CAIRO 6

A joint initiative of the Dutch Colorectal Cancer Group (DCCG)

and the Dutch Peritoneal Oncology Group (DPOG)

English scientific title

Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone: a multicentre, open-label, parallel-group, phase II-III, randomised superiority study (CAIRO6).

English lay title

Chemo-immunotherapy before and after surgery for peritoneal metastases of large bowel cancer

Dutch scientific title

Perioperatieve systemische therapie en cytoreductieve chirurgie met HIPEC versus alleen *upfront* cytoreductieve chirurgie met HIPEC: een multicenter, open-label, parallel-groep, fase II-III, gerandomiseerde superioriteitsstudie (CAIRO6).

Dutch lay title

Chemo-immunotherapie rondom de HIPEC-operatie voor buikvliesuitzaaiingen uit dikkedarmkanker.

PROTOCOL TITLE 'Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: a multicentre, open-label, parallel-group, phase II-III, randomised, superiority study (CAIRO6)'

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ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
BSA	Body surface area
CA	Competent Authority
CAPIRI	Capecitabine, irinotecan
CAPOX	Capecitabine, oxaliplatin
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRS	Cytoreductive surgery
CV	Curriculum Vitae
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DMC	Data Monitoring Committee
DW-MRI	Diffusion-weighted magnetic resonance imaging
EGFR	Epidermal growth factor receptor
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FOLFIRI	5-fluorouracil, leucovorin, irinotecan
FOLFOX	5-fluourouracil, leucovorin, oxaliplatin
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HIPEC	Hyperthermic intraperitoneal chemotherapy
IB	Investigator's Brochure
IC	Informed Consent
ICER	Incremental cost-effectiveness ratio
IKNL	Integraal Kankercentrum Nederlands (Netherlands Comprehensive Cancer Organiation)
IV	Intravenously
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MCQ	Medical consumption questionnaire
PCI	Peritoneal cancer index
PCQ	Productivity cost questionnaire
PM	Peritoneal metastases
QALY	Quality-adjusted life year
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst

Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
ULN	Upper limit of normal
WHO	World health organisation
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

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SUMMARY

Rationale: cytoreductive surgery with HIPEC (CRS-HIPEC) is a curative intent treatment for patients with isolated resectable colorectal peritoneal metastases (PM). Upfront CRS-HIPEC alone is the standard treatment in the Netherlands. The addition of neoadjuvant and adjuvant systemic therapy (together: perioperative systemic therapy) to CRS-HIPEC could have benefits and drawbacks. Potential benefits are eradication of systemic micrometastases, preoperative intraperitoneal tumour downstaging, elimination of post-surgical residual cancer cells, and improved patient selection for CRS-HIPEC. Potential drawbacks are preoperative disease progression and secondary unresectability for CRS-HIPEC, systemic therapy related toxicity, increased postoperative morbidity, decreased quality of life, and higher costs. Currently, there is a complete lack of randomised studies that prospectively compare the oncological efficacy of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone. Notwithstanding this lack of evidence, perioperative systemic therapy is widely administered to patients with isolated resectable colorectal PM. However, administration and timing of perioperative systemic therapy vary substantially between countries, hospitals, and guidelines. More importantly, it remains unknown whether perioperative systemic therapy has an intention-to-treat benefit in this setting. Therefore, this study randomises patients with isolated resectable colorectal PM to receive either perioperative systemic therapy (experimental arm) or upfront CRS-HIPEC alone (control arm).

Study design: a multicentre, open-label, parallel-group, phase II-III, superiority study that randomises eligible patients in a 1:1 ratio.

Objectives: objectives of the phase II study (80 patients) are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological and histological response of colorectal PM to neoadjuvant systemic therapy. The primary objective of the phase III study (an additional 278 patients) is to compare survival outcomes between both arms.

Secondary objectives are to compare surgical characteristics, major postoperative morbidity, health-related quality of life, and costs between both arms. Other objectives are to assess major systemic therapy related toxicity and the objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy.

Study population: adults who have a good performance status, histological or cytological proof of PM of a colorectal adenocarcinoma, resectable disease, no systemic colorectal metastases within three months prior to enrolment, no systemic therapy for colorectal cancer within six months prior to enrolment, no previous CRS-HIPEC, no contraindications for the planned systemic treatment or CRS-HIPEC, and no relevant concurrent malignancies.

Intervention: at the discretion of the treating medical oncologist, perioperative systemic therapy consists of either four 3-weekly neoadjuvant and adjuvant cycles of capecitabine with oxaliplatin (CAPOX), six 2-weekly neoadjuvant and adjuvant cycles of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX), or six 2-weekly neoadjuvant cycles of 5-fluorouracil/leucovorin with irinotecan (FOLFIRI) followed by either four 3-weekly (capecitabine) or six 2-weekly (5-fluorouracil/leucovorin) adjuvant cycles of fluoropyrimidine monotherapy. Bevacizumab is added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles.

Endpoints: Endpoints of the phase II study are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological/histological response of colorectal PM to neoadjuvant systemic therapy. The primary endpoint of the phase III study is 3-year overall survival, which is hypothesised to be 50% in the control arm and 65% in the experimental arm, thereby requiring 358 patients (179 in each arm). Secondary endpoints are surgical characteristics, grade ≥3 postoperative morbidity, progression-free survival, disease-free survival, health-related

quality of life, costs, major systemic therapy related toxicity, and objective radiological and histological response rates of colorectal PM to neoadjuvant systemic therapy.

Nature and extent of the burden, risks, and benefits associated with participation: it is hypothesised that perioperative systemic therapy and CRS-HIPEC (experimental arm) significantly improve the overall survival of patients with isolated resectable colorectal PM compared to the current standard treatment with upfront CRS-HIPEC alone (control arm). This potential overall survival benefit should be weighed against the burden and risks of the experimental arm. The most important potential burden/risks are: additional hospital visits for the perioperative systemic therapy, preoperative disease progression and secondary unresectability for CRS-HIPEC, increased postoperative complications after CRS-HIPEC, toxicity of perioperative systemic therapy, and an intensified and prolonged initial treatment that could decrease health-related quality of life. Patients in both arms are given to possibility to give separate permission for receiving questionnaires (costs, health-related quality of life) and for participation in blood and tissue collection for translational research. The investigators feel that the potential overall survival benefit of the experimental arm outweighs the burden and risks of participation.

1. INTRODUCTION AND RATIONALE

1.1 Colorectal peritoneal metastases

The peritoneum is the second most common isolated metastatic site of colorectal cancer after the liver [1,2]. Patients with isolated colorectal peritoneal metastases (PM) have a poor median survival, ranging from several months to approximately a year [2-6]. Nowadays, in the Netherlands, nearly thirty percent undergoes cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) [6]. This selected group has a median survival that approaches three years with a small chance of cure [7,8]. The increasing acceptance of CRS-HIPEC in clinical practice is supported by a randomised study and several large observational series [7,9-11]. In the Netherlands, upfront CRS-HIPEC is the

current standard treatment for isolated resectable colorectal PM [12]. The addition of neoadjuvant and adjuvant systemic therapy, together commonly referred to as perioperative systemic therapy, to CRS-HIPEC has potential benefits and drawbacks.

1.2 Potential benefits of perioperative systemic therapy

Firstly, perioperative systemic therapy may eradicate systemic micrometastases. Colorectal PM mostly arise from advanced primary tumours with a high risk of systemic spread [1,3,4]. Indeed, systemic failure is common after CRS-HIPEC [13]. Moreover, lymph node positivity is associated with poor outcomes after CRS-HIPEC [14], probably due to higher systemic recurrence rates. Perioperative systemic therapy could improve outcomes by decreasing the systemic failure risk. Secondly, neoadjuvant systemic therapy may decrease the intraperitoneal tumour load. Objective morphological and pathological responses are reported in about fifty and thirty percent of patients with colorectal PM who receive neoadjuvant systemic therapy, respectively [15,16]. Patients with a response could have favourable outcomes due to a lower intraoperative disease load, a higher chance of a complete cytoreduction, and less extensive surgery leading to a lower postoperative morbidity [17,18]. Thirdly, adjuvant systemic therapy may eradicate residual cancer cells after CRS-HIPEC. This could improve oncological outcomes by decreasing recurrence rates, as suggested by studies focusing on non-peritoneal colorectal metastases [19]. Lastly, response assessment to neoadjuvant systemic therapy could improve patient selection for CRS-HIPEC. Potentially harmful CRS-HIPEC may be avoided in patients with progression who are unlikely to benefit due to an unfavourable tumour biology, whereas patients with a favourable response could achieve relevant long-term survival [20,21].

