

# BMJ Open Concomitant intraperitoneal and systemic chemotherapy for extensive peritoneal metastases of colorectal origin: protocol of the multicentre, open-label, phase I, dose-escalation INTERACT trial

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## ABSTRACT

**Introduction** Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has become standard of care for patients with peritoneal metastases of colorectal origin with a low/moderate abdominal disease load. In case of a peritoneal cancer index (PCI) score >20, CRS-HIPEC is not considered to be beneficial. Patients with a PCI >20 are currently offered palliative systemic chemotherapy. Previous studies have shown that systemic chemotherapy is less effective against peritoneal metastases than it is against haematogenous spread of colorectal cancer. It is suggested that patients with peritoneal metastases may benefit from the addition of intraperitoneal chemotherapy to systemic chemotherapy. Aim of this study is to establish the maximum tolerated dose of intraperitoneal irinotecan, added to standard of care systemic therapy for colorectal cancer. Secondary endpoints are to determine the safety and feasibility of this treatment and to establish the pharmacokinetic profile of intraperitoneally administered irinotecan.

**Methods and analysis** This phase I, '3+3' dose-escalation, study is performed in two Dutch tertiary referral centres. The study population consists of adult patients with extensive peritoneal metastases of colorectal origin who have a good performance status and no extra-abdominal metastases. According to standard work-up for CRS-HIPEC, patients will undergo a diagnostic laparoscopy to score the PCI. In case of a PCI >20, a peritoneal access port will be placed in the abdomen of the patient. Through this port we will administer intraperitoneal irinotecan, in combination with standard systemic treatment consisting of 5-fluorouracil/leucovorin with oxaliplatin and the targeted agent bevacizumab. Therapy consists of a maximum of 12 cycles 2-weekly.

## Strengths and limitations of this study

- The INTERACT study may be the first step towards a more effective, life prolonging and possible even curative treatment for patients with extensive peritoneal metastases of colorectal cancer who are not eligible for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.
- In patients with peritoneal metastases of gastric and ovarian cancer, the addition of concomitant intraperitoneal chemotherapy to systemic chemotherapy showed promising results.
- This study will provide essential information, the maximum tolerated dose (MTD), safety and feasibility of treatment with intraperitoneal irinotecan, for the conduction of further clinical research.
- Establishing the pharmacokinetic profile of intraperitoneally administered irinotecan is an essential part of this study, because this will provide crucial information for further research on the behaviour and use of intraperitoneally administered irinotecan.
- In this phase I dose-escalation trial the added value of intraperitoneal chemotherapy to systemic chemotherapy on overall survival cannot be determined, when the MTD is determined, larger phase II and III clinical trials will be conducted to determine the effect on survival.

**Ethics and dissemination** This study protocol is approved by a research medical ethics committee (Rotterdam, Netherlands) and the Dutch Competent Authority (CCMO, The Hague, Netherlands). The results of this trial will be submitted for publication in a peer-reviewed scientific journal.

## INTRODUCTION

Colorectal cancer is the third most common cancer in the Netherlands. About 15% of patients will develop peritoneal metastases at some stage of disease. Approximately 5% already has peritoneal metastases at time of diagnosis of the primary tumour (synchronous metastases), while the other 10% develop peritoneal metastases during follow-up after treatment of the primary tumour (metachronous metastases).

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is the only curative treatment option for patients with peritoneal metastases of colorectal origin and has become standard of care for patients with a low to moderate abdominal disease load.<sup>1-4</sup> The extent of disease is evaluated using the peritoneal cancer index (PCI) which ranges from 0 (no disease) to 39 (extensive disease in all 13 regions of the abdomen); a PCI above 20 is considered to be too high for CRS-HIPEC to be beneficial.<sup>4-6</sup>

Unfortunately, most patients with peritoneal metastasis are not eligible for CRS-HIPEC.<sup>7 8</sup> In the Netherlands, approximately 23% of all patients diagnosed with peritoneal metastasis from colorectal cancer undergo CRS-HIPEC, 56% is treated with systemic therapy.<sup>8</sup> Current radiological imaging techniques are valuable in the detection of distant metastasis but underestimate the extent of peritoneal disease.<sup>9-11</sup> To prevent unnecessary open-close procedures/laparotomies in patients with a PCI >20, a diagnostic laparoscopy (DLS) is recommended during preoperative work-up for CRS-HIPEC.<sup>12 13</sup> DLS can prevent up to 40% of open-close procedures.<sup>13</sup> Patients with a PCI >20 or irresectable disease during DLS or open-close procedures are currently offered treatment with palliative systemic chemotherapy or best supportive care.

