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Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases: protocol of the multicenter, open-label, phase II, INTERACT-II trial

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Strengths and limitations of this study

- First prospective phase II study assessing the survival, safety and feasibility of treatment of Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases (CPM).
- Assessment of multiple secondary outcomes such as patient-reported outcomes, costs and the pharmacokinetics of intraperitoneally administered irinotecan.
- Translational research of the present study may provide fundamental insight in CPM
- The INTERACT-II study may be an important step towards a more effective, life-prolonging treatment modality for this specific patient group.
- It is a non-randomized phase II study and therefore no comparison can be made to a control group.

Abstract

Introduction: The peritoneum is the second most affected organ for the dissemination of colorectal cancer (CRC). Patients with colorectal peritoneal metastases (CPM) face a poor prognosis, despite the majority of patients being treated with palliative systemic therapy. The efficacy of palliative systemic therapy is limited, due to the plasma-peritoneum barrier. The poor prognosis of unresectable CPM patients has resulted in the development of new treatment strategies where systemic therapy is combined with local, intraperitoneal chemotherapy. In the recently published phase I study the maximum tolerated dose (MTD) and thus the recommended phase II dose (RP2D) of intraperitoneal Irinotecan was investigated and determined to be 75 mg. In the present study, the overall survival after treatment with 75 mg irinotecan with concomitant mFOLFOX4 and bevacizumab will be investigated.

Materials and Methods: In this single-arm phase II study in two Dutch tertiary referral centers, 85 patients are enrolled. Eligibility criteria are an adequate performance status and organ function, histologically confirmed microsatellite stable and unresectable CPM, no previous palliative therapy for CRC, no systemic therapy <6 months for CRC prior to enrolment and no previous cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC). Patients will undergo a diagnostic laparoscopy as standard work-up for CPM and if the peritoneal disease is considered unresectable (e.g. PCI >20, too extensive small bowel involvement), a peritoneal access port and a port-a-cath are placed for administration of intraperitoneal and intravenous chemotherapy, respectively. Patients may undergo up to 12 cycles of study treatment. Each cycle consists of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg), which is repeated every two weeks, with a maximum of 12 cycles. Modified FOLFOX-4 regimen consists of 85 mg/m^2 oxaliplatin plus 200 mg/m^2 LV and 5-FU 400 mg/m^2 bolus on day 1 followed by 1600 mg/m^2 5-FU as a 46-h infusion. Study treatment ends after the twelfth cycle, or earlier in case of disease progression or unacceptable toxicity. The primary outcome is overall survival and key secondary outcomes are progression-free survival, safety (measured by the amount of grade ≥3 adverse events [Common Terminology Criteria for Adverse Events V5.0]), patient-reported outcomes and pharmacokinetics of irinotecan. It is hypothesized that the trial treatment will lead to a 4 month increase in overall survival; from a median of 12.2 months, to 16.2 months.

Ethics and Dissemination: This study is approved by the Dutch Authority (CCMO, the Hague, the Netherlands), by a central medical ethics committee (MEC-U, Nieuwegein, the Netherlands) and by the institutional research boards of both research centers. Results will be submitted for publication in peer-reviewed medical journals and presented to patients and healthcare professionals.

Introduction

The peritoneum is the second most common metastatic site in colorectal cancer, affecting approximately 10% of patients (1, 2). For a long time, the presence of colorectal peritoneal metastases (CPM) was considered to render the disease non-curable (3).

The introduction of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) resulted in improved survival in selected patients with limited colorectal peritoneal metastases as compared to palliative systemic therapy (4). However, only a small portion of patients is eligible for CRS and HIPEC, as the majority of patients have too extensive colorectal peritoneal metastases (CPM) to benefit from CRS and HIPEC (5).

The extent of peritoneal metastases is evaluated with the Peritoneal Cancer Index (PCI), which divides the abdomen in nine regions and the small bowel in four regions. Each region is given a score of 0-3 and the regions are summed up subsequently; a score of 0 reflects the absence of peritoneal metastases, while a maximum score of 39 indicates extensive disease in all regions (6). In general, CRS and HIPEC is not considered beneficial when the PCI exceeds 20 or when a macroscopic complete resection is not deemed feasible, for example in case of extensive small bowel involvement (7). The situation in which the patient has a PCI>20, or when complete resection is deemed unfeasible, is referred to as unresectable CPM.

Currently, patients with unresectable CPM receive palliative systemic therapy or best supportive care. The prognosis of these patients is dismal, with a median overall survival of 6-8 months with best supportive care and 10-14 months with palliative systemic therapy (5). The plasma-peritoneum barrier is suggested to reduce efficacy of systemic therapy in the treatment of CPM, as compared to patients with lung or liver metastases from a colorectal origin. (8). The plasma-peritoneum barrier is a complex structure that regulates the intraperitoneal homeostasis, thus hampering an effective transportation of the systemic therapy to the peritoneal metastases(9).

By applying cytostatic therapies intraperitoneally, the traits of the plasma-peritoneum barrier can be used advantageously (9-13). Due to the limited absorption into the systemic circulation caused by the plasma-peritoneum barrier, higher intraperitoneal drug concentrations and prolonged exposure of PM to those drugs can be achieved compared to systemic administration(13).

The aforementioned CRS-HIPEC is based in part on these here described traits of the plasma-peritoneum barrier (10). In addition, different techniques, through which palliative chemotherapy can be applied intraperitoneally exist. With pressurized intraperitoneal aerosol chemotherapy (PIPAC), chemotherapy is administered as aerosol during repetitive laparoscopies, while the INTERACT I study investigated the intraperitoneal administration of chemotherapy through an intraperitoneal access port (14-16).

In addition to various techniques for the intraperitoneal application of chemotherapy, a variety of cytotoxic agents can be used (13, 17). One of the chemotherapeutic groups that has been studied and that shows promise is the group of topoisomerase inhibitors (13).

Irinotecan is a topoisomerase I inhibitor and was the chemotherapeutic agent that was studied in the INTERACT I study. Irinotecan is a prodrug and its main efficacy is attributed to its metabolite SN-38, which is 100-1000 fold more cytotoxic than irinotecan. The conversion to SN-38 takes place in both the liver and intraperitoneal space (18-24). Several studies showed that the intraperitoneal area under the curve of irinotecan and SN-38 was much higher after intraperitoneal administration than after systemic administration. Additionally, the peritoneal clearance of intraperitoneally administered irinotecan was 10-fold lower than after systemic administration of irinotecan (21, 25-28).

Intraperitoneal chemotherapy, such as irinotecan, can either be applied as monotherapy, or in combination with systemic therapy. In both ovarian and gastric cancer the addition of intraperitoneal chemotherapy to systemic chemotherapy showed promising results (20, 29-32). Moreover, in ovarian cancer, a beneficial effect was proven by a large randomized controlled trial (32). These findings, in combination with the promising results of the INTERACT I study, suggest that intraperitoneal chemotherapy in addition to systemic therapy could be beneficial in patients with unresectable colorectal peritoneal metastases as well (33).

The recent INTERACT study (NL63809.078.18) was a dose-escalation study and was performed to find the maximum tolerated dose (MTD) of intraperitoneal (IP) irinotecan (16). In this study, 18 patients with unresectable colorectal peritoneal metastases were treated with first-line palliative systemic therapy with FOLFOX/bevacizumab and concomitant intraperitoneal irinotecan at flat dose levels of 50 mg (n=4), 75 mg (n=9), and 100 mg (n=4). For the 50 mg and 75 mg dose cohorts, no dose-limiting toxicities were observed. After two dose-limiting toxicities at the 100 mg dose level, the MTD was thus established at 75 mg.

The INTERACT-II study is a multi-center, single-arm, phase II study, aimed to assess overall survival, progression-free survival, safety, patient reported outcomes (PRO's), costs and pharmacokinetics of 75mg IP irinotecan with concomitant first-line systemic therapy (consisting of FOLFOX and bevacizumab) in patients with unresectable CPM.

Methods and analysis

This protocol summary follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (34).