1.3 Potential drawbacks of perioperative systemic therapy

Firstly, systemic therapy appears to be less effective for colorectal PM compared to non-peritoneal colorectal metastases [22]. This phenomenon may be explained by relative insensitivity of PM to systemic treatment [23], probably as a result of a low intraperitoneal concentration of systemically

administered drugs [24]. Thereby, preoperative disease progression and secondary unresectability could occur in a substantial number of patients who receive neoadjuvant systemic therapy [25,26]. Secondly, perioperative administration of systemic therapy may decrease its reintroduction rate at disease recurrence, which occurs in the vast majority of patients [8]. As a result, perioperative systemic therapy probably only prolongs the progression-free interval without improving overall survival, as previously observed for resectable colorectal liver metastases [27,28]. Thirdly, systemic therapy is associated with toxicity [29]. Some patients could become ineligible for CRS-HIPEC due to systemic therapy related toxicity. Moreover, preoperative administration of bevacizumab may increase postoperative complications after CRS-HIPEC [30]. Perioperative systemic therapy and its toxicity intensify and prolong the initial treatment period, which could interfere with qualify of life. Lastly, perioperative systemic therapy and its toxicity could increase health care costs, especially in the era of increasing use of targeted agents [31,32].

1.4 Rationale for this study

For isolated resectable colorectal PM, there is a lack of randomised studies that prospectively compare the oncological efficacy of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone [33]. The available evidence solely consists of clinically heterogeneous, often non-consecutive observational studies with high risks of selection bias [33]. Notwithstanding the lack of evidence, perioperative systemic therapy is widely administered to patients with isolated resectable colorectal PM [33]. However, administration and timing of perioperative systemic therapy vary substantially between countries, hospitals, and guidelines [9,33-35]. More importantly, it remains unknown whether perioperative systemic therapy has an intention-to-treat benefit in this setting [33-35]. Therefore, this study randomises patients with isolated resectable colorectal PM to receive either perioperative systemic therapy and CRS-HIPEC (experimental arm) or upfront CRS-HIPEC alone (control arm). Results of this study reveal whether addition of perioperative systemic therapy to CRS-HIPEC has

an intention-to-treat benefit for these patients. The investigators hypothesise that patients in the experimental arm have a better overall survival than patients in the control arm.

1.5 Rationale for perioperative systemic regimen

Six months of perioperative systemic therapy are divided into three months of neoadjuvant systemic therapy and three months of adjuvant systemic therapy. A partially preoperative administration of systemic therapy may be beneficial, since some patients are unable to receive adjuvant systemic therapy due to postoperative morbidity [36]. Moreover, systemic therapy is probably better tolerated before than after CRS-HIPEC, hence allowing increased dose-intensity. The rationale for the neoadjuvant regimen is derived from first-line studies in metastatic colorectal cancer. Doublet chemotherapy consisting of a fluoropyrimidine with either oxaliplatin or irinotecan has higher response rates than fluoropyrimidine monotherapy [37-40]. Combinations of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX), capecitabine with oxaliplatin (CAPOX), 5-fluorouracil/leucovorin with irinotecan (FOLFIRI), and capecitabine with irinotecan (CAPIRI) have a similar efficacy [41], but the latter has an unfavourable toxicity profile [42-44]. Although triplet chemotherapy has higher response rates than doublet chemotherapy, it substantially increases toxicity [45]. Doublet chemotherapy may therefore be preferable, since patients in this study have resectable disease without a need for aggressive conversion therapy. The efficacy of doublet chemotherapy is increased by the addition of epidermal growth factor (EGFR) inhibitors or bevacizumab [46,47]. When added to doublet chemotherapy, similar response rates are observed for EGFR inhibitors and bevacizumab [48-50]. However, unexpectedly unfavourable outcomes are observed when the EGFR inhibitor cetuximab is added to perioperative doublet chemotherapy for resectable colorectal liver metastases [51]. Therefore, neoadjuvant administration of bevacizumab should be preferable, as suggested by some observational and experimental studies [16,52,53]. It is not beneficial to add EGFR inhibitors to doublet chemotherapy with bevacizumab [54,55]. Taken together, neoadjuvant systemic therapy comprises bevacizumab with either CAPOX, FOLFOX, or FOLFIRI. The rationale for the adjuvant regimen is derived

from adjuvant studies in high-risk colon cancer and colorectal liver and lung metastases. Fluoropyrimidine monotherapy is more effective than observation [19,56,57], with a similar efficacy of capecitabine and 5-fluorouracil/leucovorin [58]. Addition of oxaliplatin to fluoropyrimidines is beneficial [59-61], while addition of irinotecan is not [62-65]. It is not beneficial to add targeted therapies to adjuvant chemotherapy [66-70]. Conclusively, adjuvant systemic therapy consists of either CAPOX, FOLFOX, or fluoropyrimidine monotherapy.

1.6 Rationale for the phase II-III approach

This is the first prospective multicentre study in patients with isolated resectable colorectal PM in the Netherlands. Furthermore, this is the first prospective assessment of perioperative systemic therapy for this specific patient population. As a result, little is known about the feasibility of enrolling these patients into randomised studies in the Netherlands and about the feasibility, safety, and tolerance of perioperative systemic therapy is this setting. Therefore, the investigators decided to start with a phase II study, as previously successfully done in the multicentre FOxTROT study that investigates neoadjuvant chemotherapy for locally advanced resectable colon cancer [71]. This allows for adequate monitoring of the accrual rate and the feasibility, safety, and tolerance of the experimental treatment.

2. OBJECTIVES

2.1 Phase II study

Objectives of the phase II study are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological and histological response of colorectal PM to neoadjuvant systemic therapy.

2.2 Phase III study

The primary objective of the phase III study is to compare (overall, progression-free, disease-free) survival outcomes between both arms. Secondary objectives are to compare surgical characteristics, major postoperative morbidity, health-related quality of life, and costs between both arms. Other objectives are to assess major systemic therapy related toxicity and the objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy.

3. STUDY DESIGN

3.1 Design

This is a multicentre, open-label, parallel-group, phase II-III, superiority study that randomises eligible patients in a 1:1 ratio to receive either perioperative systemic therapy and CRS-HIPEC (experimental arm) or upfront CRS-HIPEC alone (control arm), the latter being the current standard treatment in the Netherlands.

3.2 Duration

Accrual is considered feasible when the first 80 patients of the phase II study are enrolled within one year after the start of accrual in the last study centre, since an accrual rate of 80 patients each year ensures completion of the subsequent phase III study within a maximum of four years.

3.3 Setting

In the phase II study, accrual, perioperative systemic therapy, and CRS-HIPEC are restricted to the eight study centres. These study centres include all Dutch tertiary referral centres qualified for the surgical treatment of colorectal PM, consisting of five university hospitals (Erasmus University Medical Centre, Rotterdam; Amsterdam University Medical Centre, location VUMC, Amsterdam; University Medical Centre Groningen, Groningen; Radboud University Medical Centre, Nijmegen; University Medical

Centre Utrecht, Utrecht) and four teaching hospitals (Catharina Hospital, Eindhoven; St. Antonius Hospital, Nieuwegein; Netherlands Cancer Institute, Amsterdam). In the subsequent phase III study, accrual and CRS-HIPEC remain restricted to the eight study centres

4. STUDY POPULATION

4.1 Population (base)

In 2016, 15.245 patients were diagnosed with colorectal cancer in the Netherlands (www.cijfersoverkanker.nl), of whom ±2.1% (*n*=320) had isolated synchronous PM [3]. In 2016, the 10-year prevalence of stage I-III colorectal cancer was ±50.000 (www.cijfersoverkanker.nl), of whom ±1.4% (*n*=700) developed isolated metachronous PM [4]. Therefore, an estimated number of ±1000 patients are diagnosed with isolated colorectal PM in the Netherlands each year. Of these patients, it is estimated that ±35% (*n*=350) nowadays undergoes CRS-HIPEC in a tertiary referring hospital [6]. These are the patients who can be enrolled in this study. The investigators expect that at least 80 of these 350 patients (±25%) are enrolled in the study to ensure completion of the phase II study within one year and completion of the phase III study within three more years.

4.2 Inclusion criteria

Eligible patients are adults who have:

- a World Health Organisation (WHO) performance status of ≤1;
- histological or cytological proof of PM of a non-appendiceal colorectal adenocarcinoma with ≤50% of the tumour cells being signet ring cells;
- resectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy/laparotomy;
- no evidence of systemic colorectal metastases within three months prior to enrolment;
- no systemic therapy for colorectal cancer within six months prior to enrolment;

- no contraindications for CRS-HIPEC;
- no previous CRS-HIPEC;
- no concurrent malignancies that interfere with the planned study treatment or the prognosis of resected colorectal PM.