Previous studies have shown that patients with peritoneal metastases of colorectal origin have worse survival rates than patients with colorectal cancer with non-peritoneal metastases.<sup>14-17</sup> This suggests that systemic therapy is less effective against peritoneal metastases than it is against the haematogenous metastases. Peritoneal metastases might also be a sign of poor biological behaviour of the primary tumour. Moreover, patients are often in a poor condition and not-eligible for treatment with chemotherapy. As a result of all the above, the prognosis of patients with extensive peritoneal metastases is poor. Median survival of patients not treated with systemic chemotherapy is 3–5 months.<sup>18 19</sup> In patients treated with systemic chemotherapy the median survival is 9–15 months.<sup>14 18</sup> Since the survival of patients with extensive intraperitoneal disease who are not eligible for CRS-HIPEC is poor, even with maximal treatment with systemic chemotherapy, the question raised how the treatment of these patients can be improved.

It has been suggested that intraperitoneal chemotherapy may be more effective for the treatment of peritoneal metastases than systemic chemotherapy.<sup>20-22</sup> In patients with peritoneal metastases of gastric and ovarian cancer, the addition of concomitant intraperitoneal chemotherapy to systemic chemotherapy showed promising results.<sup>21-28</sup> It is our hypothesis that adding intraperitoneal chemotherapy will also improve outcomes for patients with peritoneal metastases of colorectal origin. However, before initiating phase II and III studies that assess the potential added value of intraperitoneal chemotherapy to systemic chemotherapy, the phase I dose-finding study such as described in this protocol needs to be conducted. Aim of this classic phase I '3+3' dose escalation study is to establish the maximum tolerated dose (MTD) for the intraperitoneal chemotherapy in combination with standard of care systemic chemotherapy. Currently, the standard first line systemic therapy for the treatment of metastatic colorectal cancer in the Netherlands is a combination of a fluoropyrimidine (5-fluorouracil/leucovorin ((5-FU/LV) or capecitabine) with oxaliplatin (FOLFOX/CAPOX) and the target agent bevacizumab.<sup>29</sup>

