Joint initiative of the Dutch Colorectal Cancer Group (DCCG)

and the Dutch Peritoneal Oncology Group (DPOG)

Perioperative systemic therapy and surgery versus surgery alone for resectable colorectal peritoneal metastases: the multicentre, phase II-III, randomised **CAIRO6 study.**

Chemotherapy with surgery versus surgery alone for peritoneal metastases from colorectal cancer: the **CAIRO6 study.**

Perioperatieve systemische therapie en chirurgie versus alleen chirurgie voor resectabele colorectale peritoneale metastasen: de multicenter, fase II-III, gerandomiseerde **CAIRO6 studie.**

Chemotherapie met chirurgie versus alleen chirurgie voor buikvliesuitzaaiingen uit dikkedarmkanker: de **CAIRO6 studie.**

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PROTOCOL SIGNATURE SHEET

I confirm agreement to conduct the study in compliance with the protocol.

I have read the protocol and appendices. I understand the contents and intend to fully comply with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal protocol amendments.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

BEV	Bevacizumab
CAPOX	Capecitabine + oxaliplatin
CC	Completeness of Cytoreduction
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRC	Colorectal Carcinoma
CRF	Case Report Form
CRS	Cytoreductive Surgery
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
EudraCT	European drug regulatory affairs Clinical Trials
FOLFIRI	5-flurouracil + folic acid + irinotecan
FOLFOX	5-flurouracil + folic acid + oxaliplatin
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
ICD-O	International Classification for Diseases of Oncology
ICU	Intensive Care Unit
IV	Intravenous
IC	Informed Consent
PMCRC	Peritoneal Metastases of Colorectal Cancer
PCI	Peritoneal Cancer Index
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
(S)AE	(Serious) Adverse Event

SPSS	Statistical Package for the Social Sciences
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
WHO	World Health Organisation (performance status)

SUMMARY

Rationale: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) and systemic therapy are increasingly used for the treatment of peritoneal metastases of colorectal cancer (PMCRC). Subsequently, combined treatment strategies have been introduced, with the use of perioperative systemic therapy, either neoadjuvant or adjuvant, as adjunct to CRS + HIPEC. However, current literature on perioperative systemic therapy as adjunct to CRS + HIPEC is based on observational studies of low methodological quality, thereby leading to worldwide controversy on its benefit. A neoadjuvant treatment strategy that potentially downstages intraperitoneal tumour load, limits extensiveness of CRS, and predicts the biological behaviour of the tumour, appears to be of potential benefit. In patients who proved to respond to neoadjuvant treatment with sufficiently good clinical condition, adjuvant systemic therapy in the same regimen may be of value by further treating micro-metastases.

Objective: The primary objective of this study is to compare overall survival of CRS + HIPEC with perioperative systemic therapy versus upfront CRS + HIPEC alone in patient with potentially resectable PMCRC.

Study design: This is a prospective, multicentre, randomised, parallel group, phase II-III study with randomisation between CRS + HIPEC with perioperative systemic therapy (experimental arm) and upfront CRS + HIPEC alone (control arm). The study starts as a randomised phase II study to investigate the feasibility of accrual and the safety of neoadjuvant systemic therapy prior to CRS + HIPEC. If criteria of feasibility and safety are met, the study continues as a phase III study with 3-year overall survival as primary endpoint.

Study population: Patients with histologically proven non-signet cell synchronous or metachronous PMCRC, without systemic metastases, who are candidate for CRS + HIPEC (PCI score ≤20), and in whom (nearly) complete cytoreduction (CC-0 or CC-1) seems feasible.

Intervention: Neoadjuvant combination chemotherapy plus bevacizumab for three 3-weekly (CAPOX + BEV) or four 2-weekly (FOLFOX + BEV) cycles, followed by restaging with thoraco-abdominal CT-scan. In case of progressive systemic disease (e.g. liver or lung metastases), the best possible palliative treatment is offered. In case of progressive peritoneal disease without progressive systemic disease, patients undergo explorative laparotomy, followed by CRS in case of resectable disease, and HIPEC in case of a CC0/1 cytoreduction. In case of responsive or stable disease, one 3-weekly (CAPOX) or two 2-weekly (FOLFOX) neoadjuvant cycles of combination chemotherapy without bevacizumab are administered. Subsequently, not earlier than 3 weeks after the last day of the last cycle of combination chemotherapy, patients undergo explorative laparotomy, followed by CRS in case of resectable disease, and HIPEC in case of a CC0/1 cytoreduction. Only in patients with stable disease/response upon neoadjuvant treatment, and a sufficiently good clinical condition, adjuvant combination chemotherapy is administered according to the neoadjuvant regimen, but without bevacizumab, for four 3-weekly cycles (CAPOX) or six 2-weekly cycles (FOLFOX).