Importantly, enrolment is allowed for patients with radiologically non-measurable disease. Enrolment is also allowed for patients who are referred to a study centre after a macroscopically complete resection of colorectal PM in a referring centre, since it is assumed that microscopic (and often macroscopic) colorectal PM are still present. The diagnostic laparoscopy/laparotomy may be performed in a referring centre, provided that the peritoneal cancer index (PCI) is appropriately scored and documented before enrolment [72]. In the future, diffusion-weighted MRI (DW-MRI) may be added to the standard preoperative work-up of study patients given its promising results in detecting resectable colorectal PM [73].

4.3 Exclusion criteria

Patients are excluded in case of any comorbidity or condition that prevents safe administration of the planned perioperative systemic therapy, determined by the treating medical oncologist, e.g.:

- Inadequate bone marrow, renal, or liver functions (e.g. haemoglobin <6.0 mmol/L, neutrophils <1.5 x 10^9/L, platelets <100 x 10^9/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml/min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);
- Previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan, to such extent that the oncologist does not consider the patient eligible for systemic therapy;
- Dehydropyrimidine dehydrogenase deficiency;
- Serious active infections;
- Severe diarrhoea;

- Stomatitis or ulceration in the mouth or gastrointestinal tract;
- Recent major cardiovascular events;
- Unstable or uncompensated respiratory or cardiac disease;
- Bleeding diathesis or coagulopathy;
- Pregnancy or lactation.

4.4 Sample size calculation

The sample size of 80 (40 in each arm) for the phase II study is chosen pragmatically as a sufficient number to explore the feasibility of accrual and the feasibility, safety, and tolerance of perioperative systemic therapy. The sample size calculation of the phase III study could only be based on a combination of low-quality observational studies [15,16,20,21,36,54,74-76]. A total number of 358 patients (179 in each arm) is needed to detect a hypothesised 15% increase in 3-year overall survival (control arm 50%; experimental arm 65%) with 5% drop-out, 80% power, and a two-sided log-rank test at $p<0.05$. The primary study hypothesis may be modified when new insights or new guiding literature become available. The Data Monitoring Committee (section 9.5) and the METC are notified when the drop-out exceeds 5%.

5. TREATMENT OF PATIENTS

Figure 1 shows a general flowchart of the study. *Table 1* and *Table 2* present schedules of enrolment, interventions, and assessments of the experimental arm and the control arm, respectively.

5.1 Perioperative systemic therapy

Figure 2 shows a flowchart of the perioperative systemic therapy in the experimental arm. At the discretion of the treating medical oncologist, perioperative systemic therapy consists of either:

- Four three-weekly neoadjuvant and adjuvant cycles of CAPOX (130 mg/m^2 body-surface area [BSA] of oxaliplatin, intravenously [IV] on day 1; 1000 mg/m^2 BSA of capecitabine, orally twice daily on days 1-14), with bevacizumab (7.5 mg/kg body weight, IV on day 1) added to the first three neoadjuvant cycles, or;
- Six two-weekly neoadjuvant and adjuvant cycles of FOLFOX (85 mg/m^2 BSA of oxaliplatin, IV on day 1; 400 mg/m^2 BSA of leucovorin, IV on day 1; 400/2400 mg/m^2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2), with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles, or;
- Six two-weekly neoadjuvant cycles of FOLFIRI (180 mg/m^2 BSA of irinotecan, IV on day 1; 400 mg/m^2 BSA of leucovorin, IV on day 1; 400/2400 mg/m^2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) and either four three-weekly (capecitabine (1000 mg/m^2 BSA, orally twice daily on days 1-14) or six two-weekly (400 mg/m^2 BSA of leucovorin, IV on day 1; 400/2400 mg/m^2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) adjuvant cycles of fluoropyrimidine monotherapy, with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles.

Neoadjuvant systemic therapy should start within four weeks after randomisation. Adjuvant systemic therapy should start within twelve weeks after CRS-HIPEC. In case of unacceptable toxicity or contraindications to oxaliplatin or irinotecan in the neoadjuvant setting, CAPOX or FOLFOX may be switched to FOLFIRI and vice versa. In case of unacceptable toxicity or contraindications to oxaliplatin in the adjuvant setting, CAPOX of FOLFOX may be switched to fluoropyrimidine monotherapy. Dose reduction, co-interventions, and escape medication are not specified *a priori*, but left to the discretion of the treating medical oncologist. Perioperative systemic therapy can be prematurely discontinued due to radiological or clinical disease progression, unacceptable toxicity, physicians decision, or at patients request.

5.2 CRS-HIPEC

CRS-HIPEC is performed according to the Dutch protocol in all study centres [77]. The choice of HIPEC medication (oxaliplatin or mitomycin C) is left to the discretion of the treating physician, since neither one has a favourable safety or efficacy [78,79]. In the control arm, CRS-HIPEC should be performed within six weeks after randomisation. In the experimental arm, CRS-HIPEC should be performed within six weeks after completion of neoadjuvant systemic therapy, and at least six weeks after the last administration of bevacizumab in order to minimise the risk of bevacizumab-related postoperative complications [80].

5.3 Follow-up

In the control arm, thoracoabdominal CT is performed three, six, and twelve months after CRS-HIPEC, and every six months thereafter until five years after randomisation. In the experimental arm, thoracoabdominal CT is performed three and nine months after CRS-HIPEC, and every six months thereafter until five years after randomisation. This follow-up schedule allows for an equal comparison of progression-free survival between both arms (Figure 1).

5.4 Questionnaires

EQ-5D-5L [81,82], QLQ-C30 [83], QLQ-CR29 [84], iMTA productivity cost questionnaire (PCQ) [85], and iMTA medical consumption questionnaire (MCQ) [86] are sent to the patients before study treatment, after completion of neoadjuvant systemic therapy (experimental arm), every three months after CRS-HIPEC until one year postoperatively, and every six months thereafter until three years after randomisation, and once a year until five years after randomisation (Figure 1).

5.5 Translational research – blood

An additional 20 ml blood is drawn and collected in 10 ml Cell-free DNA BCT tubes (Streck, La Vista, NE, USA) during regular blood draws before study treatment (experimental arm), between the first and the second cycle of neoadjuvant systemic therapy (experimental arm), one day before CRS-HIPEC, seven days after CRS-HIPEC, between the first and the second cycle of adjuvant systemic therapy (experimental arm), and every follow-up visit until disease recurrence or five years after randomisation (Figure 1). According to the manufacturer's instructions, collected specimens are sent to a central lab, where they are processed for isolation and storage of plasma.

5.6 Translational research – tissue

In all patients undergoing CRS-HIPEC, tissue specimens of colorectal PM and the primary tumour are systematically collected and stored in the study centres. Three resected colorectal PM, preferably from different regions, are divided in two halves. One half is stored at -80°C and the counterpart is fixed in formalin and embedded in paraffin. When resected, three regions of ±1.5 cm^3 are excised from the primary tumour. Each region is divided in two halves. One half is stored at -80°C and the counterpart is fixed in formalin and embedded in paraffin. Lastly, a piece of normal tissue is excised from the resected materiel and stored at -80°C.

6. INVESTIGATIONAL PRODUCTS

6.1 Names and descriptions

Investigational products used in this study are:

- 5-fluorouracil (L01BC02);
- Leucovorin (V03AF03);
- Capecitabine (L01BC06);

- Oxaliplatin (L01XA03);
- Irinotecan (L01XX19);
- Bevacizumab (L01XC07).

All investigational products have a marketing authorisation and are used in the authorised form for the authorised indication (metastatic colorectal cancer) [12].

6.2 Findings from (non-)clinical studies, known risks, and known benefits

Findings from (non-)clinical studies, known risks, and known benefits can be found in the Summary of Product Characteristics of 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan, and bevacizumab.

6.3 Route and method of administration, dosage, and dosage modifications

Section 5.1 provides information on the route and method of administration, dosage, and dosage modifications, all being standard of care according to the most recent guidelines [12].

6.4 Preparation, labelling, and drug accountability

All investigational products have a marketing authorisation and are used in the authorised form for the authorised indication (metastatic colorectal cancer) [12]. Therefore, the investigational products are used from commercial stock and preparation and labelling are performed on a patient-named basis within the pharmacy departments of participating centres. No specific labelling for research purposes is performed in this study.