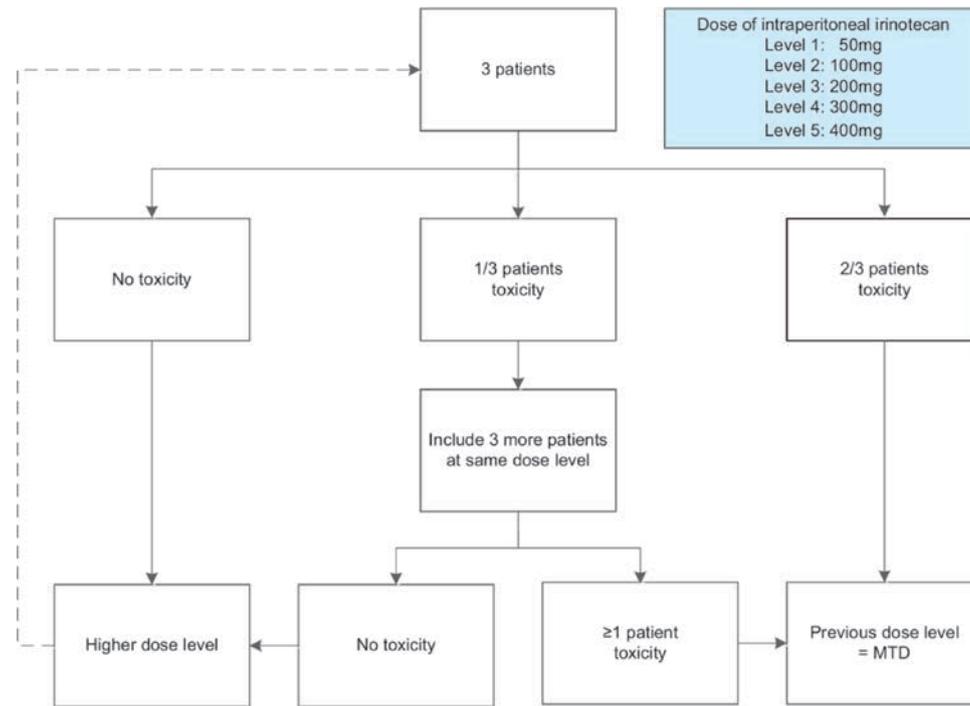
In this study it was chosen to administrate irinotecan intraperitoneally. Irinotecan is an effective anti-cancer drug for multiple malignancies, including colorectal cancer.<sup>30</sup> An additional argument for irinotecan as intraperitoneal agent is that it will not affect the plasma area under the curve of the agents 5-FU and oxaliplatin that are administered intravenously. Irinotecan's main cytotoxicity is attributed to its metabolite SN-38, which is 100–1000-fold more cytotoxic than irinotecan.<sup>31 32</sup> Conversion to SN-38 takes place in the liver by carboxylesterases, but previous studies showed this conversion also takes place in the intraperitoneal space.<sup>31-34</sup> Administration of intraperitoneal irinotecan was proven to be safe in patients with peritoneal metastases of gastric origin.<sup>23 35 36</sup> Simultaneous systemic administration of FOLFOX and irinotecan (FOLFIRINOX/FOLFOXIRI) also has been studied extensively and is considered safe and effective and is currently standard of care in patients with pancreatic cancer.<sup>29 37 38</sup> We therefore expect that that the combination of systemic FOLFOX and intraperitoneal irinotecan is feasible.

## METHODS AND ANALYSIS

This protocol summary follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement.<sup>39</sup>

### Study design

The INTERACT trial is a multicentre, single-arm, open-label, phase I dose finding study that follows the classic '3+3' dose-escalation design.<sup>40 41</sup> Explanation of the '3+3' design plus the defined dose levels ranging from 50 mg to 400 mg irinotecan are shown in [figure 1](#). All patients



**Figure 1** 3+3 dose escalation study design of the INTERACT trial. MTD, maximum tolerated dose.

included in this trial will receive concomitant intraperitoneal and systemic chemotherapy.

### Study setting

This study is conducted in two tertiary referral hospitals for the treatment of peritoneal metastases in the Netherlands; the Erasmus MC Cancer Institute in Rotterdam and the Catharina Cancer Institute in Eindhoven.

### Primary objective

The primary objective of this study is to establish the MTD and recommended phase II dose (RP2D) of intraperitoneal irinotecan added to systemic FOLFOX and bevacizumab.

### Maximum tolerated dose/recommended phase II dose

The MTD is defined as the highest dose that is given, leading to  $\leq 33\%$  dose limiting toxicity (DLT). The MTD will be considered the RP2D (figure 1). If 2/3 patients experience DLT at dose level 1, a 50% dose-de-escalation to 25 mg irinotecan i.p. may be performed. If the MTD is not reached, the RP2D will be the dose given at dose level 5.

### Dose limiting toxicity

Toxicity will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) V.4.03. A DLT is considered possibly, probably or definitely related to the addition of intraperitoneally administered irinotecan to FOLFOX. DLT is defined in the following subsections.

#### Haematology

- ▶ Absolute neutrophilic count (ANC)  $< 0.5 \times 10^9/L$  (grade 4) lasting longer than 7 days.

- ▶ Febrile neutropenia (ANC  $< 1.0 \times 10^9/L$ , fever  $> 38.5^\circ C$ ) (grade three or four).
- ▶ Platelets  $< 25 \times 10^9/L$  (grade 4).