Study parameters: Regarding feasibility and safety, endpoints of the phase II study are the number of randomised patients 1 year after the start of accrual at the last participating centre, major postoperative complications (Clavien-Dindo grade III-V) at 3 months postoperatively, and the number of patients receiving CRS + HIPEC. Secondary endpoints are minor postoperative complications (Clavien-Dindo grade II) and systemic therapy related toxicity (NCICTCAE v4.0 Grade II-V). The phase II study is deemed unfeasible if <80 patients are randomised, and deemed unsafe if:

- There is a more than 7 patients difference in major postoperative complications in disadvantage of the experimental arm compared to the control arm.

- less than 50% (20/40) of included patients in the experimental arm are able to proceed to CRS + HIPEC.

The primary endpoint of the phase III study is 3-year overall survival measured from randomisation. Secondary endpoints are 5-year overall survival, progression-free survival, procedure related characteristics (i.e. operative time, blood loss), peritoneal cancer index (PCI) score, completeness of cytoreduction (CC) score, major postoperative complications (Clavien-Dindo grade III-V) at 90-days postoperatively, hospital stay, quality of life, cost-effectiveness, and blood and tissue collection for future translational research purposes. In the experimental arm, additional secondary endpoints are severe systemic therapy-related toxicity (NCICTCAE v4.0 grade III-V), and the number of patients with progression, stable disease, and response to neoadjuvant combination chemotherapy plus bevacizumab.

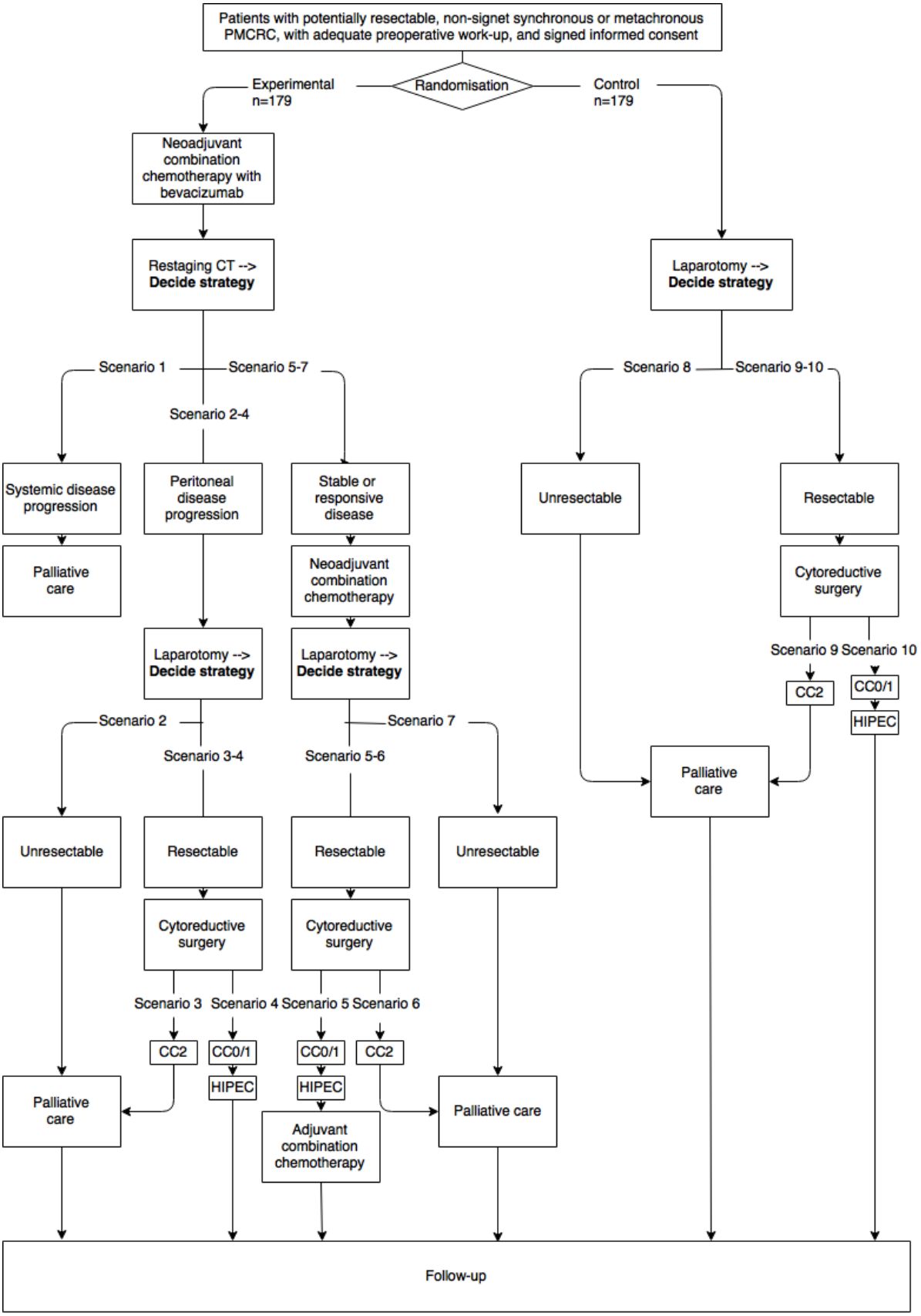
Sample size: The phase II study includes 80 patients, with 40 patients in each arm. After fulfilling the criteria of feasibility and safety criteria, the study continues as a phase III superiority study with 3 year overall survival as primary endpoint. The expected 3-year overall survival after CRS + HIPEC is 50%. We hypothesize that the experimental treatment results in a 15% increase in overall survival rate if analysed according to an intention-to-treat principle. With a 0.05 two-sided significance level, 80% power and a drop-out of 5%, a sample size of 179 patients in each arm is needed, resulting in a total of 358 patients, including the 80 patients from the phase II study.