7. NON-INVESTIGATIONAL PRODUCT

CRS-HIPEC is the non-investigational product (intervention) in this study. The procedure is performed according to the Dutch protocol in all study centres [77]. The choice of HIPEC medication (oxaliplatin or mitomycin C) is left to the discretion of the treating physician.

8. METHODS

8.1 Outcomes

8.1.1 Phase II study

Outcomes of the phase II study are to explore:

- the feasibility of accrual, based on the total accrual rate, the accrual rate in each study centre, and screening failures;
- the feasibility of perioperative systemic therapy, based on the number of patients that (1) start and complete neoadjuvant systemic therapy, with or without dose reductions, (2) are scheduled for CRS-HIPEC, (3) undergo complete CRS-HIPEC, and (4) start and complete adjuvant systemic therapy, with or without dose reductions;
- the safety of perioperative systemic therapy, based on the number of patients with (1) systemic therapy related toxicity, defined as grade ≥2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [87], up to one month after the last administration of systemic therapy, and (2) postoperative morbidity, defined as grade ≥2 according to Clavien-Dindo [88], up to three months after CRS-HIPEC;
- the tolerance of perioperative systemic therapy, based on health-related quality of life extracted from EQ-5D-5L, QLQ-C30, and QLQ-CR29 during study treatment;

- the radiological and histological response of colorectal PM to neoadjuvant systemic therapy, based on central review of thoracoabdominal CT and resected specimens during CRS-HIPEC, respectively. Classifications are not defined *a priori*.

8.1.2 Phase III study: primary outcome

The primary outcome is 3-year overall survival, defined as the number of patients who are alive three years after randomisation.

8.1.3 Phase III study: secondary outcomes

Secondary outcomes in both arms are:

- progression-free survival, defined as the time between randomisation and disease progression before CRS-HIPEC, CRS-HIPEC in case of unresectable disease, radiological proof of recurrence, or death;
- disease-free survival, defined as the time between CRS-HIPEC and radiological proof of recurrence or death;
- health-related quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different points in time (Figure 1);
- costs, extracted from questionnaires (iMTA PCQ, iMTA MCQ) at different points in time (Figure 1);
- surgical characteristics of CRS-HIPEC (e.g. PCI, intraoperative complications, operating time, visceral and peritoneal resections, completeness of cytoreduction, hospital stay);
- the number of patients with major postoperative morbidity, defined as grade ≥3 according to Clavien-Dindo, up to three months after CRS-HIPEC

Secondary outcomes in the experimental arm are:

- The number of patients with major systemic therapy related toxicity, defined as grade ≥3 according to the CTCAE, up to one month after the last administration of systemic therapy;
- The number of patients with an objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy, determined by central review of thoracoabdominal CT and resected specimens during CRS-HIPEC, respectively. Classifications are determined after exploration of the radiological and histological response in the phase II study.

8.1.4 Phase III study: other outcomes

All baseline characteristics which may intervene with the main study outcomes (confounders) are recorded in every patient (e.g. age, WHO performance status, ASA score, primary tumour location, histology, tumour differentiation, T-stage, N-stage, previous treatments).

8.2 Randomisation and treatment allocation

Eligible patients who are enrolled by physicians in study centres are centrally randomised and assigned to interventions by the coordinating investigators (KPR and CB) in a 1:1 ratio by using randomisation software (ALEA, FormsVision, Abcoude, Netherlands) with minimisation stratified by a PCI of 0-10 or 11-20, synchronous or metachronous PM, previous systemic therapy for colorectal cancer, and HIPEC with oxaliplatin or mitomycin C. Randomised patients are assigned a study number, of which a log is maintained at each study site.

8.3 Study procedures

Figure 1 shows a general flowchart of the study. *Table 1* and *Table 2* present schedules of enrolment, interventions, and assessments of the experimental arm and the control arm, respectively. *Figure 2* shows a flowchart of the perioperative systemic therapy in the experimental arm. All visits for perioperative systemic therapy, CRS-HIPEC, and CTs are part of the standard medical treatment. Extra for this study are the questionnaires and the blood and tissue collection for translational research.

8.4 Withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. Investigators can decide to withdraw a patient from the study for urgent medical reasons.

8.5 Replacement of individual patients after withdrawal

Individual patients are not replaced after withdrawal. Potential withdrawal of patients is included in the drop-out rate of 5%.

8.6 Follow-up of patients withdrawn from treatment

Randomised patients withdrawn from treatment are included in the intention-to-treat population and analysed for all major comparative endpoints (i.e. survival outcomes, health-related quality of life, costs).

8.7 Premature termination of the study

The study is terminated after the first interim analysis if less than 50% of the patients in the experimental arm undergo complete CRS-HIPEC or if the percentage of patients with major postoperative morbidity (Clavien-Dindo grade ≥3) is ≥20% higher in the experimental arm compared to the control arm.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of patient safety

In accordance to section 10, subsection 4, of the WMO, the sponsor suspends the study if there is sufficient ground that continuation of the study jeopardises patient health or safety. The sponsor notifies the accredited METC without undue delay of a temporary halt including the reason for such an action. The study is suspended pending a further positive decision by the accredited METC. The investigator takes care that all patients are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the study treatment. All grade ≥2 (phase II) or grade ≥3 (phaswe III) AEs (determined by CTCAE or Clavien-Dindo) reported spontaneously by the patient or observed by the investigator or his staff are recorded. The time window for recording AEs is from randomisation to three months after CRS-HIPEC and one month after the last administration of systemic therapy.

9.2.2 Serious adverse events (SAEs)

An SAE is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission is not considered as a serious adverse event. Physicians of study centres report all SAEs to the coordinating investigators within 24 hours and without undue delay after obtaining knowledge of the SAE. The coordinating investigators report SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs 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 are reported within a period of maximum 15 days after the coordinating investigator has first knowledge of SAE. The time window for recording SAEs is from randomisation to three months after CRS-HIPEC and one month after the last administration of systemic therapy.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are SUSARs if the following three conditions are met:

- the event must be serious (see chapter 9.2.2);
- there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
- the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
  - Summary of Product Characteristics (SPC) for an authorised medicinal product;
  - Investigator's Brochure for an unauthorised medicinal product.

Physicians of study centres report all SUSARs to the coordinating investigators within 24 hours and without undue delay after obtaining knowledge of the SUSAR. The coordinating investigators report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the patients involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that is submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority. The coordinating investigators report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States. The expedited reporting occurs not later than 15 days after the coordinating investigators have first knowledge of the adverse reactions. For fatal or life threatening cases the term is maximal 7 days for a preliminary report with another 8 days for completion of the report. The time window for recording SUSARs is from randomisation to three months after CRS-HIPEC and one month after the last administration of systemic therapy.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the coordinating investigators submit, once a year throughout the study, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States. This safety report consists of:

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

9.4 Follow-up of adverse events

All AEs are followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.5 Data Monitoring Committee

The data monitoring committee (DMC) consists of a surgeon (CV), a medical oncologist (HWL), and a statistician (AHZ), who are all independent from the sponsor and competing interests. A detailed description of the tasks and responsibilities of the DMC is provided in a separate charter. Their role is to monitor patient safety through three interim analyses after 80 (phase II study), 160, and 240 patients complete their study treatment. When the first 80 patients complete their study treatment, the accrual is temporarily stopped until it is determined that it is not necessary to terminate the study based on the predefined stopping rules and that continuation of the phase III study is appropriate. The study is terminated after the first interim analysis if less than 50% of the patients in the experimental arm undergo complete CRS-HIPEC or if the percentage of patients with major postoperative morbidity (Clavien-Dindo grade ≥3) is ≥20% higher in the experimental arm compared to the control arm. Relevant data are made available to the DMC by the central data manager (JBM) and the study statistician (MGD). After each interim analysis, the DMC reports their advice on study continuation to

the study steering committee (CJP, PJT, IHH). The study steering committee submits these reports to the ethics committee and notifies the ethics committee when and/or why (part of) the advice of the DMC is not followed. The study steering committee makes the final decision to terminate the study.

10. STATISTICAL ANALYSIS

All statistical analyses are performed by using the Statistical Package for Social Sciences (IBM Corporation, Armonk, NY, USA). *P*<0.05 is considered statistically significant in all analyses. All statistical tests are performed 2-sided. All binary and categorical variables are expressed as n (%), and continuous variables as mean with standard deviation or as median with interquartile range or 95% confidence intervals, depending on distribution. Overall survival, progression-free survival, health-related quality of life, and costs are analysed in all randomised patients (intention-to-treat population). Surgical characteristics, histological response, postoperative morbidity, and disease-free survival are analysed in all patients who receive CRS-HIPEC (operated population). Radiological response and systemic therapy related toxicity are analysed in all patients who received at least one dose of perioperative systemic therapy (systemically treated population). The median follow-up period is calculated by using the reverse Kaplan-Meier method. Data on patients who are event-free are censored on the date the patient is last seen.