Setting

This study is a single-arm, open-label, phase II study that is performed in two large Dutch tertiary referral centers for the treatment of CPM; The Catharina Cancer Institute in Eindhoven and the Erasmus MC Cancer Institute in Rotterdam. Further tertiary referral centers may join later.

Objectives

The primary objective is to explore overall survival after treatment with intraperitoneal irinotecan (75 mg) to mFOLFOX4 / bevacizumab in patients with unresectable colorectal peritoneal metastases, henceforth referred to as trial treatment.

Secondary objectives are:

- To assess progression-free survival (which is calculated from the interval from the start of trial treatment until first evidence of intraperitoneal and/or systemic disease progression and/or start of second-line systemic therapy, or last follow-up).
- To assess the feasibility of trial treatment; to assess the toxicity profile (defined as the number of grade 3-5 adverse events according to the Common Terminology Criteria for Adverse Events [CTCAE]) of trial treatment.
- To assess patient reported outcomes (PROs) during trial treatment.
- To assess costs of trial treatment
- To assess the nephrotoxicity, hepatotoxicity, and hematological toxicity during trial treatment.
- To assess tumor marker fluctuations during trial treatment.
- To determine the number of patients completing trial treatment, required dose reductions, and reasons for discontinuation.
- To determine the number of patients with an objective radiological response during and after trial treatment.
- To systematically collect, process, and store blood, tumor tissue and ascites for future translational research
- To determine the systemic and intraperitoneal pharmacokinetics of intraperitoneal irinotecan.

Exploratory objectives are to determine if, and how many patients are able to undergo salvage procedures, such as CRS and HIPEC following successful treatment with intraperitoneal irinotecan (75 mg) and concomitant palliative systemic therapy.

Eligibility criteria

Eligibility criteria are:

- Histologically confirmed colorectal carcinoma.
- Microsatellite stable (MSS) primary tumor.
- Radiologically and clinically or pathologically confirmed unresectable colorectal peritoneal metastases (e.g. PCI >20, extensive small bowel involvement, unresectable disease due to anatomical location).
- WHO performance score of 0-1 with a life expectancy of >3 months.
- Aged 18 years or older.
- Adequate organ functions (hemoglobin of ≥5 mmol/L, neutrophil count of ≥1.5 x 10^9/L, platelet count of ≥100 x 10^9/L, serum creatinine of <1.5 x upper limit of normal [ULN], creatinine clearance of ≥30 ml/min, Bilirubin <2x ULN and liver transaminases of <5 x ULN).
- Absence of extensive systemic metastases that are deemed to be the dominant factor determining prognosis in terms of life expectancy and performance status (e.g. no imminent threat of impaired organ functioning due to the presence of systemic metastases).
- No prior cytoreductive surgery.
- No prior palliative systemic therapy for colorectal cancer.
- No (neo)adjuvant/adjuvant systemic therapy for colorectal cancer within 6 months prior to enrollment.
- No homozygous UGT1A1*28 genotype(35).
- No dihydropyrimidine dehydrogenase (DPD) deficiency.
- No contra-indications for the planned chemotherapy (e.g. active infection, serious concomitant disease, severe allergy), as determined by the medical oncologist.

Study treatment

The study flowchart is presented in figure 1. The study schedule of enrollment, treatment and assessment is shown in table 1.

Diagnostic laparoscopy and port placement

Patients who are candidates for CRS and HIPEC are discussed in a multidisciplinary oncology team meeting, after which they are scheduled for a diagnostic laparoscopy. Patients who are considered to have a high chance of unresectable CPM, based on radiological or clinical investigations, may be enrolled in the study. After enrollment, a diagnostic laparoscopy is performed to inspect the peritoneal cavity. The diagnostic laparoscopy is performed under general anesthesia. If peritoneal disease is

considered unresectable (e.g. due to PCI >20, too extensive small bowel involvement or anatomical location), two ports are placed: one regular intravenous port-a-cath for the intravenous administration of chemotherapy according to local standard of care, and one peritoneal access port for the intraperitoneal administration of chemotherapy. The peritoneal access port is placed on the fascia just above or just below the lower rib cage at the discretion of the surgeon. The catheter is tunneled and inserted into the peritoneal cavity. The tip is positioned in the pelvis. Ascites (or 0.9% NaCl lavage) is collected for translational research. Patients may be discharged the same day after having received instructions for hygiene and wound care.

Chemotherapy

In the absence of post-operative complications, the first cycle will start at least one week after placement of the ports, to allow for sufficient wound healing. Each cycle consists of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg). Intraperitoneal irinotecan (75 mg) will be dissolved in 1 liter NaCl 0.9% and pre-warmed to 37^{o}C. Cycles are repeated every two weeks, with a maximum of 12 cycles. Modified FOLFOX-4 regimen consists of 85 mg/m^2 oxaliplatin plus 200 mg/m^2 LV and 5-FU 400 mg/m^2 bolus on day 1 followed by 1600 mg/m^2 5-FU as a 46-h infusion (27). In case of symptomatic ascites, the ascites will be (partly) drained through the peritoneal access port prior to the start of the therapy cycle.

Response evaluation

Before each cycle, the patient is evaluated (based on clinical and biochemical parameters) by the treating medical oncologist. After every fourth cycle, a thoracoabdominal computed tomography (CT) scan is performed for response evaluation. After each CT scan, the decision to continue trial treatment is based on disease response and clinical performance:

- In case of physician-determined disease progression (either intraperitoneal, systemic, or both), trial treatment is discontinued. The patient will receive second line palliative systemic treatment or best supportive care according to the Dutch national guideline for colorectal cancer (36).
- In case of physician-determined disease response or stable disease (both intraperitoneal and systemic) but severe clinical deterioration or unacceptable toxicity to treatment, rendering the patient unsuited to continue with treatment, trial treatment is discontinued. The patient will receive further palliative systemic treatment or best supportive care according to the Dutch national guideline for colorectal cancer (36).

- In case of physician-determined disease response or stable disease (both intraperitoneal and systemic) and sufficient clinical condition and acceptable toxicity to treatment, trial treatment is continued.

For all patients, study treatment ends after completing the twelfth cycle of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg), regardless of response on the thoracoabdominal CT performed after the twelfth cycle. On patient's request, the peritoneal access port is removed after the last cycle of trial treatment. After the evaluation after the twelfth cycle, intraperitoneal chemotherapy will be discontinued definitively and further treatment is scheduled with the medical oncologist and will be in according to local standard of care and may include of CRS-HIPEC (36).