#### Non-haematology

Grade 3 or 4 non-haematological adverse events (AEs) except nausea/vomiting, diarrhoea or fatigue for which the following DLT definitions will apply:

- ▶ Nausea  $\geq$  grade 3 despite optimal anti-emetic use.
- ▶ Diarrhoea  $\geq$  grade 3 despite optimal loperamide use.
- ▶ Grade 3 fatigue lasting longer than 7 days.

#### Other

Delay of the next cycle by more than 2 weeks.

### Secondary objectives

Secondary objectives are to explore the safety and feasibility of this treatment and to establish the pharmacokinetic profile of intraperitoneally administered irinotecan. During the study we will also systematically collect, process and store ascites for translational research purposes, including the genetic analysis of circulating tumour cells (CTCs) and the derivation of organoid cultures as an ex vivo platform for studying drug response and resistance in individual patients.

### Study population

The study population consists of adult patients diagnosed with inoperable peritoneal metastases of colorectal origin. Potentially eligible patients will be referred by their local clinician or through self-referral to a medical specialist. All potentially eligible patients will be checked at the outpatient clinic by a member of the study team,

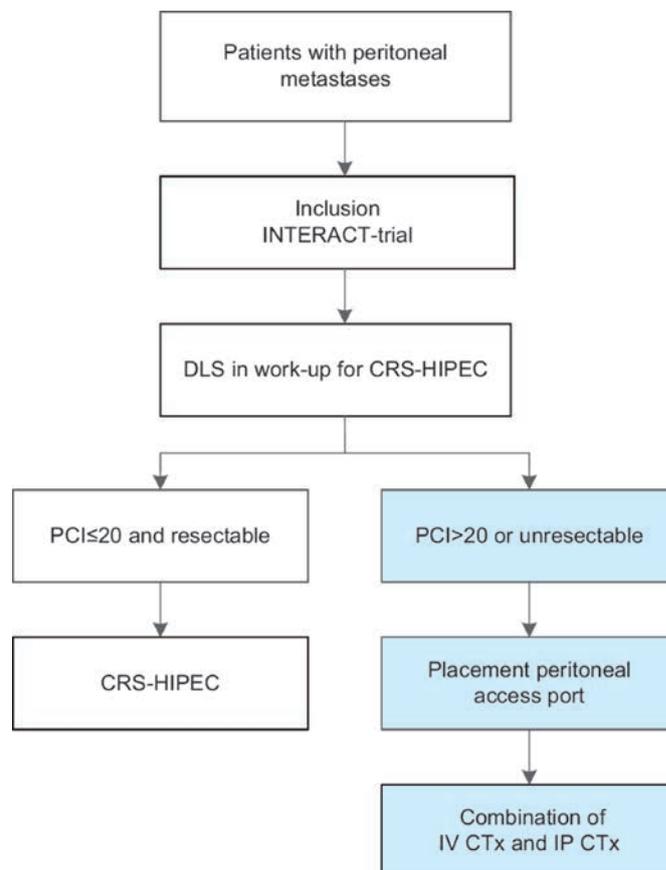
who will thoroughly inform the patient about trial and determine the eligibility of the potential participant.

In order to be eligible to participate in this study, patients must meet the following inclusion criteria:

- ▶ Patients with a histologically confirmed diagnosis of colorectal cancer.
- ▶ Radiologically or clinically confirmed diagnosis of peritoneal metastases.
- ▶ Unknown PCI for which a DLS is planned in the work-up for CRS-HIPEC or a known PCI >20 evaluated by laparoscopy or laparotomy before inclusion in this trial.
- ▶ WHO-Eastern Cooperative Oncology Group performance status of 0 or 1.
- ▶ Life expectancy of at least 3 months.
- ▶ Normal organ function and adequate bone marrow reserve, as assessed by the following laboratory requirements:
  - Absolute neutrophil count  $>1.5 \times 10^9/L$ .
  - Platelet count  $>100 \times 10^9/L$ .
  - Hb  $>6.0 \text{ mmol/L}$ .
  - Bilirubin  $<1.5 \times$  upper limit of normal (ULN).
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT)  $<2.5 \times$  ULN.
  - GFR  $>45 \text{ mL/min}$  and Creatinine clearance  $<2 \times$  ULN.
- ▶ Age  $\geq 18$  years old.
- ▶ Written informed consent according to the International Council for Harmonisation-good clinical practice and national/local regulations.
- ▶ Ability to return to the Erasmus MC Cancer Institute/Catharina Cancer Institute for adequate follow-up.

