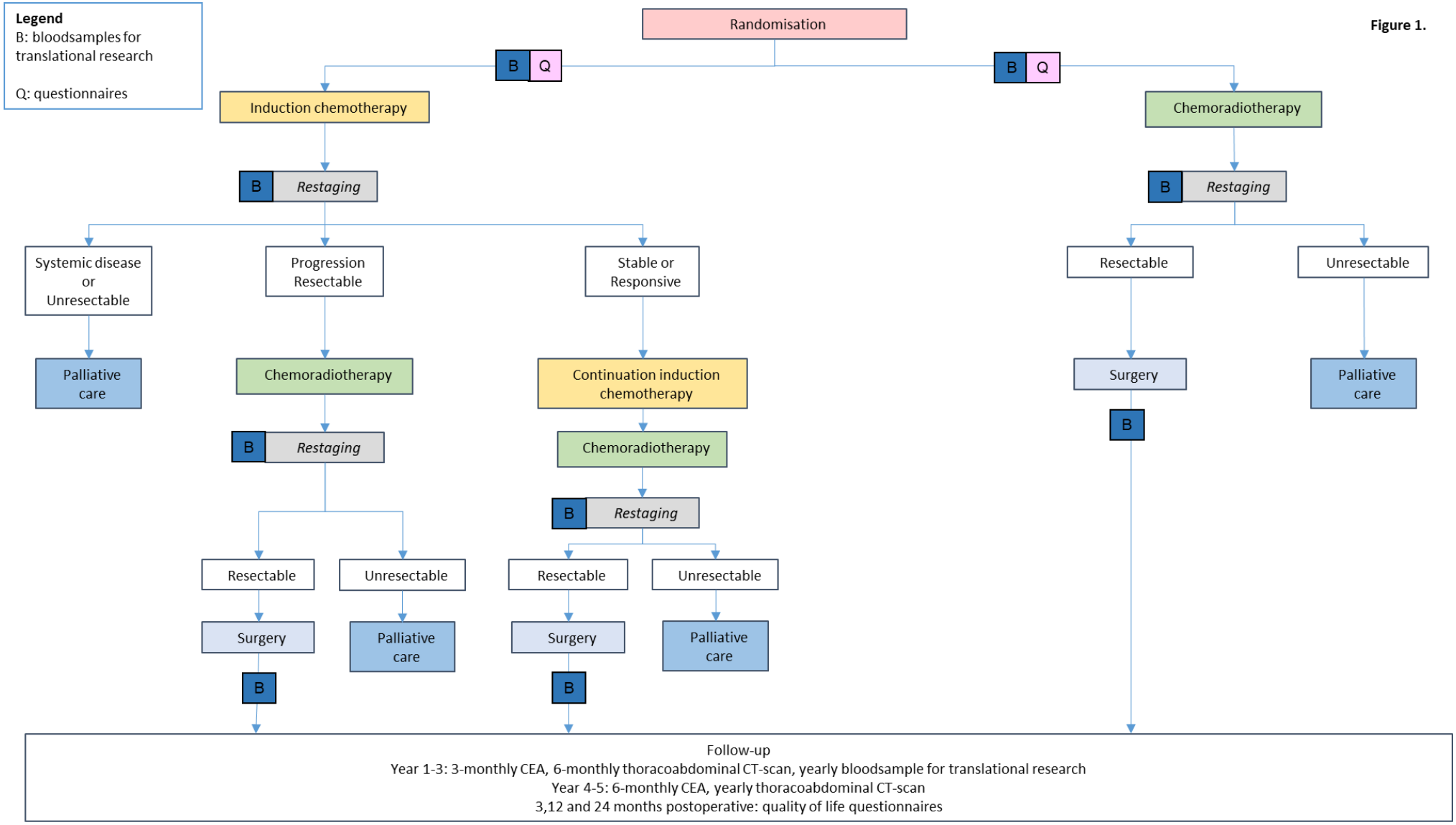


Figure 1.

6.2 Number of patients

The primary endpoint of this study is the number of patients with clear resection margins (R0 resection). Currently, in approximately 60% of patients undergoing surgery after treatment with neoadjuvant chemoradiotherapy an R0 resection is achieved. However, 25% of patients starting with neoadjuvant chemotherapy will not be eligible for surgery due to progressive disease, i.e., local progression, distant progression or death due to progression.[12] This means that in only 45% of patients (75% of 60%) starting with intentionally curative treatment an R0 resection is obtained. In this study, we will categorize patients not eligible for surgery because of progressive disease as failures (i.e., no R0 resection). We further hypothesize that, based on retrospective analyses from our own data, the R0 resection rate will be increased by 15% (45% to 60%) for patients treated in the experimental arm of this study. A chi-square test with a 5% two-sided significance level will have an 80% power to detect a significant difference of 15% between both groups (given that the percentage in the control group is 45%) when the sample size in each group is 173 patients. We expect a drop-out of 5% based on preliminary results from research performed within the consortium. This leads to a total requirement of 364 patients. Power analysis was performed with the use of nQuery advisor 7.0 software.

6.3 Overall study duration and follow-up

The investigators expect that the accrual of patients will be concluded in four years. Duration of follow-up is five years.

6.4 Patient participation

Patient participation has been actively integrated from the earliest phases of study development. The research proposal has been endorsed by the Working Group on Contributing Scientific Research (WIWO) of the Foundation for Patients with Cancer on the Digestive Tract (SPKS). The members of the WIWO also provided advice regarding the content of the summary intended for laymen and the patient information form. SPKS and the applicants will be involved, with particular attention to the intensity of the treatment process, compliance and quality of life.

7. STUDY POPULATION

7.1 Population

Yearly, 4300 patients are diagnosed with primary rectal cancer in the Netherlands.[37] With a recurrence rate of 6-10%, approximately 340 patients per year present with LRRC in the Netherlands. Of these patients, 50% will not be eligible for inclusion due to synchronous distant metastases or unresectable local disease.[38,39] This leaves approximately 170 patients potentially eligible for inclusion. Over the past three years, the expert centres performed surgery on a total of 115 of these patients per year. Assuming that 50 to 60% of these patients will be included in the study, this will lead to an accrual rate of 230-276 patients within 4 years. After successful implementation of this study protocol in the Netherlands this trial will be extended to several expert centres within Europe. Given the large catchment area of these hospitals, inclusion of the required 88-134 patients is considered realistic.

7.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 18 years or older
- Confirmed locally recurrent rectal cancer after total or partial mesorectal resection for rectal cancer or distal sigmoidal cancer, either by
    - histopathology ór;
    - clinically proven (evidence on imaging in combination with clinical findings, with consensus in MDT)
- Resectable disease determined by magnetic resonance imaging (MRI) or deemed resectable after neoadjuvant treatment with chemoradiotherapy.

    Expected gross incomplete resection with overt tumour remaining in the patient after resection, encasement of the ischiadic nerve and invasion of the cortex and/or neuroforamina from S2 and upwards are considered not resectable
- WHO performance score 0-1
- Written informed consent

7.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Radiological evidence of metastatic disease (e.g., liver, lung) at time of randomisation or in the six months prior to randomisation.
  Patients with enlarged iliac lymph nodes, enlarged inguinal lymph nodes and aspecific lung noduli are not excluded from inclusion.
- Homozygous DPD deficiency (if known in advance).
- Any chemotherapy in the past 6 months.
- Radiotherapy in the past 6 months for primary rectal cancer.
- Any contraindication for the planned chemotherapy (e.g., severe allergy, pregnancy, kidney dysfunction, thrombocytopenia), as determined by the medical oncologist.
- Any contraindication for the planned chemoradiotherapy (e.g., severe allergy to chemotherapy agent, no possibility for radiotherapy due to previous radiotherapy), as determined by the medical oncologist and/or radiation oncologist.