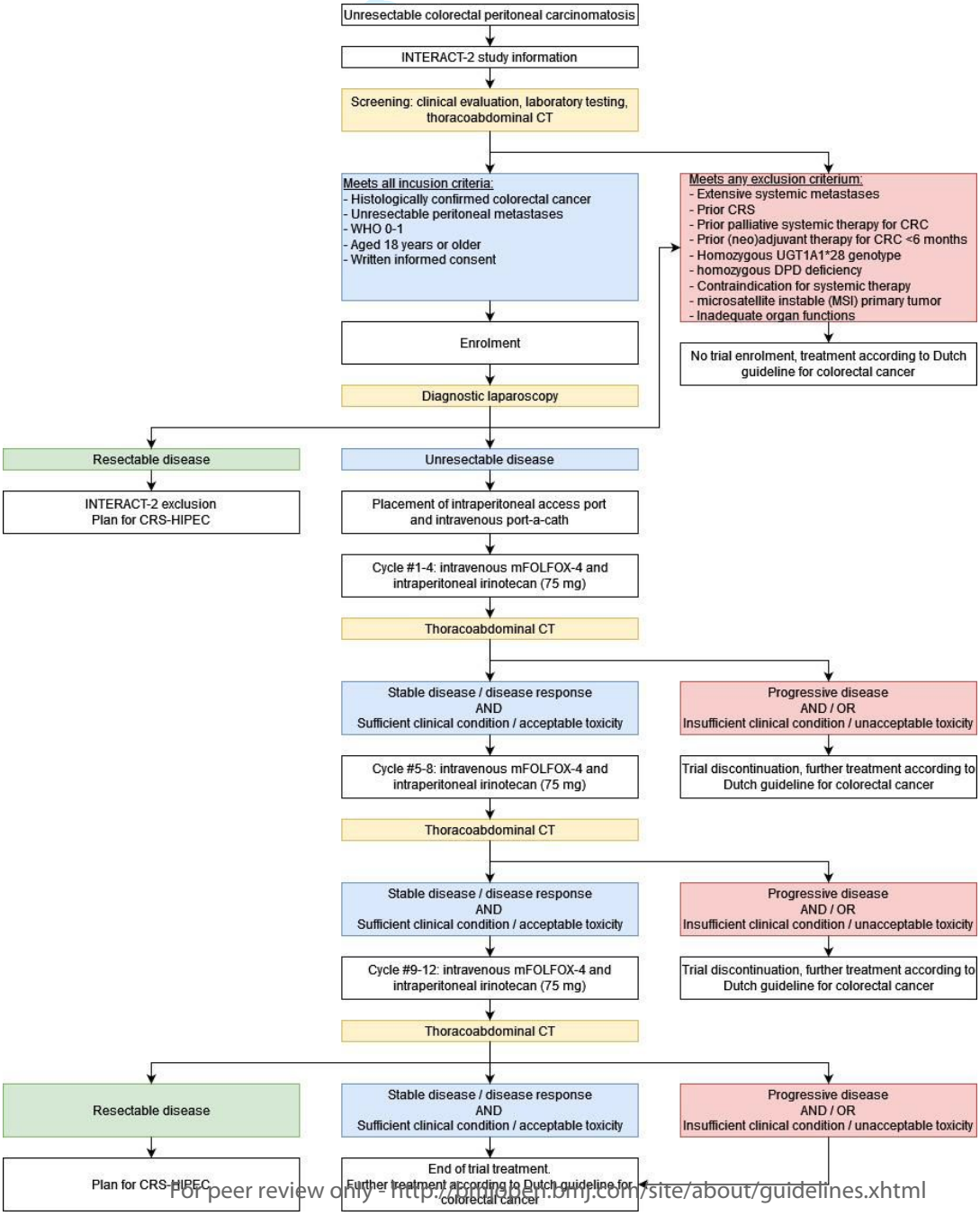

Figure 1. Study flowchart. WHO, World Health Organization performance status; CRS, cytoreductive surgery; CRC, HIPEC, hyperthermic intraperitoneal chemotherapy; colorectal cancer; DPD, dihydropyrimidine dehydrogenase.

Sample size

based on a Population

have described

an overall

survival of

Table 1. Overview of study procedures

	Screening	Enrolment	Medical oncologist: intake	Diagnostic laparoscopy	Cycle #1	Cycles #2-4	One week after cycle #4	Cycles #5-8	One week after cycle #8	Cycles #9-12	One week after cycle #12	Last study visit
Multidisciplinary tumor board	X						X		X		X	
Medical history	X	X	X									
Inclusion and exclusion criteria	X	X	X									
Provide study information	X	X	X									
Written informed consent		X										
Physical examination		X	X		X	X		X		X		
Pre-operative screening		X										
Blood test: DPD and UGT1A1 genotype		X										
Blood test: organ functions		X			X	X		X		X		
Blood test: tumor marker[a]		X			X	X		X		X		
Blood test: pregnancy[b]		X										
Electrocardiogram		X										
Placement of port-a-cath				X								
Placement of peritoneal access port				X								
Thoracoabdominal CT scan[c]		X					X		X		X	
Systemic chemotherapy					X	X		X		X		
Intraperitoneal chemotherapy					X	X		X		X		
Clinical evaluation		X	X		X	X		X		X		X
Toxicity evaluation (CTCAE)					X	X		X		X		X
Patient Reported Outcomes Questionnaires		X			X		X		X		X	
Costs Questionnaires		X			X		X		X		X	
Pharmacokinetics					X	X*						
Progression Free Survival							X		X		X	X
Overall Survival					X	X		X		X		X
Remove peritoneal access port[d]												X
Translational Research: blood		X			X		X		X		X	
Translational Research: ascites				X	X	X*						

[a]Carcino-embryonic antigen; [b]Only determined in women of fertile age (<55 years); [c]Unless already performed <6 weeks before diagnostic laparoscopy; [d]On patient's request;
CT, Computed Tomography; CTCAE, Common Terminology Criteria for Adverse Events; Marked in grey: study-specific procedures;
*only at cycle 4

approximately 12.2 months (5) for patients with isolated unresectable colorectal peritoneal metastases treated with palliative systemic chemotherapy. Based on clinical experience, expert consensus and the preliminary results of the INTERACT study, we hypothesize that the study treatment will result in a median overall survival of at least 16.2 months. This entails an expected increase of 4 months in the study population in comparison to the general population of patients with unresectable CPM. To render this assumption plausible, with a power of 80% and a type I error rate of 0.05, a sample size of 85 is needed.

Given the previous experience with the trial treatment from the INTERACT study and the low expected additional toxicity of intraperitoneal irinotecan, the investigators consider it reasonable and safe to expose 85 patients to trial treatment.

Replacement of individual patients

If a patient is withdrawn from the study prior to completing one cycle of intraperitoneal irinotecan with concomitant systemic therapy, an additional patient is enrolled to replace the withdrawn patient.

Statistical analyses

All patients who complete at least one cycle of intraperitoneal irinotecan (75 mg) with concomitant systemic therapy will be included in the analyses. Categorical variables will be presented as n (%) and compared with the Chi-square test. Continuous variables will be presented as mean ± standard deviation or median (interquartile range), depending on distribution. Paired data will be compared with the paired t-test or Wilcoxon signed rank test, depending on distribution. Unpaired data will be compared with the unpaired t-test or Kruskal Wallis test, depending on distribution. A p value <0.05 will be considered statistically significant. Correction for multiple testing will be applied if necessary. Statistical analyses will be performed with SPSS (version 25.0, Armonk, NY, United States).

Analysis of primary study parameter(s)

The overall survival is calculated from (a) the interval from diagnosis of peritoneal metastases until death or last follow-up; (b) the interval from the first day of the first cycle until death or last follow-up). Overall survival will be presented with the Kaplan Meier method, and subgroups (e.g. stratification based on the presence of systemic metastases or peritoneal carcinomatosis index) will be compared with the log rank test.

Analysis of secondary study parameter(s)

- Progression-free survival (calculated from the interval from the start of trial treatment until first evidence of intraperitoneal and/or systemic disease progression or last follow-up) will be presented with the Kaplan Meier method, and subgroups (e.g. stratification based on the presence of systemic metastases or PCI) will be compared with the log rank test.
- Toxicity, defined as the number of patients who experience / the total number of Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade 3-5 adverse events, measured up to four weeks after trial treatment. Given the non-randomized design of the study, these analyses will be exploratory and results will be presented as n (%). Differences in subgroups (e.g. stratification based on the presence of systemic metastases or peritoneal carcinomatosis index) will be compared with the unpaired t-test or Kruskall Wallis test, depending on distribution.
- Patient reported outcomes (PROs) during trial treatment, assessed with the EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-CR29 at baseline, one week after the first cycle, one week after the fourth cycle, one week after the eighth cycle, and one week after the twelfth cycle, will be analyzed according to the corresponding manuals (37-39). Given the novelty of the trial treatment, no a priori hypotheses are defined for PRO analyses. Therefore, PRO assessment will be explorative, providing the mean ± standard deviation of each PRO category at each time-point. Linear Mixed Modelling analyses will be performed to compare differential effects over time and scores at each time-point, with the use of maximum likelihood estimation and an unstructured covariance matrix with a two-level structure (i.e. repeated time-points [lower level], patients [higher level]). To correct for multiple testing, a pragmatically chosen $p<0.01$ is considered statistically significant. In case of statistically significant differences, clinical relevance is determined by a Cohen's D >0.500.
- Healthcare costs and costs due to productivity losses during trial treatment will be assessed with the iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire at baseline, one week after the first cycle, one week after the fourth cycle, one week after the eighth cycle, and one week after the twelfth cycle. An overview of the total costs of trial treatment (1, per protocol health-care costs; 2, additional health-care costs; 3, costs due to productivity losses) is established according to the Dutch Manual for Cost Analysis in Healthcare (40, 41).
- Tumor marker fluctuations during trial treatment will be assessed by carcino-embryonic antigen (CEA) analysis before each subsequent cycle. Given the novelty of the trial treatment, no a priori hypotheses are defined. Linear Mixed Modeling analyses will be performed to compare differential effects over time and scores at each time-point, with the use of maximum likelihood estimation and an unstructured covariance matrix with a two-level structure (i.e.

repeated time-points [lower level], patients [higher level]). To correct for multiple testing, a pragmatically chosen $p<0.01$ is considered statistically significant.