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

- ▶ Extra-abdominal disease, established by CT scan of thorax-abdomen and/or positron emission tomography scan. Imaging not older than 1 month at time of surgery.
- ▶ Prior cytoreductive surgery.
- ▶ Prior treatment with chemotherapy for (metastatic) colorectal cancer within the last 6 months.
- ▶ Serious concomitant disease or active/chronic infections, including HIV and viral hepatitis.
- ▶ Homozygous *UGT1A1*\*28 genotype or homozygous or (compound) heterozygous *DPYD* genotype (tested for \*2A, \*13, 2846A>T and 1236G>A).
- ▶ Current use of strong CYP3A4-inhibitors or inducers. If patients use this CYP3A4-modulating medication, it is allowed to stop it within 14 days of start of treatment.
- ▶ Concomitant participation in another competing clinical study or absence of assurance of compliance with the protocol.
- ▶ An organic brain syndrome or other significant psychiatric abnormality which would comprise the ability to give informed consent, and preclude participation in the full protocol and follow-up.
- ▶ Pregnant or lactating women.



**Figure 2** Flowchart INTERACT-trial. CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; CTx, chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal; IV, intravenous; PCI, peritoneal cancer index.

### Patient timelines and additional procedures

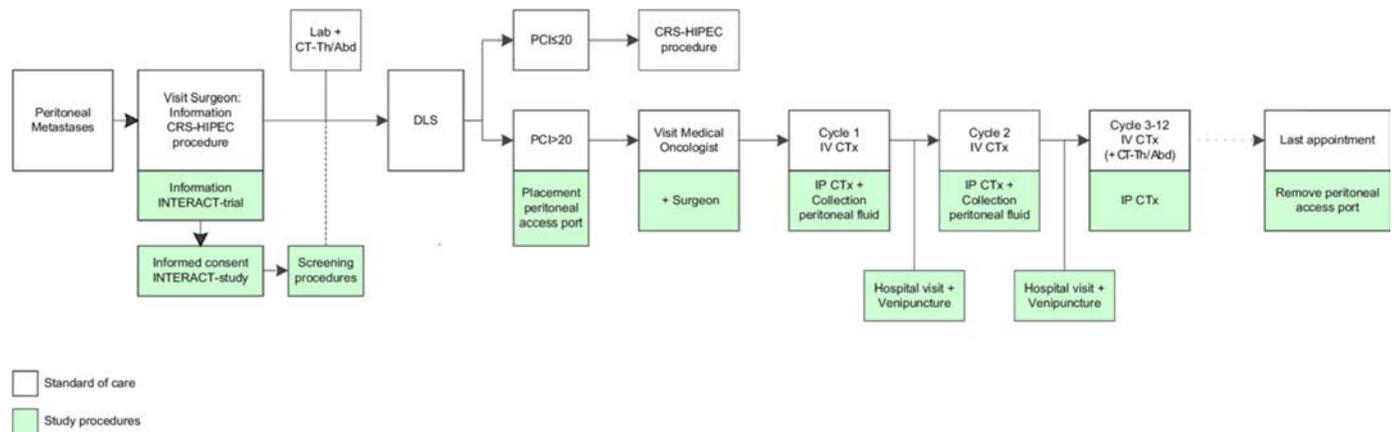
Figure 2 describes a flowchart of the study. A more detailed description of (additional) study procedures are shown in figure 3 and table 1.