10.1 Phase II study

The number of patients who undergo complete CRS-HIPEC and the number of patients with postoperative morbidity are compared between both arms by using the Chi-square test or the Fisher's exact test where appropriate. Health-related quality of life during the study treatment is graphically presented across all time points and compared between both arms by using a repeated measures analysis of variance. All other outcomes (i.e. total accrual rate, accrual rate in each study centre, screening failures, number of patients that start/complete [neo]adjuvant systemic therapy, number of

patients with systemic therapy related toxicity, radiological and histological response) are analysed by using descriptive statistics.

10.2 Phase III study: primary outcome

Kaplan-Meier curves of overall survival are compared between both arms by using the two-sided log-rank test. Unadjusted and confounder-adjusted hazard ratios with two-sided 95% confidence intervals are estimated by using Cox proportional hazards models. Confounders will be specified after completion of the phase II study and before the final dataset of the phase III study is locked. Subgroup analyses are performed stratified for relevant baseline characteristics that will be defined after completion of the phase II study and before the final dataset of the phase III study is locked.

10.3 Phase III study: secondary outcomes

Kaplan-Meier curves of secondary time-to-event outcomes (i.e. progression-free survival, disease-free survival) are compared between both arms by using the two-sided log-rank test. Unadjusted and confounder-adjusted hazard ratios with two-sided 95% confidence intervals are estimated by using Cox proportional hazards models. Subgroup analyses are performed stratified for relevant baseline characteristics that will be defined before the final dataset is locked. Secondary categorical outcomes (i.e. number of patients with major postoperative morbidity, categorical surgical characteristics such as the completeness of cytoreduction,) are compared between both arms by using the Chi-square test or the Fisher's exact test where appropriate. Secondary continuous outcomes (i.e. continuous surgical characteristics such as operating time) are compared between both arms by using the Mann-Whitney U test or the student's t test where appropriate. Health-related quality of life is graphically presented across all time points and compared between both arms by using a repeated measures analysis of variance. All other secondary outcomes (i.e. number of patients with major systemic therapy related toxicity, number of patients with objective radiological and histological response) are analysed by using descriptive statistics.

10.4 Phase III study: costs

Costs are derived from the product sum of used health care and their unit costs as provided in the most recent Dutch costing guideline for health care research at the time of analysis. The cost-effectiveness and cost-utility of the experimental versus the control treatment are analysed from a societal perspective and with the three-year time horizon. Considering this time horizon, costs and health outcomes are discounted at yearly rates of 4% and 1.5% respectively. Incremental cost-effectiveness ratios (ICER) are calculated for the extra costs per additional patient alive and the extra costs per additional quality adjusted life year (QALY) respectively. QALYs are derived from periodically observed EQ-5D-5L assessments using an existing health status valuation algorithm to transpose the scoring profile on the EQ-5D-5L into a health utility and accounting for the time periods in between successive measurements [82]. The ICERs are presented in cost-effectiveness planes with the differences in costs on the Y-axis and the differences in survival, respectively QALYs on the X-axis, after bootstrapping, drawing 5000 samples of the same size of the original one for each treatment group and with replacement. A cost-effectiveness acceptability curve is drawn to show the probability of the experimental treatment being cost-effective for various monetary values society is willing to pay per extra QALY. Considering the severity of the disease at hand, willingness-to-pay values up to 100K euro per QALY are presented.

10.5 Phase III study: other outcomes

Categorical baseline characteristics and categorical outcomes are compared between both arms by using the Chi-square test or the Fisher's exact test where appropriate. Continuous baseline characteristics and outcomes are compared between both arms by using the Mann-Whitney U test or the student's t test where appropriate. Health-related quality of life is graphically presented across all time points and compared between both arms by using a repeated measures analysis of variance.

10.6 Interim analyses

The interim analyses are performed by the central data manager and the study statistician. Results are presented to the DMC. The first interim analysis is done after 80 patients complete their study treatment. The study is terminated after the first interim analysis if less than 50% of the patients in the experimental arm undergo complete CRS-HIPEC or if the percentage of patients with major postoperative morbidity (Clavien-Dindo grade ≥3) is ≥20% higher in the experimental arm compared to the control arm. Statistical methods of the first interim analysis are presented in section 10.1.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study is conducted according to the principles of the Declaration of Helsinki (see www.wma.net for the most recent version) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Potential study candidates are enrolled by dedicated specialised physicians in high-volume study centres. Patients are informed about the study by physicians during their first visit to the outpatient clinic of the study centre. The information includes the aims and rationale of the study, the possible adverse events, the procedures and possible hazards to which patients are exposed, and the mechanism of treatment allocation. Furthermore, patients are informed about the strict confidentiality of their data, and the fact that their medical records may be reviewed for study purposes by authorised individuals other than their treating physician. It is emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he or she wants. This will not prejudice the patients' subsequent care. The patient information letter is provided after the information on the first visit to the outpatient clinic. Thereafter, patients routinely receive several diagnostic investigation (e.g. CT, laparoscopy) in order to determine

whether they qualify for CRS-HIPEC (and the study). This period usually takes several days to several weeks. During this period, patients have sufficient time to consider their decision on study participation. After the diagnostic investigations, patient return to the outpatient clinic for results of the diagnostic investigations. During this visit, patients decide on study participation after their last questions regarding the patient information letter are answered. Patients are given the possibility to give separate permission for receiving questionnaires and for participation in blood and tissue collection for translational research. When patients give permission, they give permission for sending their details (name, address, city) to the coordinating investigators solely for these purposes. The Dutch patient information letter and informed consent form can be found in a separate document.

11.3 Objection by minors or incapacitated patients

Minors and incapacitated patients are not eligible for the study.

11.4 Benefits and risks assessment

it is hypothesised that perioperative systemic therapy and CRS-HIPEC (experimental arm) significantly improve the overall survival of patients with isolated resectable colorectal PM compared to the current standard treatment with upfront CRS-HIPEC alone (control arm). This potential overall survival benefit should be weighed against the burden and risks of the experimental arm. The most important potential burden/risks are: additional hospital visits for the perioperative systemic therapy, preoperative disease progression and secondary unresectability for CRS-HIPEC, increased postoperative complications after CRS-HIPEC, toxicity of perioperative systemic therapy, and an intensified and prolonged initial treatment that could decrease health-related quality of life. The investigators feel that the potential overall survival benefit of the experimental arm outweighs the burden and risks of participation.

11.5 Compensation for injury

All study centres and satellite centres have a liability insurance which is in accordance with article 7 of the WMO. The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

This study has no special incentives, compensation, or treatment for participating patients.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Data collection and data management

Questionnaires are collected centrally by the coordinating investigators. Patients complete the questionnaires by post or digitally by using an ISO 27001 certified information security management system (De Research Manager, Deventer, Netherlands) according to their own preference. All other baseline and outcome data are collected and entered in the central study database (TRIAS, Netherlands Comprehensive Cancer Organisation [IKNL], Utrecht, Netherlands) with electronic case report forms by independent, qualified, and trained local data managers of IKNL in each study centre. Data coding, security, and storage, including processes to promote data quality, are performed by an independent, qualified, and trained central data manager of IKNL. IKNL's experience with continuous data collection and data management based on high quality CRFs guarantees accurate, complete, and timely recording, handling and storage of data and documents. Personal information about potential and enrolled patients is collected, shared, and maintained according to the Dutch law in order to protect confidentiality before, during, and after the study. After randomisation, patients are coded with a 3-digit study number. Communication occurs only with the study number. The key that links study numbers with patient data stays in the study centre of the patient. People who have access to the code

are the treating physicians, the ethics committee, the healthcare inspection (Inspectie Gezondheidszorg en Jeugd), and the coordinating investigators (only when the patient gives permission on the informed consent form). Blood samples for translational research are sent to the central lab with the 3-digit study number. All other specimens and scans (e.g. resected specimens during CRS-HIPEC, thoracoabdominal CTs) are stored at the study centres. In a later stage, specimens and scans are sent for central review of radiological and histological response with the 3-digit study number. After the study, human materials are stored anonymously for fifteen years according to the Dutch law.