- Feasibility of trial treatment is assessed through completion of twelve cycles of trial treatment, required dose reductions, and reasons for discontinuation. These results are presented as n (%);
- Radiological response (according to radiological PCI and RECIST (39)) during and after trial treatment will be assessed by thoracoabdominal CT at baseline, after the fourth cycle, after the eighth cycle, and after the twelfth cycle. These results are presented as n (%);
- To further investigate the pharmacokinetics of intraperitoneal irinotecan, peritoneal fluid and peripheral blood samples will be withdrawn at several time points during the first and fourth cycle. The maximum plasma concentration (Cmaxp), the time to maximum plasma concentration (Tmaxp), plasma area under the curve (AUCp), maximum intraperitoneal concentration (Cmaxip), the time to maximum intraperitoneal concentration (Tmaxip), intraperitoneal area under the curve (AUCip) of irinotecan (plasma only) and SN-38 (plasma and peritoneal fluid) will be determined.

Recruitment

The study commenced in November 2022 and the first patients were enrolled in December 2022. It is expected to complete accrual within 2 years. To generate more awareness and to increase referrals of potential study candidates, a short Dutch summary of the study will be published in *The Dutch Journal for Oncology* (NTvO in Dutch). Further strategies to optimize accrual have not been defined *a priori*.

Data collection and data management

Outcomes are collected in all patients who completed at least one treatment cycle. All data are prospectively collected by a local investigator in each study center using standardized electronic case report forms linked to an ISO 27001 certified central study database (De Research Manager, Deventer, the Netherlands). This ISO 27001 certified system optimizes data quality by standardized data entry, coding, security and storage.

Data monitoring

Interim analyses are performed by principal investigators and trial coordinators four weeks after the first chemotherapy cycle of the 20th included patient and after the second chemotherapy cycle of the 43th patient, after half of the study procedures and systemic cycles have been performed and applied. These analyses will only focus on the safety aspect. The study may be prematurely terminated by the sponsor if there is evidence of an unacceptable risk for study patients. The sponsor will notify all

concerned investigators, the medical ethics committee and regulatory authorities of the decision to terminate the study.

Serious adverse events (SAEs) and suspected unexpected serious adverse reaction (SUSARs)

The investigator will report all SAEs and SUSARs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs and SUSARs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs or SUSARs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs and SUSARS will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Auditing

Auditing is performed by independent qualified monitors of the study centers. The study is considered a low-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centers.

Ethics and dissemination

Research ethics approval

The present study is approved by a central ethics committee (MEC-U, Nieuwegein, Netherlands, number R22.052) and the institutional review boards of both study centers.

Protocol amendments

Important modifications to the study protocol need to be authorized by the central ethics committee. After authorization, these modifications are communicated to the Dutch competent authority, the institutional review boards of both study centers, all investigators, study registries and patients (if required by the central ethics committee).

Informed consent

Patients are enrolled by their treating physician and provide written informed consent. Patients are able to consent to questionnaires and participation in translational side studies separately.

Confidentiality

Personal data of patients is collected and processed in strict adherence to the Dutch law.

Access to data

All authors have access to the final dataset, without any contractual agreements that limit access.

Ancillary or post-study care

The Catharina Hospital is insured to cover harms caused by study participation and extends its insurance to any participating hospital. After trial treatment is stopped, patients will be treated according to Dutch guidelines, as aforementioned in section *"response evaluation"*.

Dissemination policy

Study results will be submitted for publication in peer-reviewed medical journals and presented to patients, healthcare professionals and the public, during (inter)national meetings. Authorship eligibility guidelines are not defined a priori. The full study protocol and the Dutch informed consent form are

made available upon written request to the corresponding author. After study completion, the participant-level dataset and statistical code will be made available upon reasonable request.

Discussion

In this single-arm, open-label, phase II, patients with unresectable colorectal peritoneal metastases are treated with concomitant intraperitoneal and systemic cytotoxic therapy. The primary objective of the study is to assess overall survival (OS) after treatment with intraperitoneal irinotecan with concomitant mFOLFOX4 and bevacizumab. Secondary objectives are to assess progression-free survival (PFS), safety, patient reported outcomes (PRO's), costs, feasibility and pharmacokinetic parameters of intraperitoneal irinotecan with concomitant mFOLFOX4 and bevacizumab.

During this study, ascites and peritoneal biopsy samples will be collected and processed for translational research purposes. These samples will be used to establish organoids, in order to study drug response and resistance ex vivo in detail. This might aid in improved patient selection for both palliative and curative treatments, as well as enable a more personalized treatment approach (42).

Multiple studies have studied the effect of another strategy to apply chemotherapy intraperitoneally: pressurized intraperitoneal aerosol chemotherapy (PIPAC) (15, 43, 44). In contrast to PIPAC, the intraperitoneal chemotherapy administered in this study is applied simultaneously with systemic chemotherapy without the need for complex (and expensive) devices or surgery. Furthermore, in comparison to PIPAC, INTERACT treatment has the potential benefit of exposing tumor cells to the cytotoxic agent much more frequent and for a much longer timespan (33)

To the best of our knowledge, after the INTERACT study, this is only the second study in patients with peritoneal metastases of colorectal origin that combines standard of care systemic chemotherapy with intraperitoneally administered chemotherapy. As such, the present study will provide essential information about overall survival and progression-free survival, as well as on safety, feasibility, costs and PROs of treatment with intraperitoneal irinotecan, and will provide a framework for the conduction of further clinical research. The INTERACT-II study may be an important step towards a more effective, life-prolonging treatment modality for this specific patient group, with the possibility for curative treatment consisting of CRS-HIPEC in specific patients with excellent response to the treatment.

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TBMvdH and NADG are the coordinating investigators. VCJvdV, RJL, TBMvdH, RJFB, IvH, GJMC, SWN, IHJTdH and JWAB are the local investigators of the first study center. NADG, SLWK, EvM, CV, RHJM are the local investigators of the second study center. SK is the study pharmacologist supervising the pharmacokinetic analyses. JN is the study radiologist performing the central radiological review. SLWK is responsible for translational research on blood. OK is responsible for translational research on ascites and peritoneal lavage. JWAB is the principal investigator. VCJvdV, NADG, RJL, RHJM, and JWAB made substantial contributions to the conception and design of the study, drafted the protocol and drafted the manuscript. IEGvH, GJMC, IHJTdH, SWN, OK, SK, CV, TBMvdH and EvM made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interest

None to declare

Patient consent for publication

Not required

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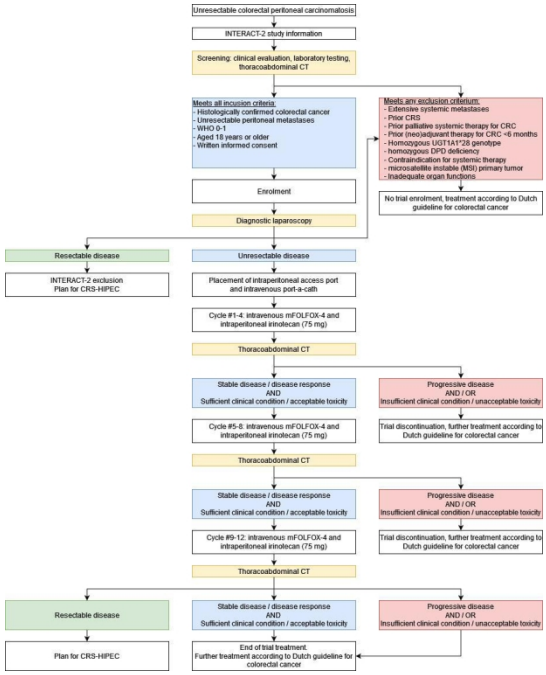

Figure 1. Study flowchart. WHO, World Health Organization performance status; CRS, cytoreductive surgery; CRC, HIPEC, hyperthermic intraperitoneal chemotherapy; colorectal cancer; DPD, dihydropyrimidine dehydrogenase.