- Any contraindication for surgery, as determined by the surgeon and/or anaesthesiologist.
- Concurrent malignancies that interfere with the planned study treatment or the prognosis of resected LRRC.

7.4 Vulnerable populations and clinical trials in emergency situations

There is no expectation of encountering a more vulnerable population than the overall study population.

8. STUDY TREATMENTS

8.1 Investigational Medicinal Product(s) (IMP(s))

8.1.1 Name and description of the IMP

The following investigational products are used in this study:

- Oxaliplatin (chemical name: L01XA03; trade name: Oxaliplatin Accord; formulation: concentrate for solution for injection)
- 5-fluorouracil (chemical name: L01BC02; trade name: 5-Fluorouracil; formulation: concentrate for solution for injection)
- Leucovorin (chemical name: V03AF03; trade name: Leucovorine Sandoz; formulation: concentrate for solution for injection; formulation: oral capsules)
- Irinotecan (chemical name: L01XX19; trade name: Camptosar; formulation: concentrate for solution for injection; formulation: oral capsules)

All investigational products have a marketing authorisation and are used in the authorised form for the authorised indication. More information about the used drug is listed in the Summary of Product Characteristics (SPC) in Appendix A.

8.1.2 Status of development of the IMP

All investigation medicinal products have received marketing authorisation and are used within their approved indications. The regimen has been extensively studied in colorectal cancer. The safety profile of each drug is well-documented in their respective Summary of Product Characteristics (SmPCs) which can be found here (oxaliplatin), here (leucovorin), here (5-fluorouracil), and here (irinotecan).

8.1.3 Description and justification of dosage and route of administration

Induction chemotherapy consists of either three three-weekly cycles of CAPOX or four two-weekly cycles of FOLFOX. It is left to the discretion of the treating medical oncologist which of the two will be administered. In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFIRI may be prescribed. FOLFIRI consists of four two-weekly cycles.

CAPOX consist of capecitabine and oxaliplatin. CAPOX is administered according to standard operating procedure:

Day 1: Oxaliplatin 130 mg/m2 body-surface area [BSA], intravenously [IV].
Day 1-14: Capecitabine 1000 mg/m2 BSA, orally, twice daily
Day 15-21: Rest days.

This regimen is initially administered for three cycles. In case of responsive or stable disease, a 4th cycle of CAPOX will be administered.

In case of unacceptable toxicity (physician's discretion) to oxaliplatin, CAPOX may be continued as FOLFIRI.

FOLFOX consist of 5-fluorouracil, leucovorin and oxaliplatin. FOLFOX is administered according to standard operating procedure:

Day 1: 85 mg/m2 BSA of oxaliplatin IV, 400 mg/m2 BSA of leucovorin IV, 400 mg/m2 BSA of bolus 5-fluorouracil IV
Day 1-2: 2400 mg/m2 BSA of continuous 5-fluorouracil IV
Day 3-14: Rest days.

This regimen is initially administered for four cycles. In case of responsive or stable disease, a 5th and 6th cycle of FOLFOX will be administered.

In case of unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFOX may be continued as FOLFIRI.

In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFIRI may be prescribed. FOLFIRI consist of 5-fluorouracil, leucovorin and irinotecan. FOLFIRI is administered according to standard operating procedure:

Day 1: 180 mg/m2 BSA of irinotecan IV, 400 mg/m2 BSA of leucovorin IV, 400 mg/m2 BSA of bolus 5-fluorouracil IV
Day 1-2: 2400 mg/m2 BSA of continuous 5-fluorouracil IV
Day 3-14: Rest days.

In case of unacceptable toxicity to capecitabine or 5-fluorouracil (physician's discretion), S1 (Teysuno) administered orally with a dose of 25mg/m^2 twice daily may be prescribed as an alternative to capecitabine or 5-fluorouracil, as done in standard clinical practice.

After three cycles of CAPOX or four cycles of FOLFOX/FOLFIRI, a pelvic MRI is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT-scan is optional. Assessment and reporting of the MRI will be done according to a standard operating procedure. All restaging imaging will be assessed during one of the multidisciplinary tumour board meetings in one of the before mentioned expert centres. If a patient developed distant metastases or local disease became unresectable, best palliative treatment is offered according to standard of care. If a patient has progressive local disease, but surgery is still considered feasible, no further systemic therapy will be administered and patients will start treatment with chemoradiotherapy. If a patient has stable or responsive disease, induction chemotherapy will be continued with either one three-weekly cycle of CAPOX or two two-weekly cycles of FOLFOX/FOLFIRI. The timing of the restaging MRI must be in such way that a potential continuation of the induction chemotherapy will not be delayed.

8.1.4 Dosage adjustments and modifications

To ensure patient safety and optimize treatment tolerability, dose adjustments may be implemented based on toxicity assessment. Modifications are at the discretion of the medical oncologist, as is the current standard of care. Modifications may be implemented from the start of neoadjuvant chemotherapy, and may include: dose reductions of all aforementioned CAPOX or FOLFOX/FOLFIRI component agents, omission of one or more CAPOX or FOLFOX/FOLFIRI component agents from the regiment after the first cycle or delayment of administration.

8.2 Comparator IMP(s)

Not applicable.

8.3 Placebo

Not applicable.

8.4 Auxiliary Medicinal Product(s) (AxMP(s))

8.4.1 Name and description of the AxMP

Chemoradiotherapy is an auxiliary medicinal product in this study. It represents a standard component of standard-of-care neoadjuvant treatment for locally recurrent rectal cancer. Chemoradiotherapy is administered in accordance with the Dutch national guidelines.

- Capecitabine (chemical name: L01BC06; trade name: Capecitabine Accord; formulation: oral tablets)
- Tagefur/gimeracil/oteracil (chemical name: L01BC53; trade name: Teysuno)

Surgery and intra-operative radiotherapy (IORT) are non-investigational products in this study. These non-investigational products are standard of care for patients with locally recurrent rectal cancer.

8.4.2 Statement on authorisation and justification unauthorised AxMP (if applicable)

Not applicable. Capecitabine and S1 (Teysuno) will be used in the clinical trial in accordance with the terms of its marketing authorisation. The safety profile of each drug is well-documented in their respective Summary of Product Characteristics (SmPCs) which can be found here (capecitabine) and here (S1 (Teysuno)). Surgery and IORT non-investigational products are standard of care for patients with locally recurrent rectal cancer.

8.4.3 Description and justification of dosage and route of administration

Chemoradiotherapy

All patients receive chemoradiotherapy. In the control arm, patients are referred to the radiation oncologist within 2 weeks after randomisation, and chemoradiotherapy starts within 4 weeks after randomisation. Patients in the experimental group will start chemoradiotherapy within 3-6 weeks after the first day of the last cycle of chemotherapy. Concurrent chemoradiotherapy will be delivered according to standard operating procedures.

The radiotherapy dose depends on whether the patient previously received radiotherapy. In radiotherapy-naïve patients, full course radiotherapy will consist of 25x2.0 or 28x1.8 Gy radiotherapy. In case of previous radiotherapy, the radiotherapy dose will consist of 15x2.0 Gy. Concomitant chemotherapy will be capecitabine, administered orally with a dose of 825 mg/m2 twice daily on radiotherapy days. In case of unacceptable toxicity to capecitabine during chemoradiotherapy, concomitant Teysuno administered orally with a dose of 25mg/m2 twice daily on radiotherapy days may be prescribed (physician's discretion). Delineation of the clinical target volume will be done according to the delineation guidelines that are described in a Standard Operating Procedure. To ensure uniform delivery of radiotherapy a quality-assurance (QA) procedure with central assessment of individual cases will be performed. The QA procedure is described in more detail in a Standard Operating Procedure.