12.2 Data monitoring

The study is monitored by independent qualified monitors of IKNL as a study with a moderate risk for patients according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centres. During the phase II study, each study centre is audited twice, with a focus on essential study documents, informed consent procedures, eligibility criteria, source data verification, and SAEs/SUSARs. A comprehensive description of the aspects and frequency of monitoring can be found in a separate monitoring plan. Frequency and procedures for auditing of the phase III study are not specified and depend on auditing reports of the phase II study.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments are notified to the METC and to the competent authority. Non-substantial amendments are not notified to the accredited METC and the competent authority, but recorded and filed by the sponsor.

12.4 Annual progress report

The coordinating investigators submit a summary of the progress of the trial to the accredited METC once a year. Information is provided on the date of inclusion of the first patients, numbers of patients included and numbers of patients that have completed the trial, SAEs/SUSARs, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor notifies the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient is five years after randomisation. The sponsor notifies the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor notifies the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigators submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The central data manager, study statistician, coordinating investigators, and the study steering committee have access to the final datasets, without any contractual agreements that limit such access. The subsiding parties have no role in the design of the study, in the collection, analysis, and interpretation of data, and in writing the manuscripts. Results of the phase II and phase III studies are

personally communicated to participating patients. Results are communicated to healthcare professionals through publication in peer-reviewed medical journals without any publication restrictions. The manuscripts are written by the coordinating investigators, the study statistician, the study steering committee, and a professional English writer. Authorship is granted to the central data manager, the DMC, and investigators who analyse secondary outcomes (e.g. radiological or histological response). Authorship for physicians of study centres is granted based on the number of enrolled patients: one author for five (phase II) and twenty (phase III) patients, and an additional author for each three (phase II) and fifteen (phase III) additional patients. All other physicians and other healthcare professionals who contributed to the study are listed as collaborators. Criteria for authorship are described in the Clinical Trial Agreements between the sponsor and the participating sites. Manuscripts are offered for publication on behalf of the CAIRO6 study group. The Dutch Peritoneal Oncology Group (DPOG), the Dutch Colorectal Cancer Group (DCCG), and all participating centres and investigators are acknowledged in all publications and presentations. A summary of this study protocol is submitted to *BMC Cancer.*

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

All investigational products (5-fluorouracil, leucovorin, oxaliplatin, irinotecan, bevacizumab) have a marketing authorisation and are used in the authorised form for the authorised indication (metastatic colorectal cancer) [12]. Therefore, section 13.1 is skipped. Findings from (non-)clinical studies, known risks, and known benefits of the investigational products can be found in the Summary of Product Characteristics of 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan, and bevacizumab.

13.2 Synthesis

It is hypothesised that perioperative systemic therapy and CRS-HIPEC (experimental arm) significantly improve the overall survival of patients with isolated resectable colorectal PM compared to the current

standard treatment with upfront CRS-HIPEC alone (control arm). This potential overall survival benefit should be weighed against the burden and risks of the experimental arm. The most important potential burden/risks are: additional hospital visits for the perioperative systemic therapy, preoperative disease progression and secondary unresectability for CRS-HIPEC, increased postoperative complications after CRS-HIPEC, toxicity of perioperative systemic therapy, and an intensified and prolonged initial treatment that could decrease health-related quality of life. The phase II study has been designed to investigate the abovementioned risks in an early stage, with the most important endpoints being the feasibility, safety, and tolerance of perioperative systemic therapy (section 8.1.1). Results of the phase II study are presented to the DMC, with clear stopping rules when the criteria for feasibility and safety are not met. Questionnaires and participation in blood and tissue collection for translational research could be an additional burden for patients in both arms. However, all patients are given to possibility to give separate permission for questionnaires (costs, health-related quality of life) and for participation in blood and tissue collection. Conclusively, the investigators feel that the potential overall survival benefit of the experimental arm outweighs the burden and risks of participation.

14. REFERENCES

[1] van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol. 2014;38:448-54.

[2] van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015;32:457-65.

[3] Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717-25.

[4] van Gestel YR, Thomassen I, Lemmens VE, Pruijt JF, van Herk-Sukel MP, Rutten HJ, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. Eur J Surg Oncol. 2014;40:693-9.

[5] Quere P, Facy O, Manfredi S, Jooste V, Faivre J, Lepage C, et al. Epidemiology, management, and survival of peritoneal carcinomatosis from colorectal cancer: a population-based study. Dis Colon Rectum. 2015;58:743-52.

[6] Razenberg LG, Lemmens VE, Verwaal VJ, Punt CJ, Tanis PJ, Creemers GJ, et al. Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: results of a population-based study. Eur J Cancer. 2016;65:113-20.

[7] Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. Crit Rev Oncol Hematol. 2016;100:209-22.

[8] Goéré D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg. 2013;257:1065-71.

[9] Klaver CE, Groenen H, Morton DG, Laurberg S, Bemelman WA, Tanis PJ. Recommendations and consensus on the treatment of peritoneal metastases of colorectal origin: a systematic review of national and international guidelines. Colorectal Dis. 2017;19:224-36.

[10] Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24:4011-9.

[11] Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2009;16:2152-65.

[12] Landelijke werkgroep Gastro Intestinale Tumoren. Richtlijn colorectaal carcinoom. 2014. https://www.oncoline.nl/colorectaalcarcinoom. Accessed 10 Dec 2018.

[13] Braam HJ, van Oudheusden TR, de Hingh IH, Nienhuijs SW, Boerma D, Wiezer MJ, et al. Patterns of recurrence following complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. J Surg Oncol. 2014;109(8):841-7.

[14] Kwakman R, Schrama AM, van Olmen JP, Otten RH, de Lange-de Klerk ES, de Cuba EM, et al. Clinicopathological parameters in patients election for cytoreductve surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer metastases: a meta-analysis. Ann Surg. 2016;263:1102-11.

[15] Passot G, Vaudoyer D, Cotte E, You B, Isaac C, Gilly FN, et al. Progression following neoadjuvant systemic chemotherapy may not be a contraindication to a curative approach for colorectal carcinomatosis. Ann Surg. 2012;256:125-9. .

[16] Passot G, You B, Boschetti G, Fontaine J, Isaac S, Decullier E, et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol. 2014;21:2608-14.

[17] Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63-8.

[18] Baratti D, Kusamura S, Iusco D, Bonomi S, Grassi A, Virzi S, et al. Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: a two-center study of 101 patients. Dis Colon Rectum. 2014;57:858-68.

[19] Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26:4906-11.

[20] Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681-5.

[21] Devilee RA, Simkens GA, van Oudheusden TR, Rutten HJ, Creemers GJ, ten Tije AJ, et al. Increased survival of patients with synchronous colorectal peritoneal metastases receiving preoperative chemotherapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2016;23:2841-8.

[22] Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016;17:1709-19.

[23] Klaver YL, Simkens LH, Lemmens VE, Koopman M, Teerenstra S, Bleichrodt RP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. Eur J Surg Oncol. 2012;38:617-23.

[24] Sugarbaker PH, Stuart OH, Vidal-Jove J, Pessagno AM, de Bruijn EA. Pharmacokinetics of the peritoneal-plasma barrier after systemic mitomycin C administration. Cancer Treat Res. 1996;82:41-52.

[25] Hompes D, Aalbers A, Boot H, van Velthuysen ML, Vogel W, Prevoo W, et al. A prospective pilot study to assess neoadjuvant chemotherapy for unresectable peritoneal carcinomatosis from colorectal cancer. Colorectal Dis. 2014;16:264-72.

[26] Glockzin G, Zeman F, Croner RS, Königsrainer A, Pelz J, Ströhlein MA, et al. Perioperative systemic chemotherapy, cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy in patients with colorectal peritoneal metastasis: results of the prospective multicenter phase 2 COMBATAC trial. Clin Colorectal Cancer. 2018;17:285-96.

[27] Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from

colorectal cancer (EORTC Integroup trial 40983): a randomised controlled trial. Lancet. 2008371:1007-16.

[28] Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised controlled, phase 3 trial. Lancet Oncol. 2013;14:1208-15.

[29] Niraula S, Seruga B, Ocana A, Shao T, Goldstein R, Tannock IF, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol. 2012;3:43-52.

[30] Eveno C, Passot G, Goéré D, Soyer P, Gayat E, Glehen O, et al. Bevacizumab doubles the early postoperative complication rate after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2014;21:1792-800.

[31] Niraula S, Amir E, Vera-Badillo F, Seruga B, Ocana A, Tannock IF. Risk of incremental toxicities and associated costs of new anticancer drugs: a meta-analysis. J Clin Oncol. 2014;32:3634-42.