### Screening

After informed consent is acquired by a member of the study team, a screening will be performed. Screening procedures include laboratory testing (including genotype testing), an ECG, and a (new) CT-scan of the thorax and abdomen (only when the previous imaging is older than 1 month at time of surgery). When patients comply to all previously described eligibility criteria, they will be scheduled for a DLS. All patients require formal anaesthetic assessment prior to surgery.

### Surgical procedures

All patients will be operated under general anaesthesia, according to local hospital procedures. During the DLS the extent of peritoneal disease is scored using the PCI-score. In case of a PCI >20, a peritoneal access port will be placed on the fascia of the right lower rib-cage. The catheter is inserted in the abdomen and the tip will be positioned in the pouch of Douglas. Laparoscopic placement is considered the golden standard.<sup>42</sup> After surgery,



**Figure 3** Study procedures. CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; CT-Th/Abd, CT tomography thorax and abdomen; CTx, Chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal; IV, intravenous; PCI, peritoneal cancer index.

patients may leave the hospital on the same day, with careful instructions. Postoperative patients are seen in the outpatient department by both the surgeon and the medical oncologist. The start date of the first treatment cycle of chemotherapy will be determined according to patients' individual recovery after the DLS.

### Chemotherapy

Patients will receive intraperitoneal irinotecan (according to dose-level, see figure 1) dissolved in one litre sodium chloride solution 0.9% 37°C through the peritoneal access port. The intraperitoneal chemotherapy will be administered by a member of the study team at the start of the first day of the cycle of systemic chemotherapy, this will take 1.5 hour. The treatment with intraperitoneal chemotherapy will take place in the medical oncology department, since simultaneous administration of systemic chemotherapy (FOLFOX and bevacizumab) will be performed according to the local standard protocol including premedication and anti-emetics. If any surgical problems occur during the treatment, a surgical oncologist is always available for consultation or clinical assessment of the patient.

The combination therapy of intraperitoneal and systemic chemotherapy will be continued until disease progression, unacceptable toxicity, irreversible complications related to the peritoneal access port, or patients wish to discontinue the treatment for a maximum of 12 cycles.

### Follow-up

Patients are assessed weekly during the first two cycles. Further follow-up and response evaluation of the combination therapy is according to the local standard protocol for patients receiving systemic FOLFOX and bevacizumab. To evaluate the response of the combination therapy a CT-scan will be obtained after every fourth cycle of chemotherapy. If the CT-scan shows stable disease or a partial response, treatment with chemotherapy will be continued.

### Problems related to the peritoneal access port

In case complications related to the peritoneal port occur the treating physician should be informed, discuss the problem with the study team, and handle in the patient's best medical interest. Previous studies that administered intraperitoneal chemotherapy reported problems like catheter obstruction, port dysfunction, infection, and abdominal pain during administration of chemotherapy.<sup>43–45</sup> In certain cases the peritoneal port might have to be replaced to continue treatment, in others cases patients might have to discontinue study participation. Pain medication (oral or intravenous) could be administered to relieve discomfort during administration of chemotherapy.

### Removal of the peritoneal access port

After completion of the cycles of chemotherapy, or after discontinuation of the trial, the peritoneal access port will be removed by the surgeon. Removal of the access port will be performed under local anaesthesia, or if there is any reason why this is not deemed feasible, the peritoneal access port can also be removed under general anaesthesia with a laparoscopy.

### Withdrawal of individual subjects

Subjects can discontinue participation in 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. In case a patient or the study coordinator decides to withdraw from further participation, all efforts will be made to complete and report the observations as thoroughly as possible.

The investigators also have the right to withdraw patients from the study if one of more of the following events occur:

- ▶ Significant protocol violation or non-compliance on the part of the patient or investigator.
- ▶ Refusal of the patient to continue treatment or observations.