The treating radiation oncologist is responsible for the counselling, administration and follow-up with regard to the neoadjuvant treatment.

Surgery and IORT

Surgery is performed according to the national standard of care by experienced surgical oncologists within 10-14 weeks after completing chemoradiotherapy. Type of surgery depends on the location of the recurrence and involvement of adjacent structures and is left to the discretion of the operating surgeon. In case of the need for reconstructive surgery (e.g., after complete cystectomy), the required specialist is consulted and will attend the surgical procedure. When deemed necessarily, e.g., when there is tumour adherence or no adequate soft tissue margin for a clear resection, and feasible by the surgeon and radiation oncologist intra-operative radiotherapy will be administered. Intra-operative radiotherapy (IORT) is delivered by either intra-operative external beam radiotherapy (IOERT) or high-dose-rate intra-operative brachytherapy (HDR-IOBT), and dose is left to the discretion of the treating radiation oncologist.[40,41]

8.5 Additional considerations for trials involving a medical device

Not applicable.

8.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable.

8.7 Preparation and labelling of the study treatment(s)

All investigational and auxiliary medicinal products in this study have been authorised to be used in the form and for the authorised indication. Consequently, the products will be used out of the commercial stock with labelling according to patient name and corresponding details. This will be done in the pharmacies providing the medication. Preparation and labelling are performed by the hospital (trial) pharmacy according to local protocol.

9. OTHER TREATMENTS AND RESTRICTIONS

There are no additional specifically restricted or specifically permitted medications or lifestyle factors before or during the study. Permitted or prohibited use of co-intervention is left to the discretion of the treating physician.

10. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

As aforementioned, all investigational and auxiliary medicinal products in this study have been authorised to be used in the form and for the authorised indication. As such, no additional documentation regarding traceability and storage of study treatments, or additional documentation regarding administration of study treatment or subject compliance is necessary beyond routinely-maintained pharmacy documentation and patient medical records. Storage and further procedures are done according to the corresponding hospitals protocol.

11. STUDY ASSESSMENTS AND PROCEDURES

11.1 Screening procedure

The work-up described below is standard of care in the Netherlands, and therefore not considered as study interventions.

If a patient is referred to one of the expert centres, the completeness of the work-up will be determined. Work-up should at least include a high-dose thoracoabdominal CT-scan to detect distant metastases and a pelvic MRI to assess the resectability of the local recurrence. An additional FDG-PET/CT-scan is optional. CT-scan and MRI must be performed no longer than 6 weeks prior to randomization. In case of incomplete or insufficient work-up, radiological imaging will be performed in the expert centre.

MRI acquisition should adhere to the following minimal requirements:

- 1.5T or 3T MR equipment.
- Phased-array receiver coil for pelvic-/body imaging.
- T2-weighted high-resolution sequences in 3 standard planes (true sagittal, coronal, transverse). Minimal slice thickness of ≤ 3 mm. No fat suppression.
- Diffusion-weighted imaging (DWI): axial plane, b-value ≥ b800, including ADC maps.
- Field of view (FOV) of both T2 and DWI needs to cover the entire tumour area.

Optionally, but not routinely required are:

- Angulated sequences
- T1-weighted sequences
- Fat suppressed sequences
- (Dynamic) Post-contrast sequences
- Patient preparation (e.g., spasmolytic agents, endorectal filling)

Minimal requirements for assessment and reporting will be described in a *Standard Operating Procedure*.

After complete work-up is performed patients will be discussed in the multidisciplinary tumour board (MDT) in one of the expert centres. The MDT consists of at least one surgical oncologist, one medical oncologist, one radiation oncologist and one radiologist who are experienced in the diagnosis and treatment of LRRC. Only if there is consensus in the MDT about whether or not a patient meets the inclusion and exclusion criteria, the patient will be randomised.

11.2 Randomisation, blinding and treatment allocation

Eligible patients who signed informed consent will be randomised by the coordinating investigator. Randomisation will be performed by a central automatic randomisation tool using a minimisation procedure and with an intervention:control ratio of 1:1. Patients will be stratified for previous radiotherapy, previous systemic therapy and *expert centre*. Each randomised patient is assigned a sequential subject number.

The allocation is not blinded to the patient, the investigators or the treating physicians. After randomisation, the treating physician informs the patient about the arm he or she has been randomised to and arranges an appointment with the medical oncologist (experimental arm) or the radiation oncologist (control arm).

Patients will be allocated to one of the following treatment arms:

- The experimental arm: neoadjuvant induction chemotherapy followed by chemoradiotherapy and surgery
- The control arm: neoadjuvant chemotherapy and surgery alone

11.3 Study procedures and assessments

Table 1 and *Table 2* (chapter 15) present schedules of all interventions and assessments patients undergo in the experimental and control arm, respectively.

11.3.1 Induction chemotherapy

Patients allocated to the experimental arm start treatment with induction chemotherapy. Patients are referred to the medical oncologists within 2 weeks after randomisation, and induction chemotherapy starts within 4 weeks after randomisation. The treating medical oncologist is responsible for the counselling, administration and follow-up with regard to the neoadjuvant treatment. Before starting the treatment, the patient will be checked for a possible homozygous DPD deficiency (if this was not performed before). If so, patient will be excluded from the study.

Induction chemotherapy consists of either three three-weekly cycles of CAPOX or four two-weekly cycles of FOLFOX. It is left to the discretion of the treating medical oncologist which of the two will be administered. In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFIRI may be prescribed. FOLFIRI consists of four two-weekly cycles.

CAPOX consist of capecitabine and oxaliplatin. CAPOX is administered according to standard operating procedure:

Day 1: Oxaliplatin 130 mg/m2 body-surface area [BSA], intravenously [IV].
Day 1-14: Capecitabine 1000 mg/m2 BSA, orally, twice daily
Day 15-21: Rest days.

This regimen is initially administered for three cycles. In case of responsive or stable disease, a 4th cycle of CAPOX will be administered.

In case of unacceptable toxicity (physician's discretion) to oxaliplatin, CAPOX may be continued as FOLFIRI.

FOLFOX consist of 5-fluorouracil, leucovorin and oxaliplatin. FOLFOX is administered according to standard operating procedure:

Day 1: 85 mg/m2 BSA of oxaliplatin IV, 400 mg/m2 BSA of leucovorin IV, 400 mg/m2 BSA of bolus 5-fluorouracil IV
Day 1-2: 2400 mg/m2 BSA of continuous 5-fluorouracil IV
Day 3-14: Rest days.

This regimen is initially administered for four cycles. In case of responsive or stable disease, a 5th and 6th cycle of FOLFOX will be administered.

In case of unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFOX may be continued as FOLFIRI.

In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, FOLFIRI may be prescribed. FOLFIRI consist of 5-fluorouracil, leucovorin and irinotecan. FOLFIRI is administered according to standard operating procedure:

Day 1: 180 mg/m2 BSA of irinotecan IV, 400 mg/m2 BSA of leucovorin IV, 400 mg/m2 BSA of bolus 5-fluorouracil IV
Day 1-2: 2400 mg/m2 BSA of continuous 5-fluorouracil IV
Day 3-14: Rest days.