[32] Shih YC, Smieliauskas F, Geynisman DM, Kelly RJ, Smith TJ. Trends in the cost and use of targeted cancer therapies for the privately insured nonelderly: 2001 to 2011. J Clin Oncol. 2015;33:2190-6.

[33] Rovers KP, Simkens GA, Punt CJ, van Dieren S, Tanis PJ, de Hingh IH. Perioperative systemic therapy for resectable colorectal peritoneal metastases: sufficient evidence for its widespread use? A critical systematic review. Crit Rev Oncol Hematol. 2017;114:53-62.

[34] Bushati M, Rovers KP, Sommariva A, Sugarbaker PH, Morris DL, Yonemura Y, et al. The current practice of cytoreductive surgery and HIPEC for colorectal peritoneal metastases: results of a worldwide web-based survey of the Peritoneal Surface Oncology Group International (PSOGI). Eur J Surg Oncol. 2018;44:1942-8.

[35] Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. Ann Surg Oncol. 2007;14:128-33.

[36] Maillet M, Glehen O, Lambert J, Goéré D, Pocard M, Msika S, et al. Early postoperative chemotherapy after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for isolated peritoneal carcinomatosis of colon cancer: a multicenter study. Ann Surg Oncol. 2016;23:863-9.

[37] de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938-47.

[38] Giacchetti S, Perpoint B, Zidani R, le Bail N, Faggiuolo R, Focan C, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2000;18:136-47.

[39] Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343:905-14.

[40] Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomised trial. Lancet. 2000;355:1041-7.

[41] Sobrero A, Bennicelli E. Chemotherapy: which drug and when? Ann Oncol. 2010;21 Suppl 7:vii130-3.

[42] Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet. 2007;370:135-42.

[43] Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C study. J Clin Oncol. 2007;25:4779-86

[44] Köhne CH, de Greve J, Hartmann JT, Lang I, Vergauwe P, Becker K, et al. Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line

treatment of patients with metastatic colorectal cancer. EORTC study 40015. Ann Oncol. 2008;19:920-6.

[45] Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25:1670-6.

[46] Chan DL, Segelov E, Wong RS, Smith A, Herbertson RA, Li BT, et al. Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer. Cochrane Database Syst Rev. 2017;6:CD007047.

[47] Wagner AD, Arnold D, Grothey AA, Haerting J, Unverzagt S. Anti-angiogenic therapies for metastastic colorectal cancer. Cochrane Database Syst Rev. 2009;3:CD005392.

[48] Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1065-75.

[49] Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32:2240-7.

[50] Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017;317:2392-401.

[51] Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, Hornbuckle J, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the new EPOC randomised controlled trial. Lancet Oncol. 2014;15:601-11.

[52] Ceelen W, van Nieuwenhove Y, Putte DV, Pattyn P. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis. Ann Surg Oncol. 2014;21:3023-8.

[53] Gremonprez F, Descamps B, Izmer A, Vanhove C, Vanhaecke F, de Wever O, et al. Pretreatment with VEGF(R)-inhibitors reduces interstitial fluid pressure, increases intraperitoneal chemotherapy drug penetration, and impedes tumor growth in a mouse colorectal carcinomatosis model. Oncotarget. 2015;6:29889-900.

[54] Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563-72.

[55] Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672-80.

[56] Wilkinson NW, Yothers G, Lopa S, Constantino JP, Petrelli NJ, Wolmark N. Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. Ann Surg Oncol. 2010;17:959-66.

[57] Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370:2020-9.

[58] Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696-704.

[59] André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33:4176-87.

[60] Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol. 2015;33:3733-40.

[61] Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29:3768-74.

[62] Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol. 2007;25:3456-61.

[63] van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol. 2009;27:3117-25.

[64] Ychou M, Raoul JL, Douillard JY, Gourgou-Bourgade S, Bugat R, Mineur L, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol. 2009;20:674-80.

[65] Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluoruoracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009;20:1964-70.

[66] de Gramont A, van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol. 2012;13(12):1225-33.

[67] Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307:1383-93.

[68] Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, van Laethem JL, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(8):862-73.

[69] Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2011;29:11-6.

[70] Kerr RS, Love S, Segelov E, Johnstone E, Falcon B, Hewett P, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. Lancet Oncol. 2016;17:1543-57.

[71] Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. Lancet Oncol. 2012;13:1152-60.

[72] Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359-74.

[73] van 't Sant I, van Eden WJ, Engbersen MP, Kok NF, Woensdregt K, Lambregts DM, et al. Diffusion-weighted MRI assessment of the peritoneal cancer index before cytoreductive surgery. Br J Surg. 2018; doi:10.1002/bjs.10989.

[74] Chua TC, Morris DL, Saxena A, Esquivel J, Liauw W, Doerfer J, et al. Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. Ann Surg Oncol. 2011;18:1560-7.

[75] Kuijpers AM, Mehta AM, Boot H, van Leerdam ME, Hauptmann M, Aalbers AG, et al. Perioperative systemic chemotherapy in peritoneal carcinomatosis of lymph node positive colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Oncol. 2014;25:864.

[76] van Eden WJ, Kok NF, Józwiak K, Lahaye ML, Geets GL, van Leerdam ME, et al. Timing of systemic chemotherapy in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Dis Colon Rectum. 2017;60:477-87.

[77] Kuijpers AM, Mirck B, Aalbers AG, Nienhuijs SW, de Hingh IH, Wiezer MJ, et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. Ann Surg Oncol. 2013;20:4224-30.

[78] van Eden WJ, Kok NF, Woensdregt K, Huitema AD, Boot H, Aalbers AG. Safety of intraperitoneal mitomycin C versus intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and HIPEC. Eur J Surg Oncol. 2018;44:220-7.

[79] Hompes D, D'Hoore A, Wolthuis A, Fieuws S, Mirck B, Bruin S, et al. The use of oxaliplatin or mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. J Surg Oncol. 2014;109:527-32.

[80] Hompes D, Ruers T. Review: incidence and clinical significance of bevacizumab-related non-surgical and surgical serious adverse events in metastatic colorectal cancer. Eur J Surg Oncol. 2011;37:737-46.

[81] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727-36.

[82] Versteegh M, Vermeulen K, Evers S, de Wit GA, Prenger R, Stolk E. Dutch tariff for the five-level version of EQ-5D. Value Health. 2016;19:343-52.

[83] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-76.

[84] Stiggelbout AM, Kunneman M, Baas-Thijssen MC, Neijenhuis PA, Loor AK, Jägers S, et al. The EORTC QLQ-CR29 quality of life questionnaire for colorectal cancer: validation of the Dutch version. Qual Life Res. 2016;25:1853-8.

[85] Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. Value Health. 2015;18:753-8.

[86] iMTA: questionnaires. https://www.imta.nl/questionnaires/. Accessed 10 Dec 2018.

[87] Common Terminology Criteria for Adverse Events (CTCAE) v4.0. National Cancer Institute. 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Accessed 10 Dec 2018.

[88] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.

15. TABLES 1 & 2

	STUDY PERIOD								
	Enrolment/allocation	Post-allocation							Close-out
Table 1. Schedule of enrolment, interventions, and assessments of the experimental arm	*Outpatient clinics*	*Neoadjuvant treatment*	*CRS-HIPEC*	*Adjuvant treatment*	*Three months after CRS-HIPEC*	*Six months after CRS-HIPEC*	*Nine months after CRS-HIPEC*	*Every six months*	*Five years after randomization*
ENROLMENT/ALLOCATION									
Eligibility screen	X								
Informed consent	X								
Allocation	X								
INTERVENTIONS									
Chemotherapy		X		X					
Bevacizumab		X							
CRS-HIPEC			X						
Thoracoabdominal CT		X[A]			X		X	X	X
Questionnaires	X	X[B]			X	X	X	X	X
Translational research: blood	X	X[C]	X[D]	X[C]	X		X	X	X
Translational research: tissue			X						
ASSESSMENTS									
Baseline characteristics	X								
Feasibility of systemic therapy		X	X	X					
Safety/toxicity of systemic therapy		X	X	X					
Radiological response		X							
Histological response			X						
Surgical characteristics			X						
Postoperative morbidity			X		X				
Progression-free survival		X	X	X	X	X	X	X	X
Disease-free survival			X	X	X	X	X	X	X
Overall survival		X	X	X	X	X	X	X	X
Health-related quality of life	X	X	X		X	X	X	X	X
Costs	X	X	X		X	X	X	X	X