1144x762mm (38 x 38 DPI)

	Screening	Enrolment	Medical oncologist: intake	Diagnostic laparoscopy	Cycle #1	Cycles #2-4	One week after cycle #4	Cycles #5-8	One week after cycle #8	Cycles #9-12	One week after cycle #12	Last study visit
Multidisciplinary tumor board	X						X		X		X	
Medical history	X	X	X									
Inclusion and exclusion criteria	X	X	X									
Provide study information	X	X	X									
Written informed consent		X										
Physical examination		X	X		X	X		X		X		
Pre-operative screening		X										
Blood test: DPD and UGT1A1 genotype		X										
Blood test: organ functions		X			X	X		X		X		
Blood test: tumor marker[a]		X			X	X		X		X		
Blood test: pregnancy[b]		X										
Electrocardiogram		X										
Placement of port-a-cath				X								
Placement of peritoneal access port				X								
Thoracoabdominal CT scan[c]		X					X		X		X	
Systemic chemotherapy					X	X		X		X		
Intraperitoneal chemotherapy					X	X		X		X		
Clinical evaluation		X	X		X	X		X		X		X
Toxicity evaluation (CTCAE)					X	X		X		X		X
Patient Reported Outcomes Questionnaires		X			X		X		X		X	
Costs Questionnaires		X			X		X		X		X	
Pharmacokinetics					X							

Progression Free Survival							X		X		X	X
Overall Survival					X	X		X		X		X
Remove peritoneal access port[d]												X
Translational Research: blood		X					X		X		X	
Translational Research: ascites				X	X	X						
[a]Carcino-embryonic antigen; [b]Only determined in women of fertile age (<55 years); [c]Unless already performed <6 weeks before diagnostic laparoscopy; [d]On patient's request; CT, Computed Tomography; CTCAE, Common Terminology Criteria for Adverse Events; Marked in grey: study-specific procedures;												

Table 1: overview of study procedures

BMJ Open

Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases: protocol of the multicenter, open-label, phase II, INTERACT-II trial

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery
Keywords:	CHEMOTHERAPY, Clinical Trial, Gastrointestinal tumours < ONCOLOGY, Colorectal surgery < SURGERY

Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases: protocol of the multicenter, open-label, phase II, INTERACT-II trial

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Abstract

Introduction: The peritoneum is the second most affected organ for the dissemination of colorectal cancer (CRC). Patients with colorectal peritoneal metastases (CPM) face a poor prognosis, despite the majority of patients being treated with palliative systemic therapy. The efficacy of palliative systemic therapy is limited, due to the plasma-peritoneum barrier. The poor prognosis of unresectable CPM patients has resulted in the development of new treatment strategies where systemic therapy is combined with local, intraperitoneal chemotherapy. In the recently published phase I study the maximum tolerated dose (MTD) and thus the recommended phase II dose (RP2D) of intraperitoneal Irinotecan was investigated and determined to be 75 mg. In the present study, the overall survival after treatment with 75 mg irinotecan with concomitant mFOLFOX4 and bevacizumab will be investigated.

Materials and Methods: In this single-arm phase II study in two Dutch tertiary referral centers, 85 patients are enrolled. Eligibility criteria are an adequate performance status and organ function, histologically confirmed microsatellite stable and unresectable CPM, no previous palliative therapy for CRC, no systemic therapy <6 months for CRC prior to enrolment and no previous cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC). Patients will undergo a diagnostic laparoscopy as standard work-up for CPM and if the peritoneal disease is considered unresectable (e.g. PCI >20, too extensive small bowel involvement), a peritoneal access port and a port-a-cath are placed for administration of intraperitoneal and intravenous chemotherapy, respectively. Patients may undergo up to 12 cycles of study treatment. Each cycle consists of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg), which is repeated every two weeks, with a maximum of 12 cycles. Modified FOLFOX-4 regimen consists of 85 mg/m^2 oxaliplatin plus 200 mg/m^2 LV and 5-FU 400 mg/m^2 bolus on day 1 followed by 1600 mg/m^2 5-FU as a 46-h infusion. Study treatment ends after the twelfth cycle, or earlier in case of disease progression or unacceptable toxicity. The primary outcome is overall survival and key secondary outcomes are progression-free survival, safety (measured by the amount of grade ≥3 adverse events [Common Terminology Criteria for Adverse Events V5.0]), patient-reported outcomes and pharmacokinetics of irinotecan. It is hypothesized that the trial treatment will lead to a 4 month increase in overall survival; from a median of 12.2 months, to 16.2 months.

Ethics and Dissemination: This study is approved by the Dutch Authority (CCMO, the Hague, the Netherlands), by a central medical ethics committee (MEC-U, Nieuwegein, the Netherlands) and by the institutional research boards of both research centers. Results will be submitted for publication in peer-reviewed medical journals and presented to patients and healthcare professionals.

Strengths and limitations of this study

- First prospective phase II study assessing the survival, safety and feasibility of treatment of Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases (CPM).
- Assessment of multiple secondary outcomes such as patient-reported outcomes, costs and the pharmacokinetics of intraperitoneally administered irinotecan.
- Translational research of the present study may provide fundamental insight in CPM.
- The INTERACT-II study may be an important step towards a more effective, life-prolonging treatment modality for this specific patient group.
- It is a non-randomized phase II study and therefore no comparison can be made to a control group.

Introduction

The peritoneum is the second most common metastatic site in colorectal cancer, affecting approximately 10% of patients (1, 2). For a long time, the presence of colorectal peritoneal metastases (CPM) was considered to render the disease non-curable (3).

The introduction of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) resulted in improved survival in selected patients with limited colorectal peritoneal metastases as compared to palliative systemic therapy (4). However, only a small portion of patients is eligible for CRS and HIPEC, as the majority of patients have too extensive colorectal peritoneal metastases (CPM) to benefit from CRS and HIPEC (5).

The extent of peritoneal metastases is evaluated with the Peritoneal Cancer Index (PCI), which divides the abdomen in nine regions and the small bowel in four regions. Each region is given a score of 0-3 and the regions are summed up subsequently; a score of 0 reflects the absence of peritoneal metastases, while a maximum score of 39 indicates extensive disease in all regions (6). In general, CRS and HIPEC is not considered beneficial when the PCI exceeds 20 or when a macroscopic complete resection is not deemed feasible, for example in case of extensive small bowel involvement (7). The situation in which the patient has a PCI>20, or when complete resection is deemed unfeasible, is referred to as unresectable CPM.

Currently, patients with unresectable CPM receive palliative systemic therapy or best supportive care. The prognosis of these patients is dismal, with a median overall survival of 6-8 months with best supportive care and 10-14 months with palliative systemic therapy (5). The plasma-peritoneum barrier is suggested to reduce efficacy of systemic therapy in the treatment of CPM, as compared to patients with lung or liver metastases from a colorectal origin. (8). The plasma-peritoneum barrier is a complex structure that regulates the intraperitoneal homeostasis, thus hampering an effective transportation of the systemic therapy to the peritoneal metastases(9).

By applying cytostatic therapies intraperitoneally, the traits of the plasma-peritoneum barrier can be used advantageously (9-13). Due to the limited absorption into the systemic circulation caused by the plasma-peritoneum barrier, higher intraperitoneal drug concentrations and prolonged exposure of PM to those drugs can be achieved compared to systemic administration(13).