In case of unacceptable toxicity to capecitabine or 5-fluorouracil (physician's discretion), S1 (Teysuno) administered orally with a dose of 25mg/m^2 twice daily may be prescribed as an alternative to capecitabine or 5-fluorouracil, as done in standard clinical practice.

After three cycles of CAPOX or four cycles of FOLFOX/FOLFIRI, a pelvic MRI is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT-scan is optional.

Assessment and reporting of the MRI will be done according to a standard operating procedure. All restaging imaging will be assessed during one of the multidisciplinary tumour board meetings in one of the before mentioned expert centres.

If a patient developed distant metastases or local disease became unresectable, best palliative treatment is offered according to standard of care.

If a patient has progressive local disease, but surgery is still considered feasible, no further systemic therapy will be administered and patients will start treatment with chemoradiotherapy.
If a patient has stable or responsive disease, induction chemotherapy will be continued with either one three-weekly cycle of CAPOX or two two-weekly cycles of FOLFOX/FOLFIRI.
The timing of the restaging MRI must be in such way that a potential continuation of the induction chemotherapy will not be delayed.

11.3.2 Chemoradiotherapy

All patients receive chemoradiotherapy. In the control arm, patients are referred to the radiation oncologist within 2 weeks after randomisation, and chemoradiotherapy starts within 4 weeks after randomisation. Patients in the experimental group will start chemoradiotherapy within 3-6 weeks after the first day of the last cycle of chemotherapy. Concurrent chemoradiotherapy will be delivered according to standard operating procedures.

The radiotherapy dose depends on whether the patient previously received radiotherapy. In radiotherapy-naïve patients, full course radiotherapy will consist of 25x2.0 or 28x1.8 Gy radiotherapy. In case of previous radiotherapy, the radiotherapy dose will consist of 15x2.0 Gy. Concomitant chemotherapy will be capecitabine, administered orally with a dose of 825 mg/m^2 twice daily on radiotherapy days. In case of unacceptable toxicity to capecitabine during chemoradiotherapy, concomitant Teysuno administered orally with a dose of 25mg/m^2 twice daily on radiotherapy days may be prescribed (physician's discretion). Delineation of the clinical target volume will be done according to the delineation guidelines that are described in a *Standard Operating Procedure*. To ensure uniform delivery of radiotherapy a quality-assurance (QA) procedure with central assessment of individual cases will be performed. The QA procedure is described in more detail in a *Standard Operating Procedure.*

11.3.3The treating radiation oncologist is responsible for the counselling, administration and follow-up with regard to the neoadjuvant treatment.

11.3.4 Restaging

Between 4-6 weeks after the last day of the radiotherapy course an MRI of the pelvis is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT scan is optional.

Assessment and reporting of the MRI will be done according to a standard operating procedure. Restaging imaging will be discussed during a specialised MDT including surgeons, radiologist, radiation oncologists and medical oncologists in one of the aforementioned *expert centres*.

In case of distant metastases or unresectable local disease, best palliative treatment is offered. In case of resectable disease, patient will undergo surgery.

11.3.5 Surgery

Surgery is performed according to the national standard of care by experienced surgical oncologists within 10-14 weeks after completing chemoradiotherapy. Type of surgery depends on the location of the recurrence and involvement of adjacent structures and is left to the discretion of the operating surgeon. In case of the need for reconstructive surgery (e.g., after complete cystectomy), the required specialist is consulted and will attend the surgical procedure. When deemed necessarily, e.g., when there is tumour adherence or no adequate soft tissue margin for a clear resection, and feasible by the surgeon and radiation oncologist intra-operative radiotherapy will be administered. Intra-operative radiotherapy (IORT) is delivered by either intra-operative external beam radiotherapy (IOERT) or high-dose-rate intra-operative brachytherapy (HDR-IOBT), and dose is left to the discretion of the treating radiation oncologist.[40,41]

11.3.6 Follow-up

Patients are followed-up at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54 and 60 months postoperatively, which is according to standard of care. At every follow-up moment a blood sample is taken to determine the level of carcinoembryonic antigen (CEA).

An additional high-dose thoracoabdominal CT-scan will be performed;

- if the CEA level exceeds the normal value (> 5 ng/ml), or
- if there is a doubling in relation to the initial value, or
- on a repeated rise

At 6, 12, 18, 24, 30, 36, 48 and 60 months post-operative a high-dose thoracoabdominal CT-scan will be performed independent of CEA level. An additional FDG-PET/CT-scan is optional.

11.3.7 Questionnaires

All patients participating in the study receive validated quality of life questionnaires. Patients are asked to complete QLQ-C30, QLQ-CR29 and EQ-5D-5L at inclusion, 3,12- and 24-months post-operative. Patients receive questionnaires either by mail or digitally, according to their own preference.

11.3.8 Translational research – blood

All patients participating in the study are asked for separate informed consent to collect blood samples for future translational research. If patients give consent, an additional 20ml blood is drawn during regular blood draws before start of the induction chemotherapy (experimental arm), before chemoradiotherapy, before surgery, three months after surgery and once a year during three years of follow-up, resulting in 7 samples for patients in the experimental arm and 6 samples for patients in the control arm. Blood draws for research purposes will be combined with planned routine blood draws. In short, 20 ml blood intended for translational research is drawn into two 10 mL evacuated blood draw tubes, maintained at room temperature and processed within 96 hours after drawing the blood. In the end, all samples will be sent to the Department of Medical Oncology of the Erasmus MC.

11.3.9 Translational research – tissue

All patients participating in the study are asked for separate informed consent to collect tumour tissue for future translational research and to enable correlative studies between tumour-derived parameters in the blood and the original tumour tissue. Tumour tissue will be collected by the pathologist, fresh frozen and stored at -80C. By the end of the study, all tumour samples will be shipped to the Antoni van Leeuwenhoek and stored at -80C until further use.

11.3.10 Central multidisciplinary tumour board meeting (MDT)

During the inclusion period of the study a monthly central MDT will be organised. This central MDT will be designed as a teleconference and will be attended by the coordinating investigator, a surgeon from each of the expert centres and at least one radiologist from one of the expert centres. All newly included patients will be discussed, serving as a quality control. Eligible patients will be discussed in case of uncertainty about whether the patient meets the in- and/or exclusion criteria. An ad hoc central MDT may be planned, in case the time to the scheduled monthly MDT is too long. Patients who are under treatment at the time of the MDT or who completed treatment, will only be discussed in case of remarkable findings.

Table 1. Schedule interventions and assessments experimental arm	**Pre-allocation**	**Post-allocation**			**Follow-up**	
	Outpatient clinic	**Induction chemotherapy**	**Chemoradiotherapy**	**Surgery**	**Year 1-3**	**Year 4-5**
Screening						
Eligibility screen	☒					
Informed consent	☒					
Randomization	☒					
Interventions						
Induction chemotherapy		☒				
Chemoradiotherapy			☒			
Surgery				☒		
Thoracoabdominal CT		☒ A	☒ B		☒ E	☒ H
Pelvic MRI		☒ A	☒ B			
Questionnaires	☒				☒ F	
CEA level					☒ G	☒ E
Translational research: blood	☒	☒ A	☒ C	☒ D	☒ H	
Translational research: tissue				☒		
Assessments						
Baseline characteristics	☒					
Toxicity induction chemotherapy		☒ C				
Toxicity chemoradiotherapy			☒ C			
Radiological response		☒ A	☒ B			
Pathological response				☒ D		
Surgical characteristics				☒ D		
Postoperative morbidity				☒ D		
Adverse events			☒ I	☒ I		
Progression free survival					☒ G	☒ E
Local recurrence free survival					☒ G	☒ E
Disease free survival					☒ G	☒ E
Overall survival					☒ G	☒ E
Quality of life	☒				☒ F	
Costs	☒				☒ F	

A after 3 (CAPOX) or 4 (FOLFOX/FOLFIRI) cycles; **B** 4-6 weeks after finishing chemoradiotherapy; **C** after finishing chemoradiotherapy and before surgery; **D** 3 months post-surgery; **E** 6-monthly; **F** 3, 12 and 24 months postoperative; **G** 3-monthly; **H** yearly; **I** 3 months after surgery or 1 month after last day of neoadjuvant treatment.