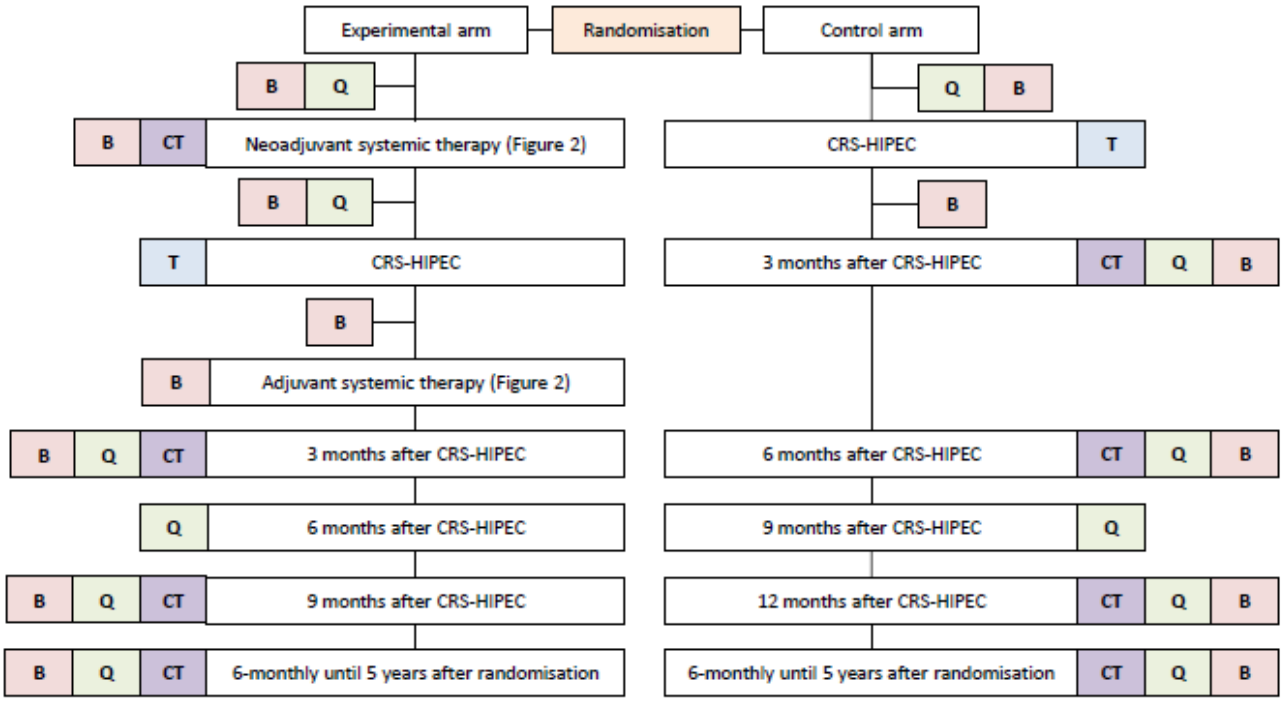
[A]After 3 (CAPOX with bevacizumab) or 4 (FOLFOX/FOLFIRI with bevacizumab) cycles; [B]After completion of neoadjuvant systemic therapy, before CRS-HIPEC; [C]Between the first and the second cycle of (neo)adjuvant systemic therapy; [D]1 day before CRS-HIPEC and 7 days after CRS-HIPEC; *CRS-HIPEC* cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; *CT* computed tomography

	STUDY PERIOD							
	Enrolment/allocation	**Post-allocation**						**Close-out**
Table 2. Schedule of enrolment, interventions, and assessments of the controll arm	*Outpatient clinics*	*CRS-HIPEC*	*Three months after CRS-HIPEC*	*Six months after CRS-HIPEC*	*Nine months after CRS-HIPEC*	*Twelve months after CRS-HIPEC*	*Every six months*	*Five years after randomisation*
ENROLMENT/ALLOCATION								
Eligibility screen	X							
Informed consent	X							
Allocation	X							
INTERVENTIONS								
CRS-HIPEC		X						
Thoracoabdominal CT			X	X		X	X	X
Questionnaires	X		X	X	X	X	X	X
Translational research: blood	X	X[A]	X	X		X	X	X
Translational research: tissue		X						
ASSESSMENTS								
Baseline characteristics	X							
Surgical characteristics		X						
Postoperative morbidity		X	X					
Progression-free survival		X	X	X	X	X	X	X
Disease-free survival		X	X	X	X	X	X	X
Overall survival		X	X	X	X	X	X	X
Health-related quality of life	X	X	X	X	X	X	X	X
Costs	X	X	X	X	X	X	X	X

[A]1 day before CRS-HIPEC and 7 days after CRS-HIPEC*; CRS-HIPEC* cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; *CT* computed tomograph

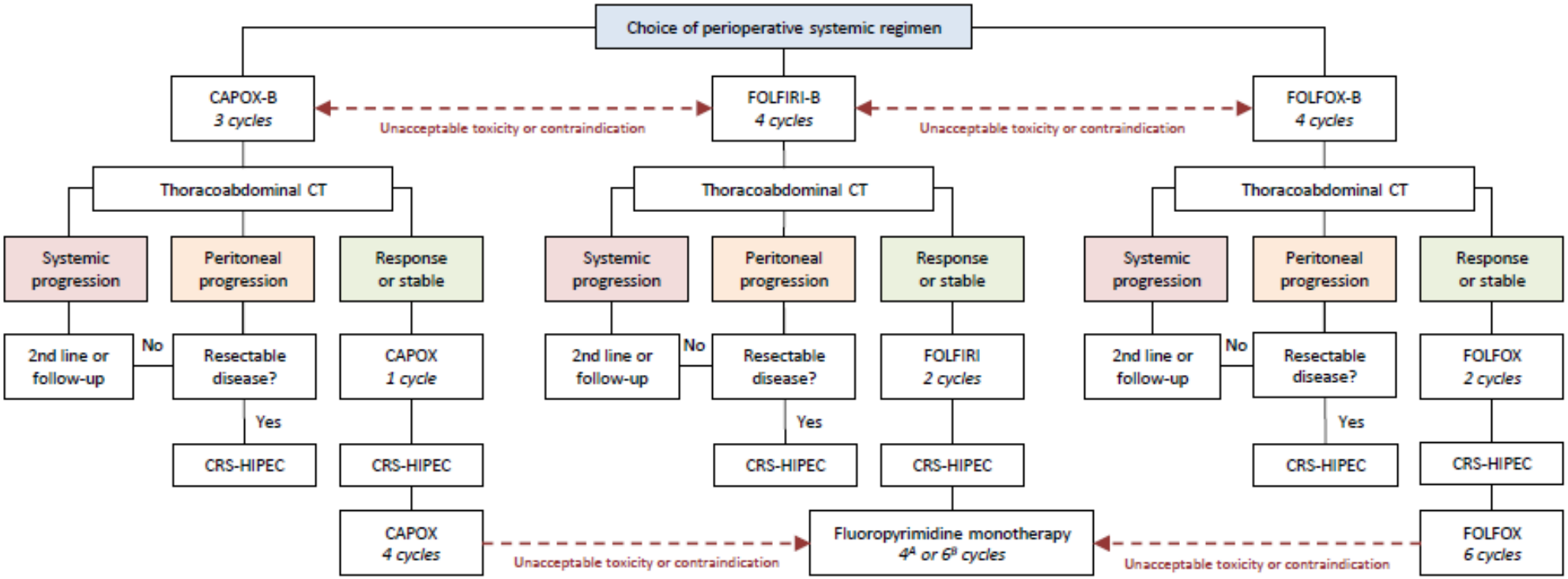
16. FIGURES 1 & 2

Figure 1. general flowchart of the CAIRO6 study.



B blood for translational research; *CRS-HIPEC* cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; *CT* thoracoabdominal computed tomography; *Q* questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29, iMTA Productivity Cost Questionnaire, iMTA Medical Consumption Questionnaire); *T* tissue for translational research

Figure 2. flowchart of the perioperative systemic therapy in the experimental arm.



[A]capecitabine; [B]5-fluorouracil, leucovorin; *CAPOX* capecitabine, oxaliplatin; *CAPOX-B* capecitabine, oxaliplatin, bevacizumab; *CRS-HIPEC* cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; *CT* computed tomography; *FOLFIRI* 5-fluorouracil, leucovorin, irinotecan; *FOLFIRI-B* 5-fluorouracil, leucovorin, irinotecan, bevacizumab; *FOLFOX* 5-fluorouracil, leucovorin, oxaliplatin; *FOLFOX-B* 5-fluorouracil, leucovorin, oxaliplatin, bevacizumab.