The aforementioned CRS-HIPEC is based in part on these here described traits of the plasma-peritoneum barrier (10). In addition, different techniques, through which palliative chemotherapy can be applied intraperitoneally exist. With pressurized intraperitoneal aerosol chemotherapy (PIPAC), chemotherapy is administered as aerosol during repetitive laparoscopies, while the INTERACT I study investigated the intraperitoneal administration of chemotherapy through an intraperitoneal access port (14-16).

In addition to various techniques for the intraperitoneal application of chemotherapy, a variety of cytotoxic agents can be used (13, 17). One of the chemotherapeutic groups that has been studied and that shows promise is the group of topoisomerase inhibitors (13).

Irinotecan is a topoisomerase I inhibitor and was the chemotherapeutic agent that was studied in the INTERACT I study. Irinotecan is a prodrug and its main efficacy is attributed to its metabolite SN-38, which is 100-1000 fold more cytotoxic than irinotecan. The conversion to SN-38 takes place in both the liver and intraperitoneal space (18-24). Several studies showed that the intraperitoneal area under the curve of irinotecan and SN-38 was much higher after intraperitoneal administration than after systemic administration. Additionally, the peritoneal clearance of intraperitoneally administered irinotecan was 10-fold lower than after systemic administration of irinotecan (21, 25-28).

Intraperitoneal chemotherapy, such as irinotecan, can either be applied as monotherapy, or in combination with systemic therapy. In both ovarian and gastric cancer the addition of intraperitoneal chemotherapy to systemic chemotherapy showed promising results (20, 29-32). Moreover, in ovarian cancer, a beneficial effect was proven by a large randomized controlled trial (32). These findings, in combination with the promising results of the INTERACT I study, suggest that intraperitoneal chemotherapy in addition to systemic therapy could be beneficial in patients with unresectable colorectal peritoneal metastases as well (33).

The recent INTERACT study (NL63809.078.18) was a dose-escalation study and was performed to find the maximum tolerated dose (MTD) of intraperitoneal (IP) irinotecan (16). In this study, 18 patients with unresectable colorectal peritoneal metastases were treated with first-line palliative systemic therapy with FOLFOX/bevacizumab and concomitant intraperitoneal irinotecan at flat dose levels of 50 mg (n=4), 75 mg (n=9), and 100 mg (n=4). For the 50 mg and 75 mg dose cohorts, no dose-limiting toxicities were observed. After two dose-limiting toxicities at the 100 mg dose level, the MTD was thus established at 75 mg.

The INTERACT-II study is a multi-center, single-arm, phase II study, aimed to assess overall survival, progression-free survival, safety, patient reported outcomes (PRO's), costs and pharmacokinetics of 75mg IP irinotecan with concomitant first-line systemic therapy (consisting of FOLFOX and bevacizumab) in patients with unresectable CPM.

Methods and analysis

This protocol summary follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (34).

Setting

This study is a single-arm, open-label, phase II study that is performed in two large Dutch tertiary referral centers for the treatment of CPM; The Catharina Cancer Institute in Eindhoven and the Erasmus MC Cancer Institute in Rotterdam. Further tertiary referral centers may join later.

Objectives

The primary objective is to explore overall survival after treatment with intraperitoneal irinotecan (75 mg) to mFOLFOX4 / bevacizumab in patients with unresectable colorectal peritoneal metastases, henceforth referred to as trial treatment.

Secondary objectives are:

- To assess progression-free survival (which is calculated from the interval from the start of trial treatment until first evidence of intraperitoneal and/or systemic disease progression and/or start of second-line systemic therapy, or last follow-up).
- To assess the feasibility of trial treatment; to assess the toxicity profile (defined as the number of grade 3-5 adverse events according to the Common Terminology Criteria for Adverse Events [CTCAE]) of trial treatment.
- To assess patient reported outcomes (PROs) during trial treatment.
- To assess costs of trial treatment
- To assess the nephrotoxicity, hepatotoxicity, and hematological toxicity during trial treatment.
- To assess tumor marker fluctuations during trial treatment.
- To determine the number of patients completing trial treatment, required dose reductions, and reasons for discontinuation.
- To determine the number of patients with an objective radiological response during and after trial treatment.
- To systematically collect, process, and store blood, tumor tissue and ascites for future translational research
- To determine the systemic and intraperitoneal pharmacokinetics of intraperitoneal irinotecan.

Exploratory objectives are to determine if, and how many patients are able to undergo salvage procedures, such as CRS and HIPEC following successful treatment with intraperitoneal irinotecan (75 mg) and concomitant palliative systemic therapy.

Eligibility criteria

Eligibility criteria are:

- Histologically confirmed colorectal carcinoma.
- Microsatellite stable (MSS) primary tumor.
- Radiologically and clinically or pathologically confirmed unresectable colorectal peritoneal metastases (e.g. PCI >20, extensive small bowel involvement, unresectable disease due to anatomical location).
- WHO performance score of 0-1 with a life expectancy of >3 months.
- Aged 18 years or older.
- Adequate organ functions (hemoglobin of ≥5 mmol/L, neutrophil count of ≥1.5 x 10^9/L, platelet count of ≥100 x 10^9/L, serum creatinine of <1.5 x upper limit of normal [ULN], creatinine clearance of ≥30 ml/min, Bilirubin <2x ULN and liver transaminases of <5 x ULN).
- Absence of extensive systemic metastases that are deemed to be the dominant factor determining prognosis in terms of life expectancy and performance status (e.g. no imminent threat of impaired organ functioning due to the presence of systemic metastases).
- No prior cytoreductive surgery.
- No prior palliative systemic therapy for colorectal cancer.
- No (neo)adjuvant/adjuvant systemic therapy for colorectal cancer within 6 months prior to enrollment.
- No homozygous UGT1A1*28 genotype(35).
- No dihydropyrimidine dehydrogenase (DPD) deficiency.
- No contra-indications for the planned chemotherapy (e.g. active infection, serious concomitant disease, severe allergy), as determined by the medical oncologist.

Study treatment

The study flowchart is presented in figure 1. The study schedule of enrollment, treatment and assessment is shown in supplementary table 1.

Diagnostic laparoscopy and port placement

Patients who are candidates for CRS and HIPEC are discussed in a multidisciplinary oncology team meeting, after which they are scheduled for a diagnostic laparoscopy. Patients who are considered to have a high chance of unresectable CPM, based on radiological or clinical investigations, may be enrolled in the study. After enrollment, a diagnostic laparoscopy is performed to inspect the peritoneal cavity. The diagnostic laparoscopy is performed under general anesthesia. If peritoneal disease is

considered unresectable (e.g. due to PCI >20, too extensive small bowel involvement or anatomical location), two ports are placed: one regular intravenous port-a-cath for the intravenous administration of chemotherapy according to local standard of care, and one peritoneal access port for the intraperitoneal administration of chemotherapy. The peritoneal access port is placed on the fascia just above or just below the lower rib cage at the discretion of the surgeon. The catheter is tunneled and inserted into the peritoneal cavity. The tip is positioned in the pelvis. In case of adhesions during the laparoscopy that hampers the positioning of the tip in the pelvis, a different place in the peritoneal cavity may be chosen to place the tip of the catheter. Ascites (or 0.9% NaCl lavage) is collected for translational research. Patients may be discharged the same day after having received instructions for hygiene and wound care.

Chemotherapy

In the absence of post-operative complications, the first cycle will start at least one week after placement of the ports, to allow for sufficient wound healing. Each cycle consists of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg). Intraperitoneal irinotecan (75 mg) will be dissolved in 1 liter NaCl 0.9% and pre-warmed to 37^{o}C. Cycles are repeated every two weeks, with a maximum of 12 cycles. Modified FOLFOX-4 regimen consists of 85 mg/m^2 oxaliplatin plus 200 mg/m^2 LV and 5-FU 400 mg/m^2 bolus on day 1 followed by 1600 mg/m^2 5-FU as a 46-h infusion (27). In case of symptomatic ascites, the ascites will be (partly) drained through the peritoneal access port prior to the start of the therapy cycle.