*Baseline characteristics obtained: confounders (age, gender, WHO performance status, ASA score), primary tumour characteristics (staging/treatment/radicality of surgery), tumour topography of recurrent tumour.

Table 2. Schedule interventions and assessments control arm	**Pre-allocation**	**Post-allocation**		**Follow-up**	
	Outpatient clinic	**Chemoradiotherapy**	**Surgery**	**Year 1-3**	**Year 4-5**
Screening					
Eligibility screen	☒				
Informed consent	☒				
Randomization	☒				
Interventions					
Induction chemotherapy					
Chemoradiotherapy		☒			
Surgery			☒		
Thoracoabdominal CT		☒ A		☒ D	☒ G
Pelvic MRI		☒ A			
Questionnaires	☒			☒ E	
CEA level				☒ F	☒ D
Translational research: blood	☒	☒ B	☒ C	☒ G	
Translational research: tissue			☒		
Assessments					
Baseline characteristics	☒				
Toxicity chemoradiotherapy		☒ C			
Radiological response		☒ B			
Pathological response			☒ D		
Surgical characteristics			☒ D		
Postoperative morbidity			☒ D		
Progression free survival				☒ F	☒ D
Local recurrence free survival				☒ F	☒ D
Disease free survival				☒ F	☒ D
Overall survival				☒ F	☒ D
Quality of life	☒			☒ E	
Costs	☒			☒ E	
A 4-6 weeks after finishing chemoradiotherapy; **B** after finishing chemoradiotherapy and before surgery; **C** 3 months post-surgery; **D** 6-monthly; **E** 3, 12 and 24 months postoperative; **F** 3-monthly; **G** yearly					

11.3.11 Efficacy assessments

Efficacy of the administered treatment is determined by the resection margin which is assessed by examining the resected tumour tissue, obtained during surgery. A pathologist working in one of the *expert centres* assesses whether a resection margin is considered clear (i.e., if there are no tumour cells in any of the resection surfaces as determined by microscopy, resection margin >0mm). An R1 resection is considered a resection with the presence of tumour cells in any of the resection surfaces as determined by microscopy (resection margin = 0 mm). An R2 resection is considered a gross incomplete resection with clinically overt tumour remaining in the patient, with involved margins confirmed by the pathologist. In case of a clear resection margin, the margin in millimetre is recorded in the pathology report as well. The criteria for histopathological evaluation and recording will be defined in a standard operating procedure. A standardized evaluation form will be provided; all pathologists involved will use this form for all patients included in the trial. Additionally, a pathological response will also be evaluated, as determined by the Mandard Tumour Regression Grading (TRG): TRG 1 i.e., no vital tumour (pathological complete response); TRG 2 i.e., sporadic tumour (near complete response); TRG 3 i.e., up to 50% vital tumour; TRG 4 i.e., any response, but tumour dominates; and TRG 5 i.e., no response.

Next to pathological resection margin and response, radiological response will be measured by restaging MRI scans. After three cycles of CAPOX or four cycles of FOLFOX/FOLFIRI, a pelvic MRI is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT-scan is optional. Assessment and reporting of the MRI will be done according to a standard operating procedure. Between 4-6 weeks after the last day of the radiotherapy course an MRI of the pelvis is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT scan is optional. All restaging imaging will be assessed during one of the multidisciplinary tumour board meetings in one of the before mentioned expert centres. Radiological response will be assessed according to the Tumour Response Grade (T2W-MRI, according to mrTRG): TRG 5 i.e., no fibrosis; TRG 4 i.e., <25% fibrosis, predominant tumour signal; TRG 3 i.e., 50% tumour/fibrosis; TRG 2 i.e., >75% fibrosis, minimal tumour signal intensity and TRG 1 i.e., low signal fibrosis only no intermediate tumour signal. Additionally, response on DWI is recorded (5-point score): 5 definitely residual tumour; 4 probably residual tumour; 3 possibly residual tumour/possibly complete response; 2 probably complete response; 1 definitely complete response; and 0 initial tumour without diffusion restriction. The overall estimated response is determined by the following assessment: poor response (limited volume reduction <25%, obvious residual solid mass on T2W and/or focal high signal mass on DWI), good response (obvious volume reduction 25-75%, predominant fibrosis with only limited heterogeneous signal on T2 and/or small foci on DWI signal), complete or near complete response (obvious volume reduction >75%, homogeneous fibrosis, no high signal foci on DWI) and progression.

Other trial specific assessments are limited to the daily questionnaires (QLQ-C30, QLQ-CR29 and EQ-5D-5L), which are sent to the patient by mail or digitally at inclusion and 3-, 12- and 24-months post-surgery. In case the questionnaire is sent by email, the questionnaire will be sent by an electronic case report form (eCRF) within an ISO 27001-certified study database, allowing participants to complete it digitally. Scores are used for the analysis of quality of life as a secondary objective of this study.

Patients participating in this study will not undergo any extra procedures or assessments beyond standard care. Any additional information required for the study will be obtained from the patient's medical file, where it has been documented as part of routine medical care (see Chapter 5).

11.3.12 Safety assessments

For therapy with induction chemotherapy, a clinical evaluation, routine laboratory assessment and assessment of adverse events is performed before each cycle of chemotherapy. In case of unacceptable toxicity to capecitabine or 5-fluorouracil (physician's discretion), S1 (Teysuno) administered orally with a dose of 25mg/m^2 twice daily may be prescribed as an alternative to capecitabine or 5-fluorouracil, as done in standard clinical practice. After three cycles of CAPOX or four cycles of FOLFOX/FOLFIRI, a pelvic MRI is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT-scan is optional. If a patient developed distant metastases or local disease became unresectable, best palliative treatment is offered according to standard of care. If a patient has progressive local disease, but surgery is still considered feasible, no further systemic therapy will be administered and patients will start treatment with chemoradiotherapy. If a patient has stable or responsive disease, induction chemotherapy will be continued with either one three-weekly cycle of CAPOX or two two-weekly cycles of FOLFOX/FOLFIRI.

For chemoradiotherapy, the treating radiation oncologist is responsible for the counselling, administration, clinical evaluation, assessment of adverse events and follow-up with regard to the neoadjuvant treatment. Between 4-6 weeks after the last day of the radiotherapy course an MRI of the pelvis is performed for local restaging and a high-dose thoracoabdominal CT-scan is performed for restaging for distant metastases. An additional FDG-PET/CT scan is optional. In case of distant metastases or unresectable local disease, best palliative treatment is offered. In case of resectable disease, patient will undergo surgery.

12. STUDY DISCONTINUATION AND COMPLETION

12.1 Definition End of Trial

The end of the study is defined as the last patient's last visit. In accordance with Article 37, Chapter VI, of the CTR, the sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through the EU portal. That notification shall be made within 15 days from the end of the clinical trial in the last of the Member States concerned and third countries in which the clinical trial has been conducted.

Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial, the content of which is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

12.2 Criteria for temporary halt and early termination of the clinical trial

In accordance with section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance shall be notified to the Member States concerned through the EU portal. That notification shall be made without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state. The investigator will take care that all subjects are kept informed. The restart of the clinical trial following a temporary halt for reasons of a change of the benefit-risk balance shall be deemed to be a substantial modification subject to the authorisation procedure laid down in CTR Chapter III.

This study may be prematurely terminated after 100 patients have undergone surgery if the percentage of patients not able to complete neoadjuvant chemoradiotherapy due to treatment related toxicity in the experimental arm is 20% higher compared to patients in the control arm or if the percentage of patients with major post-operative morbidities (Clavien-Dindo ≥3) is 25% higher in the experimental arm compared to the control arm.

12.3 Discontinuation/withdrawal of individual subjects

Subjects can leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. No further study assessments are performed after the subject has withdrawn. Individual patients are not replaced after withdrawal. Potential withdrawal of patients is included in the drop-out rate of 5%. Randomised patients withdrawn from the treatment are included in the intention-to-treat population and will be followed-up and analysed for all major outcomes.

12.4 Arrangements for subjects after their participation in the clinical trial ended

Not applicable. Patients continue standard of care according to Dutch guidelines.

13. SAFETY REPORTING

13.1 Definitions

13.1.1 Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with the study treatment.

13.1.2 Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial subject that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

An elective hospital admission will not be considered as a SAE.

13.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI).

13.2 Recording of AEs/SAEs/SUSARS

All grade ≥3 non-haematological adverse events determined by NCI-CTCAE v5, all grade ≥4 haematological adverse events determined by NCI-CTCAE v5 and all grade ≥3 adverse events determined by Clavien-Dindo reported spontaneously by the subject or observed by the investigator or his staff will be recorded. The time window for recording AEs is from randomisation till three months after surgery, or 1 month after the last day of neoadjuvant treatment (for patients with progressive disease and no surgery). The details of each AE, including the onset, duration, severity, and outcome, as well as the investigator's assessment of the causal relationship to the IMP, will be documents. SAE's are to be reported immediately to the sponsor once the investigator becomes aware of the event. The time window for recording SAEs is from randomisation till three months after surgery, or 1 month after the last day of neoadjuvant treatment (for patients with progressive disease and no surgery). Information on all SAEs is recorded in the eCRF.

The sponsor is responsible for reporting SUSARs to the European Medicines Agency (EMA) via the Eudravigilance database. Fatal or life-threatening SUSARs must be reported within 7 days of the sponsor becoming aware of the event, with a follow-up report within an additional 8 days.

Non-fatal or non-life threatening SUSARs must be reported within 15 days. Information on all SUSARs is recorded in the eCRF.

13.3 Reporting of AEs and SAEs

13.3.1 Reporting of SAEs by the investigator to the sponsor

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

13.3.2 List of SAEs which do not require immediate reporting and procedure for reporting

Not applicable.

13.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

13.5 Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators (CTR: Article 41(3)).

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR (CTR: Article 42).

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction (CTR: Article 42(2(a))];
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction (CTR: Article 42(2(b))];
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening (CTR: Article 42(2(c))).

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report (CTR: Article 42(2)).

13.6 Annual safety report

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical trial (CTR: Article 43).
The annual safety report will be combined with the annual progress report. In addition to the expedited reporting of SUSARs, the coordinating investigator will submit, once a year throughout the clinical trial,

a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

13.7 Unblinding procedures for safety reporting

Not applicable.

13.8 Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state (CTR: Article 38). The investigator will take care that all subjects are kept informed.

13.9 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken (CTR: Article 54).

13.10 Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

The central DSMB consists of a medical oncologist and a surgical oncologist, both experts in the field, as well as a statistician who are not involved in the study and have no competing interest. All relevant data is made available to the DSMB by the central datamanager and the study statistician. The DSMB reviews the safety data after 100 patients have undergone surgery. Cessation of the study is warranted if the criteria for termination as described in section 8.7 have been met. In all other situations, the DSMB advices the study steering committee on study continuation or termination based on the available data and their expertise. The advice(s) of the DSMB will only be sent to the study steering committee. The study steering committee will send the advice to the reviewing METC. Should the study steering committee decide not to fully implement the advice of the DSMB, the study steering committee should include a note to substantiate why (part of) the advice of the DSMB will not be followed.

14. STATISTICAL ANALYSIS

14.1 Description of statistical methods

Before any statistical analysis is done, a detailed Statistical Analysis Plan (SAP) will be prepared.

Demographics, patient and tumour characteristics will be presented by treatment arm. Continuous data are reported as mean with standard deviation or as median with interquartile range or 95% confidence intervals, depending on the distribution. Categorical data are reported as count with percentage. All statistical tests will be two-sided and a p-value of less than 0.05 will be classified as statistically significant. Patients initially randomised but considered ineligible afterwards based on information that should have been available before randomisation, will be excluded from all analysis.

14.2 Analysis sets

Full Analysis Set (FAS)

The full analysis set consists of all randomised patients regardless of whether they started the intervention. Patients in the FAS will be analysed 'as randomised'.

Surgery Analysis Set

The surgery analysis set includes all patients of the FAS who completed surgery. Patients in the surgery analysis will be analysed 'as randomised'.

Per Protocol Analysis Set (PPS)

The per protocol analysis set only includes patients from the FAS who have no major protocol deviations. The following will be considered major protocol deviations:

- Patients who did not receive any neoadjuvant treatment
- Patients who switch treatment groups (i.e., patients randomised to the experimental group who only receive chemoradiotherapy)
- Patients who did not meet the in- and exclusion criteria
- Patients in whom another chemotherapy agent was prescribed then mentioned in the protocol
- Patients in whom another dose of radiotherapy was prescribed then mentioned in the protocol

Safety Analysis Set

The safety analysis set includes all patients from the FAS who receive at least one course of induction chemotherapy (experimental group) or chemoradiotherapy (control group). Patients in the safety analysis set will be analysed 'as treated'.

Protocol Deviations

The full list of major protocol deviations for the study report will be compiled prior to database closure.

14.3 Participant demographics and other baseline characteristics

Baseline characteristics and demographic data will be summarized for each treatment group by presenting frequency distributions and/or descriptive statistics. Continuous variables are presented as means (with SD) or medians (with IQR), as appropriate.

Demographic data:

- Age, sex, WHO performance status, height, weight, BMI

Primary tumour:

- TNM stage (clinical and pathological)
- Location metastases

Primary treatment:

- Type of neoadjuvant treatment, type of neoadjuvant chemotherapy, type of neoadjuvant radiotherapy, type of (primary) surgery including radicality resection, type of adjuvant treatment, type of adjuvant chemotherapy, type of adjuvant radiotherapy

Tumour characteristics recurrent tumour

- Type of tumour, number of lesions, (number of) involved compartments, interval between primary surgery and recurrent tumour in days (derived as the difference between primary surgery and date current recurrence +1).

14.4 Randomisation and blinding

This is a multicentre, open-label, phase III, parallel arms, randomised controlled trial. The study randomises eligible patients in a 1:1 ratio to receive either induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm), the latter being the current standard of care in the Netherlands.

This is an open-label study, so blinding is not applicable.