**Table 1** Study procedures

	Before			Combination chemotherapy										Last study visit			
	First visit	Second visit	First post-op visit	First cycle	Second cycle	+1 wk	Third cycle	Fourth cycle	Fifth cycle	Sixth cycle	Seventh cycle	Eighth cycle	Ninth cycle		Tenth cycle	11th cycle	12th cycle
MTB*	X																
Medical history	X																
Inclusion/exclusion criteria	X																
Provide information about the study	X	X															
Written informed consent		X															
Physical examination (incl. vital signs and weight <sup>2</sup> )		X	X														
Operability check (anaesthetist)		X															
Genotype blood tests		X															
Haematology and blood chemistry		X															
Pregnancy test†		X															
ECG		X															
Placement of peritoneal access port in case PCI-score >20				X													
Determine start date chemotherapy																	
CT-scan chest/abdomen	‡																
Systemic chemotherapy																	
Intraperitoneal chemotherapy																	

Continued

**Table 1** Continued

	Before first visit		First post-op visit		Combination chemotherapy												Last study visit
	First visit	Second visit	DLS	First cycle +1wk	Second cycle +1wk	Third cycle	Fourth cycle	Fifth cycle	Sixth cycle	Seventh cycle	Eighth cycle	Ninth cycle	Tenth cycle	11th cycle	12th cycle		
Performance status				X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemotherapy toxicity evaluation (CTCAE 4.03)				X	X												
Collection of blood and peritoneal fluid for pharmacokinetic analysis			X		X												
Collection of peritoneal fluid for research purposes			X		X												
Remove peritoneal access port																X	

\*Scans and reports of (referred) patients are first discussed in a multidisciplinary tumour board (MTB). When patients are considered candidates for CRS-HIPEC, they are seen in the outpatient clinic. †If applicable.

‡If not performed by reversing centre.

§Blue background: additional study procedures (not standard of care).

||CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

- ▶ Any change in the condition of the patient that justifies discontinuation of treatment.
- ▶ Progressive disease during response evaluation (CT-scan).
- ▶ Decision by the study coordinator that termination is in the patient's best medical interest.
- ▶ Unrelated medical illness or complication.

### Sample size calculation and statistical analysis

Because of the nature of this study (dose-escalation study), the number of patients to be included is variable pending on data obtained during different dose levels (see figure 1 for dose-escalation design and for dose-levels). A minimum of three patients will be entered on each dose-level and a maximum of six. The total number of predefined dose levels is five. No intra-patient dose-escalation will be applied. When the MTD is established, a total of nine patients will be treated with this dose. This comes to a sample size calculation of a minimum of four patients (in case 2/3 patients experience DLT at dose level 1, a dose a dose-de-escalation will be performed with again a minimum of two patients) and a maximum of 33 patients.

The statistical analyses and data summaries will be performed using SPSS version 25.0.0.1. Other tools may be used for exploratory summaries and graphical presentations.

### Data collection and data management

Data collection, data assessment and data analysis will be performed according to the local guidelines for data management of the Erasmus MC Cancer Institute and Catharina Cancer Institute. All patient data will be collected in a central database according to the European law; General Data Protection Regulation (in Dutch; Algemene verordening gegevensbescherming) to protect confidentiality. Data collection and management will also be monitored on correctness by an independent trained monitor.

### Harms and auditing

All AEs, serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) will be recorded. All (S)AEs and SUSARs as a consequence of the administration of intraperitoneal irinotecan will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for (S)AEs and 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 (S)AEs and SUSARs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the SAEs. In addition to the reporting of AEs, SAEs and SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC. The sponsor (Erasmus MC Cancer Institute, the Netherlands) is insured to provide cover for any patients who suffer harm from study participation.

Since this is a phase I '3+3' dose-escalation study, all (S)AEs and SUSARs will be evaluated by the study team before the decision will be made to continue with the next dose-level. Therefore, no data safety monitoring board will be installed. The study is audited by an independent, qualified monitor according to the local guidelines of the participating hospitals.

### Patient and public involvement

The Dutch patient association for patients with cancer in the digestive tract (Stichting voor Patiënten met Kanker aan het Spijverteringskanaal, 'SPKS' In Dutch) and the Erasmus MC Cancer Institute work together closely. The patient association has received a copy of the study protocol and also received the patient information folder. Feedback on these documents was provided and the study was discussed during a brainstorm meeting at 'SKPS' headquarters in Amersfoort, the Netherlands. The results of the study will be communicated to the patient association which can then distribute them among their members.