Response evaluation

Before each cycle, the patient is evaluated (based on clinical and biochemical parameters) by the treating medical oncologist. After every fourth cycle, a thoracoabdominal computed tomography (CT) scan is performed for response evaluation. After each CT scan, the decision to continue trial treatment is based on disease response and clinical performance:

- In case of physician-determined disease progression (either intraperitoneal, systemic, or both), trial treatment is discontinued. The patient will receive second line palliative systemic treatment or best supportive care according to the Dutch national guideline for colorectal cancer (36).
- In case of physician-determined disease response or stable disease (both intraperitoneal and systemic) but severe clinical deterioration or unacceptable toxicity to treatment, rendering the patient unsuited to continue with treatment, trial treatment is discontinued. The patient will

receive further palliative systemic treatment or best supportive care according to the Dutch national guideline for colorectal cancer (36).

- In case of physician-determined disease response or stable disease (both intraperitoneal and systemic) and sufficient clinical condition and acceptable toxicity to treatment, trial treatment is continued.

For all patients, study treatment ends after completing the twelfth cycle of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg), regardless of response on the thoracoabdominal CT performed after the twelfth cycle. On patient's request, the peritoneal access port is removed after the last cycle of trial treatment. After the evaluation after the twelfth cycle, intraperitoneal chemotherapy will be discontinued definitively and further treatment is scheduled with the medical oncologist and will be in according to local standard of care and may include of CRS-HIPEC (36).

Figure 1. Study flowchart. WHO, World Health Organization performance status; CRS, cytoreductive surgery; CRC, HIPEC, hyperthermic intraperitoneal chemotherapy; colorectal cancer; DPD, dihydropyrimidine dehydrogenase.

Supplementary table 1: overview of study procedures

Sample size

Population based studies have described an overall survival of approximately 12.2 months (5) for patients with isolated unresectable colorectal peritoneal metastases treated with palliative systemic chemotherapy. Based on clinical experience, expert consensus and the preliminary results of the INTERACT study, we hypothesize that the study treatment will result in a median overall survival of at least 16.2 months. This entails an expected increase of 4 months in the study population in comparison to the general population of patients with unresectable CPM. To render this assumption plausible, with a power of 80% and a type I error rate of 0.05, a sample size of 85 is needed.

Given the previous experience with the trial treatment from the INTERACT study and the low expected additional toxicity of intraperitoneal irinotecan, the investigators consider it reasonable and safe to expose 85 patients to trial treatment.

Replacement of individual patients

If a patient is withdrawn from the study prior to completing one cycle of intraperitoneal irinotecan with concomitant systemic therapy, an additional patient is enrolled to replace the withdrawn patient.

Statistical analyses

All patients who complete at least one cycle of intraperitoneal irinotecan (75 mg) with concomitant systemic therapy will be included in the analyses. Categorical variables will be presented as n (%) and compared with the Chi-square test. Continuous variables will be presented as mean ± standard deviation or median (interquartile range), depending on distribution. Paired data will be compared with the paired t-test or Wilcoxon signed rank test, depending on distribution. Unpaired data will be compared with the unpaired t-test or Kruskal Wallis test, depending on distribution. A p value <0.05 will be considered statistically significant. Correction for multiple testing will be applied if necessary. Statistical analyses will be performed with SPSS (version 25.0, Armonk, NY, United States).

Analysis of primary study parameter(s)

The overall survival is calculated from (a) the interval from diagnosis of peritoneal metastases until death or last follow-up; (b) the interval from the first day of the first cycle until death or last follow-up). Overall survival will be presented with the Kaplan Meier method, and subgroups (e.g. stratification based on the presence of systemic metastases or peritoneal carcinomatosis index) will be compared with the log rank test.

Analysis of secondary study parameter(s)

- Progression-free survival (calculated from the interval from the start of trial treatment until first evidence of intraperitoneal and/or systemic disease progression or last follow-up) will be presented with the Kaplan Meier method, and subgroups (e.g. stratification based on the presence of systemic metastases or PCI) will be compared with the log rank test.
- Toxicity, defined as the number of patients who experience / the total number of Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade 3-5 adverse events, measured up to four weeks after trial treatment. Given the non-randomized design of the study, these analyses will be exploratory and results will be presented as n (%). Differences in subgroups (e.g. stratification based on the presence of systemic metastases or peritoneal carcinomatosis index) will be compared with the unpaired t-test or Kruskall Wallis test, depending on distribution.
- Patient reported outcomes (PROs) during trial treatment, assessed with the EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-CR29 at baseline, one week after the first cycle, one week after the fourth cycle, one week after the eighth cycle, and one week after the twelfth cycle, will be analyzed according to the corresponding manuals (37-39). Given the novelty of the trial treatment, no a priori hypotheses are defined for PRO analyses. Therefore, PRO assessment will be explorative, providing the mean ± standard deviation of each PRO category at each time-point. Linear Mixed Modelling analyses will be performed to compare differential effects over time and scores at each time-point, with the use of maximum likelihood estimation and an unstructured covariance matrix with a two-level structure (i.e. repeated time-points [lower level], patients [higher level]). To correct for multiple testing, a post-hoc Bonferroni correction will be performed per item, where the p-value will be divided by the number of timepoint-comparisons. In case of statistically significant differences, clinical relevance is determined by a Cohen's D >0.500.
- Healthcare costs and costs due to productivity losses during trial treatment will be assessed with the iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire at baseline, one week after the first cycle, one week after the fourth cycle, one week after the eighth cycle, and one week after the twelfth cycle. An overview of the total costs of trial treatment (1, per protocol health-care costs; 2, additional health-care costs; 3, costs due to productivity losses) is established according to the Dutch Manual for Cost Analysis in Healthcare (40, 41).
- Tumor marker fluctuations during trial treatment will be assessed by carcino-embryonic antigen (CEA) analysis before each subsequent cycle. Given the novelty of the trial treatment, no a priori hypotheses are defined. Linear Mixed Modeling analyses will be performed to compare differential effects over time and scores at each time-point, with the use of maximum

likelihood estimation and an unstructured covariance matrix with a two-level structure (i.e. repeated time-points [lower level], patients [higher level]). To correct for multiple testing, a pragmatically chosen $p<0.01$ is considered statistically significant.

- Feasibility of trial treatment is assessed through completion of twelve cycles of trial treatment, required dose reductions, and reasons for discontinuation. These results are presented as n (%);
- Radiological response (according to radiological PCI and RECIST (39)) during and after trial treatment will be assessed by thoracoabdominal CT at baseline, after the fourth cycle, after the eighth cycle, and after the twelfth cycle. These results are presented as n (%);
- To further investigate the pharmacokinetics of intraperitoneal irinotecan, peritoneal fluid and peripheral blood samples will be withdrawn at several time points during the first and fourth cycle. The maximum plasma concentration (Cmaxp), the time to maximum plasma concentration (Tmaxp), plasma area under the curve (AUCp), maximum intraperitoneal concentration (Cmaxip), the time to maximum intraperitoneal concentration (Tmaxip), intraperitoneal area under the curve (AUCip) of irinotecan (plasma only) and SN-38 (plasma and peritoneal fluid) will be determined.

Recruitment

The study commenced in November 2022 and the first patients were enrolled in December 2022. It is expected to complete accrual within 2 years. To generate more awareness and to increase referrals of potential study candidates, a short Dutch summary of the study will be published in *The Dutch Journal for Oncology* (NTvO in Dutch). Further strategies to optimize accrual have not been defined *a priori*.

Data collection and data management

Outcomes are collected in all patients who completed at least one treatment cycle. All data are prospectively collected by a local investigator in each study center using standardized electronic case report forms linked to an ISO 27001 certified central study database (De Research Manager, Deventer, the Netherlands). This ISO 27001 certified system optimizes data quality by standardized data entry, coding, security and storage.

Data monitoring

Interim analyses are performed by principal investigators and trial coordinators four weeks after the first chemotherapy cycle of the 20th included patient and after the second chemotherapy cycle of the 43th patient, after half of the study procedures and systemic cycles have been performed and applied. These analyses will only focus on the safety aspect. The study may be prematurely terminated by the

sponsor if there is evidence of an unacceptable risk for study patients. The sponsor will notify all concerned investigators, the medical ethics committee and regulatory authorities of the decision to terminate the study.