14.5 Sample size, trail power and level of significance used

The primary endpoint of this study is the number of patients with clear resection margins (R0 resection). Currently, in approximately 60% of patients undergoing surgery after treatment with neoadjuvant chemoradiotherapy an R0 resection is achieved. However, 25% of patients starting with neoadjuvant chemotherapy will not be eligible for surgery due to progressive disease, i.e. local progression, distant progression or death due to progression.[12] This means that in only 45% of patients (75% of 60%) starting with intentionally curative treatment an R0 resection is obtained. In this study, we will categorize patients not eligible for surgery because of progressive disease as failures (i.e., no R0 resection). We further hypothesize that, based on retrospective analyses from our own data, the R0 resection rate will be increased by 15% (45% to 60%) for patients treated in the experimental arm of this study. A chi-square test with a 5% two-sided significance level will have an 80% power to detect a significant difference of 15% between both groups (given that the percentage in the control group is 45%) when the sample size in each group is 173 patients. We expect a drop-out of 5% based on preliminary results from research performed within the consortium. This leads to a total requirement of 364 patients. Power analysis was performed with the use of nQuery advisor 7.0 software.

14.6 Planned analysis

14.6.1 Analysis primary endpoint

The primary endpoint of this study is the proportion of patients with clear resection margins (R0 resection). This endpoint will be based on the intention to treat principal; i.e., patients will be analysed

according to the treatment arms they were assigned to regardless of whether they started the intervention. In addition to the intention-to-treat analysis, a per protocol analysis will be performed as a sensitivity analysis. Comparison of proportions by treatment arm will be done by means of the Fisher's exact test. A sensitivity analysis will be performed using a logistic regression model adjusting for stratification factors at randomization.

14.6.2 Analysis secondary endpoint(s)

All survival curves will be constructed using the Kaplan-Meier method and the log-rank test will be used to compare both treatment arms adjusting for the stratification factors at randomisation (previous radiotherapy, previous systemic therapy and expert centre). In addition, Hazard Ratio's will be calculated using the Cox proportional hazard regression model, also adjusting for stratification factors.

Local re-recurrence free survival will be calculated from the date of surgery until the date of local re-recurrence detected by imaging or histologically proven. Death as first event will be censored as well as patients without any local re-recurrence at last follow-up. A sensitivity analysis will be performed using competing risk analysis considering patients dying without local re-recurrence and local re-recurrence as separate events. Progression free survival will be calculated from the date of randomisation until the date of progression of the local recurrence, the date of clinically proven distant metastases, the date of local re-recurrence detected by imaging or histologically proven or the date of death from any cause, whichever occurs first. Patients who are still alive at last follow-up will be censored. Metastasis free survival will be calculated from the date of randomisation until the date of clinically proven distant metastases. Death as first events will be censored as well as patients without any distant metastases at last follow-up. A sensitivity analysis will be performed using competing risk analysis considering patients dying without distant metastases and distant metastases as separate events. Disease free survival will be calculated from the date of surgery until the date of local re-recurrence, the date of distant metastases or the date of death from any cause whichever occurs first. Patients who are still alive at last follow-up will be censored. Overall survival will be calculated from the date of randomisation until the date of death from any cause, censoring patients who are still alive at last follow-up.

The metastasis free survival, progression free survival and overall survival will be based on the intention to treat group. The local re-recurrence free survival and the disease free survival will only be analysed using patients who underwent surgery.

Surgical characteristics, histopathological characteristics and major surgical morbidity will be presented by treatment arm and will only be derived for patients who underwent surgery.
Number of patients undergoing surgery will be analysed in the intention-to-treat population. Comparison between treatment arms will be done by means of the Fisher's exact test.

Absolute and relative incidence of toxicities related to the administration of induction chemotherapy or chemoradiotherapy will be presented per treatment arm and analysed in all patients who received at least one dose of neoadjuvant chemotherapy (experimental group) or chemoradiotherapy (control group). Comparison between treatment arms will be done by means of the Fisher's exact test.

Health-related quality of life is graphically presented across all time points. Comparison between both treatment arms at baseline level and across time will be performed by a random effects regression model and will be based on the intention to treat group.

Incremental cost-effectiveness and cost-utility ratios are calculated for the extra costs per additional patient alive and the extra costs per additional quality adjusted life year, respectively. Non-parametric bootstrapping, drawing samples of the same size as the original samples and with replacement, is applied to generate 95% confidence intervals for (differences in) costs and health outcomes. Cost-effectiveness planes are displayed and cost-effectiveness acceptability curves are drawn for willingness-to-pay values up to €100.000,-.

14.7 Interim analysis

An interim analysis will be performed by the central data manager and the study statistician after 100 patients have undergone surgery. Inclusion will not be stopped at interim analysis. At the interim analysis, the number of patients that cannot complete the full course chemoradiotherapy, and the number of patients with major postoperative morbidity (Clavien-Dindo ≥ 3) will be tabulated and discussed with the DSMB. Looking at these safety and logistic aspects will have no consequences on the total sample size or the actual alpha level at final analysis. After the interim analyses, the DSMB will recommend continuation or discontinuation of the study. Criteria for termination are defined in section 12.2.

14.8 (Statistical) criteria for termination of the trial

This study may be prematurely terminated after 100 patients have undergone surgery if the percentage of patients not able to complete neoadjuvant chemoradiotherapy due to treatment related toxicity in the experimental arm is 20% higher compared to patients in the control arm or if the percentage of patients with major post-operative morbidities (Clavien-Dindo ≥3) is 25% higher in the experimental arm compared to the control arm.

14.9 Procedure for accounting for missing, unused and spurious data

In general missing data should be avoided. No imputation will be used. The baseline value will be defined as the last non-missing value prior to first dose of induction chemotherapy (experimental arm) or chemoradiotherapy (control arm), unless specifically stated otherwise.

Partial dates are handled in the following way:

- If the month and year are present but the day is missing, date is set 1st of the month. A missing day is set to 00 in the database.
- If day and month are missing, date is set to 1st of January of that year. Missing days and months are set to 00 in the database.
- If date is completely missing, it is set 00-00-0000 in the database, but these dates are considered missing and will not be used for derivation (e.g., treatment duration).

15. ETHICAL CONSIDERATIONS

15.1 Declaration of Helsinki

The study is conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the Good Clinical Practice (ICH-GCP) guidelines and the General Data Protection Regulation (in Dutch AVG).

15.2 Recruitment and informed consent procedures

All eligible patients with locally recurrent rectal cancer who previously underwent total or partial mesorectal excision for rectal cancer presenting in one of the expert centres will be informed about the study by their treating physician. If a patient meets the in- and exclusion criteria the treating physician will ask the patient to participate in the study. Hereafter, patients are informed in more detail about the study by the local investigator or physician assistant. Thereafter, the patient information form is provided. The patient information form contains contact details of the study team in case of additional questions from the patient. After a sufficient amount of time patients will be asked to participate in the study. Written informed consent will be signed in two-fold and dated by hand at the outpatient department by either the treating physician, local investigator or physician assistant and the patient. After informed consent the contact information of the patient will be send to the coordinating investigator with the purpose of sending the questionnaires. Patients are given the possibility to give separate permission for storage of blood and tissue samples for translational research. If patients decide not to participate, they will receive standard of care and further treatment will not be affected by their decision.

15.3 Benefits and risks assessment, group relatedness

The potential benefit from adding induction chemotherapy to the neoadjuvant treatment regimen of patients with locally recurrent rectal cancer has to be weighed against the risks. The potential risks are related to toxicity of the treatment. However, there is extensive experience with the investigational chemotherapy agents in human beings with colorectal cancer and they are proven to be feasible and safe. Nevertheless, when chemotherapy agents are administered prior to subsequent chemoradiotherapy and surgery cumulative toxicity may be increased. Furthermore, it may lead to more postoperative complications. However, several phase 2 trials in patients with locally advanced rectal cancer showed high compliance rates to the subsequent chemoradiotherapy as well as acceptable toxicity and postoperative morbidity.[27,32,34] In addition, an interim analysis will be performed to detect unacceptable toxicity or surgical morbidity following induction chemotherapy in an early stage, namely after 100 patients have undergone surgery.