## ETHICS AND DISSEMINATION

### Ethics approval and consent to participate

This study is approved by a research medical ethics committee (METC, Rotterdam, Netherlands, MEC-2018-059) and the Dutch Competent Authority (CCMO, The Hague, Netherlands, EudraCT/NL2018-000479-33).

Written informed consent will be obtained from all patients participating in this study. The study will be conducted in compliance with the 'Medical Research Involving Human Subjects Act' (WMO) and according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013).

### Protocol amendments

Important protocol modifications are communicated to all investigators, the research METC, the Dutch competent authority (CCMO), and trial registries. The new protocol has to be approved by the METC and the CCMO, before it can be implemented.

### Dissemination

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). Also, the study has been presented at the Dutch Society of Surgery meeting 2019 and at the 38th Congress of the European Society of Surgical Oncology in Budapest, Hungary. The results of this clinical trial will be submitted for publication in a peer-reviewed scientific journal.

## DISCUSSION

In this phase I, dose-escalation study patients are treated with concomitant intraperitoneal and systemic cytotoxic

therapy. The main goal of this study is to establish the MTD and RP2D of intraperitoneal irinotecan added to systemic FOLFOX and bevacizumab. Secondary goals are to explore the safety and feasibility of this treatment and to establish the pharmacokinetic profile of intraperitoneally administered irinotecan.

Previous research showed that the conversion of irinotecan to its active metabolite SN-38 takes place in the liver, but also occurs in the intraperitoneal cavity. However, little details are known about the process of the intraperitoneal conversion, and the amount, of irinotecan to SN-38. Therefore, establishing the pharmacokinetic profile of intraperitoneally administered irinotecan is an essential part of this study, because this will provide crucial information for further research on the behaviour and use of intraperitoneally administered irinotecan.

During this study we will also collect, process, and store ascites for translational research purposes. By systematically collecting ascites and isolating CTCs prior to each treatment cycle the opportunity is given to us to follow tumour heterogeneity and chemotherapy resistance. Furthermore, we will establish organoid cultures from ascites-derived CTCs as an ex vivo platform for studying drug response in individual patients. Gaining a deeper understanding into chemo-resistance will possibly allow us to determine which patients will respond best to which chemotherapeutic agent, and to which treatment they are resistant. This could be valuable information for both the palliative treatment with chemotherapy, as well as for the curative approach, for example, patients who are still eligible for CRS-HIPEC.

To the best of our knowledge, this is the first study in patients with peritoneal metastases of colorectal origin that combines standard of care systemic chemotherapy with intraperitoneal chemotherapy. This study will give us essential information, the MTD/RP2D, safety and feasibility of treatment with intraperitoneal irinotecan, for the conduction of further clinical research. A phase II clinical trial is already being designed to follow this phase I trial, which will shed more light on actual effects of the addition of intraperitoneal irinotecan to systemic FOLFOX and bevacizumab on the oncological outcomes and survival rates of these patients. The INTERACT study may be the first step towards a more effective, life prolonging and possible even curative treatment for this specific patient group.

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

**Contributors** NLdB is the coordinating investigator and drafted this manuscript. NLdB, ARMB-K, JWAB, CV, EvM, and RHJM drafted the original study protocol. JWAB, ARMB-K, and CV initiated the trial. JWAB acquired funding for implementation of the trial protocol. EVEM, MD, RAGvE, FMdM, RB, SLWK, IdH, CB, KR, G-JC, MJD, OK and AC are all active members of the study team and contributed to the implementation of the study protocol. All authors, NLdB, ARMB-K, EVEM, MD, EvM, RAGvE, FMdM, RB, SLWK, IdH, CB, KR, G-JC, MJD, OK, AC, RHJM, JWAB and CV revised the manuscript for content and approved the final version of the manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study is approved by a research medical ethics committee (METC, Rotterdam, Netherlands, MEC-2018-059) and the Dutch Competent Authority (CCMO, The Hague, Netherlands, EudraCT / NL2018-000479-33).

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