Serious adverse events (SAEs) and suspected unexpected serious adverse reaction (SUSARs)

The investigator will report all SAEs and SUSARs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs and SUSARs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs or SUSARs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs and SUSARS will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Auditing

Auditing is performed by independent qualified monitors of the study centers. The study is considered a low-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centers.

Patient and public involvement

None

Ethics and dissemination

Research ethics approval

The present study is approved by a central ethics committee (MEC-U, Nieuwegein, Netherlands, number R22.052) and the institutional review boards of both study centers.

Protocol amendments

Important modifications to the study protocol need to be authorized by the central ethics committee. After authorization, these modifications are communicated to the Dutch competent authority, the institutional review boards of both study centers, all investigators, study registries and patients (if required by the central ethics committee).

Informed consent

Patients are enrolled by their treating physician and provide written informed consent. Patients are able to consent to questionnaires and participation in translational side studies separately.

Confidentiality

Personal data of patients is collected and processed in strict adherence to the Dutch law.

Access to data

All authors have access to the final dataset, without any contractual agreements that limit access.

Ancillary or post-study care

The Catharina Hospital is insured to cover harms caused by study participation and extends its insurance to any participating hospital. After trial treatment is stopped, patients will be treated according to Dutch guidelines, as aforementioned in section *"response evaluation"*.

Dissemination policy

Study results will be submitted for publication in peer-reviewed medical journals and presented to patients, healthcare professionals and the public, during (inter)national meetings. Authorship eligibility guidelines are not defined a priori. The full study protocol and the Dutch informed consent form are made available upon written request to the corresponding author. After study completion, the participant-level dataset and statistical code will be made available upon reasonable request.

Discussion

In this single-arm, open-label, phase II, patients with unresectable colorectal peritoneal metastases are treated with concomitant intraperitoneal and systemic cytotoxic therapy. The primary objective of the study is to assess overall survival (OS) after treatment with intraperitoneal irinotecan with concomitant mFOLFOX4 and bevacizumab. Secondary objectives are to assess progression-free survival (PFS), safety, patient reported outcomes (PRO's), costs, feasibility and pharmacokinetic parameters of intraperitoneal irinotecan with concomitant mFOLFOX4 and bevacizumab.

During this study, ascites and peritoneal biopsy samples will be collected and processed for translational research purposes. These samples will be used to establish organoids, in order to study drug response and resistance ex vivo in detail. This might aid in improved patient selection for both palliative and curative treatments, as well as enable a more personalized treatment approach (42).

Multiple studies have studied the effect of another strategy to apply chemotherapy intraperitoneally: pressurized intraperitoneal aerosol chemotherapy (PIPAC) (15, 43, 44). In contrast to PIPAC, the

intraperitoneal chemotherapy administered in this study is applied simultaneously with systemic chemotherapy without the need for complex (and expensive) devices or surgery. Furthermore, in comparison to PIPAC, INTERACT treatment has the potential benefit of exposing tumor cells to the cytotoxic agent much more frequent and for a much longer timespan (33)

To the best of our knowledge, after the INTERACT study, this is only the second study in patients with peritoneal metastases of colorectal origin that combines standard of care systemic chemotherapy with intraperitoneally administered chemotherapy. As such, the present study will provide essential information about overall survival and progression-free survival, as well as on safety, feasibility, costs and PROs of treatment with intraperitoneal irinotecan, and will provide a framework for the conduction of further clinical research. The INTERACT-II study may be an important step towards a more effective, life-prolonging treatment modality for this specific patient group, with the possibility for curative treatment consisting of CRS-HIPEC in specific patients with excellent response to the treatment.

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Collaborators

Dutch Peritoneal Oncology Group (DPOG); Dutch Colorectal Cancer Group (DCCG).

Author Contributions

TBMvdH and NADG are the coordinating investigators. VCJvdV, RJL, TBMvdH, RJFB, IvH, GJMC, SWN, IHJTdH and JWAB are the local investigators of the first study center. NADG, SLWK, EvM, ARMBK, EVEM, CV and RHJM are the local investigators of the second study center. SK is the study pharmacologist supervising the pharmacokinetic analyses. JN is the study radiologist performing the central radiological review. SLWK is responsible for translational research on blood. OK is responsible for translational research on ascites and peritoneal lavage. JWAB is the principal investigator. VCJvdV, NADG, RJL, RHJM, and JWAB made substantial contributions to the conception and design of the study, drafted the protocol and drafted the manuscript. IEGvH, GJMC, IHJTdH, SWN, OK, SK, CV, TBMvdH and EvM made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interest

None to declare

Patient consent for publication

Not required

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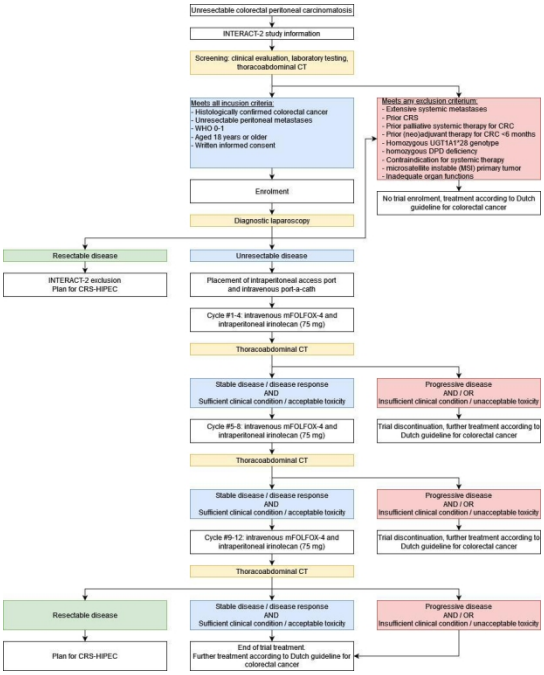

Figure 1. Study flowchart. WHO, World Health Organization performance status; CRS, cytoreductive surgery; CRC, HIPEC, hyperthermic intraperitoneal chemotherapy; colorectal cancer; DPD, dihydropyrimidine dehydrogenase.

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Table 1: overview of study procedures

	Screening	Enrolment	Medical oncologist: intake	Diagnostic laparoscopy	Cycle #1	Cycles #2-4	One week after cycle #4	Cycles #5-8	One week after cycle #8	Cycles #9-12	One week after cycle #12	Last study visit
Multidisciplinary tumor board	X						X		X		X	
Medical history	X	X	X									
Inclusion and exclusion criteria	X	X	X									
Provide study information	X	X	X									
Written informed consent		X										
Physical examination		X	X		X	X		X		X		
Pre-operative screening		X										
Blood test: DPD and UGT1A1 genotype		X										
Blood test: organ functions		X			X	X		X		X		
Blood test: tumor marker[a]		X			X	X		X		X		
Blood test: pregnancy[b]		X										
Electrocardiogram		X										
Placement of port-a-cath				X								
Placement of peritoneal access port				X								
Thoracoabdominal CT scan[c]		X					X		X		X	
Systemic chemotherapy					X	X		X		X		
Intraperitoneal chemotherapy					X	X		X		X		
Clinical evaluation		X	X		X	X		X		X		X
Toxicity evaluation (CTCAE)					X	X		X		X		X
Patient Reported Outcomes Questionnaires		X			X		X		X		X	
Costs Questionnaires		X			X		X		X		X	
Pharmacokinetics					X							
Progression Free Survival							X		X		X	X
Overall Survival					X	X		X		X		X
Remove peritoneal access port[d]												X
Translational Research: blood		X					X		X		X	
Translational Research: ascites				X	X	X						

[a]Carcino-embryonic antigen; [b]Only determined in women of fertile age (<55 years); [c]Unless already performed <6 weeks before diagnostic laparoscopy; [d]On patient's request;
CT, Computed Tomography; CTCAE, Common Terminology Criteria for Adverse Events; Marked in grey: study-specific procedures;

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Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	14, 15

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8,9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8,9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	N/A

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12,13,14

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13,14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13,14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13,14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	14,15

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14,15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14,15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	16
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16,17

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17