Another potential risk is that the prolonged neoadjuvant treatment may increase the risk for disease progression and secondary unresectablity. However, it is unlikely that patients with disease progression under induction chemotherapy would have benefited from surgery as this progression reflects an unfavourable tumour biology. In these patients induction chemotherapy offers the opportunity to avoid potentially harmful surgery.

The extra burden for patients in the experimental arm consists of additional visits to the outpatient department during the administration of induction chemotherapy, as well as one thoracoabdominal CT-scan and one pelvic MRI.

All participating patients who signed informed consent for participation in blood collection for translational research will undergo an extra 20ml blood withdrawal during routine standard of care at 6 or 7 points in time. The risk of an additional 20ml blood withdrawal is assessed as negligible, as no additional venepuncture will be performed. All participants will be asked to complete questionnaires, which is considered a minimal burden since the questionnaires contain brief and intuitive questions and are not very time consuming.

The investigators feel that the potential benefit of the experimental arm, which is more R0 resections, outweighs the burdens and risks of participation.

No vulnerable populations will be included in this study.

15.4 Compensation for injury

The sponsor has a liability insurance which is in accordance with the article 7. The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

The sponsor/investigator has a liability insurance that is in accordance with article 7, under 9, of the WMO.

15.5 Compensation for subjects

Not applicable.

15.6 Compensation for investigators

Not applicable.

16. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice.

16.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

16.2 Monitoring

The study will be monitored based on the recommendations as described in the brochure "Kwaliteitsborging mensgebonden onderzoek 2.0", published in October 2012 by the Dutch Federation of University Medical Centres (NFU). The monitor plan is based on the judgement of the project leader that the study treatment takes moderate risk for the participating patients. In the Netherlands, the study will be monitored by independent qualified monitors from the Netherlands Comprehensive Cancer Organisation (IKNL). Further detail on the aspects and frequency of monitoring and quality assurance can be found in a separate monitoring plan.

16.3 Recording, handling and storage of information

16.3.1 Handling of data and data protection

Individual patient information obtained as a result of this study is considered confidential and is handled conform the Dutch Personal Data Protection Act (AVG). Patients confidentiality will be ensured by using study numbers. Every randomised patient is assigned a study number. Communication occurs only with this number. A subject identification code list is safeguarded by the coordinating investigator. Blood and tissue samples collected for translational research will be coded using the same number. Disclosure to third parties is prohibited, except for authorities involved with monitoring and quality control of the study.

All data required to answer the primary and secondary objectives will be collected using only study numbers in an ISO 27001 certified study database with an electronic case report form (eCRF). Data management is performed by the local investigator. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

16.3.2 Source documents and case report forms (CRF)

A central study database (Castor, Netherlands Comprehensive Cancer Institute [IKNL], Utrecht, Netherlands) with an electronic case report form (eCRF) will be used to record all data required to answer the primary and secondary objectives.

Source documents for this study will include hospital records and procedure reports and data collection forms. These source documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

Information regarding Quality of Life will be collected digitally via a web-based questionnaire from an ISO 27001 certified study database with an electronic case report form (eCRF); this data will therefore be collected directly on the CRF's.

16.3.3 Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated (CTR: Article 57).

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law (CTR: Article 58).

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request (CTR: Article 57).

16.3.4 Collection and storage of biological samples

Blood and tissue samples collected for translational research will be coded using a study number. All samples will be collected and stored for future supplementary translational research outside the immediate scope of this trial. All patients participating in the study are asked for separate informed consent to collect blood samples for future translational research. If patients give consent, an additional 20ml blood is drawn during regular blood draws before start of the induction chemotherapy (experimental arm), before chemoradiotherapy, before surgery, three months after surgery and once a year during three years of follow-up, resulting in 7 samples for patients in the experimental arm and 6 samples for patients in the control arm. Blood draws for research purposes will be combined with planned routine blood draws. In short, 20 ml blood intended for translational research is drawn into two 10 mL evacuated blood draw tubes, maintained at room temperature and processed within 96 hours after drawing the blood. In the end, all samples will be sent to the Department of Medical Oncology of the Erasmus MC. All patients participating in the study are asked for separate informed consent to collect tumour tissue for future translational research and to enable correlative studies between tumour-derived parameters in the blood and the original tumour tissue. Tumour tissue will be collected by the pathologist, fresh frozen and stored at -80C. By the end of the study, all tumour samples will be shipped to the Antoni van Leeuwenhoek and stored at -80C until further use. Samples will be stored for 20 years.

16.4 Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

16.5 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach (CTR: Article 52).

16.6 Data breach response procedures

In the event of a data security breach, the sponsor will implement a series of measures to prevent or reduce further impact. These measures will at minimum include:

- The sponsor will prioritise immediate containment, i.e. will stop the data breach if it is ongoing. Additionally, the sponsor will take efforts to mitigate and limit the damage as applicable, for example through remotely wiping or encrypting compromised devices, or removing published files from online platforms.
- The sponsor will assess the breach to determine the cause and scope. This may include identifying what type of data was involved, the number of affected individuals, and whether the data has been accessed by unauthorized parties.
- The sponsor will promptly notify and report the incident to the Dutch Data Protection Authority within 72 hours of detection. This will be accomplished via the designated national data leak reporting desk. In the event of a serious breach, the sponsor will additionally notify the Member States affected by the breach. This will be done through the Clinical Trials Information System (CTIS) in accordance with section 16.5 of the study protocol.
- Should the data breach present a high risk to the individuals participating in the study, the affected subjects will also be informed without delay. This notification will include detailed information about the nature of the breach, potential consequences, and recommended protective measures, ensuring that study subjects are fully aware and can take appropriate actions to safeguard their personal information.
- The sponsor will record all breaches in a data breach register, documenting the cause, affected data, consequences, and remedial actions taken, to learn from past incidents and improve future data security measures.

16.7 Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS (CTR: Article 36(1)).

The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS (CTR: Article 36(2)).

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU (CTR: Article 36(3)).

16.8 Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS (CTR: Article 37(1)).

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3)).

16.8.1 Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS (CTR: Article 37(5)).

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS (CTR: Article 37(6)).

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well (CTR: Article 37(7)).

16.8.2 Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR (CTR: Article 38).

16.9 Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V (CTR: Article 37(4)).

16.10Public disclosure and publication policy

This study will be registered before start of accrual in the prospective Nederlands Trial Register (NTR) and clinicaltrials.gov. The central data manager, study statistician, coordinating investigator, and the study steering committee have access to the final datasets. Within one year after the primary endpoint has been reached, final results of the study will be submitted to an international peer-reviewed journal. The steering committee and coordinating investigator will prepare the manuscript together with

those who substantially contributed to the study. Any publication, abstract or presentation based on patients included in this study must be approved by the steering committee and coordinating investigator. The principal manuscript resulting from this study will be published by group authorship ("PelvEx Collaborative"). The study steering committee, the coordinating investigator, the principal investigators of all expert centres, investigators who are involved for analysing secondary outcomes (e.g., radiological or pathological response) and all others who make a sufficient contribution with regard to initiating, implementing or executing the study will be added to this Collaborative if they are not part of it yet.

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