Time schedule: In 2016, the expected number of patients referred for CRS + HIPEC for PMCRC in the Netherlands was 420. With an expected participation rate of 20%, accrual should be completed in 4 years.

Nature and extent of the burden and risks: In the experimental arm, the risk of this study primarily consists of treatment-related toxicity and morbidity of combination chemotherapy and bevacizumab,

which should be weighed against potential survival benefit. Furthermore, some patients in the experimental arm may have disease progression upon neoadjuvant treatment to an extent that does not allow CRS + HIPEC. However, it is highly questionable whether these patients would have derived a benefit from upfront CRS + HIPEC at all, and the investigators hypothesise that a neoadjuvant treatment strategy allows for better patient selection and spares the morbidity of this intervention to patients who are unlikely to benefit.

General flowchart:



1. INTRODUCTION AND RATIONALE

1.1 Peritoneal metastases of colorectal cancer

Synchronous peritoneal metastases of colorectal cancer (PMCRC) are diagnosed in approximately 5% of patients who are diagnosed with colorectal cancer.[1,2] The incidence of metachronous PMCRC is more difficult to determine and ranges from 4 to 19%.[3] PMCRC rates up to even 44% have been reported during reoperation for CRC.[3] In autopsy series, PMCRC rates are even higher, thereby underlining the challenge to detect PMCRC in an early phase.[3]

PMCRC is traditionally associated with a poor prognosis, with a median survival of approximately 6 months if treated with supportive care, palliative surgery, and conventional palliative chemotherapy.[4,5] Quality of life is often significantly impaired because of ascites and bowel obstruction. Palliative interventions like percutaneous drainage of ascites, intestinal bypass or stoma formation are often needed and associated with poor outcomes. During the last few months until death, the patient often requires intensive palliative care at a hospital, nursing home, hospice or home care setting. This translates into a significant disease burden.

In most patients with PMCRC, only palliative treatment options remain at time of diagnosis. Two decades ago, Sugarbaker and colleagues developed a locoregional treatment modality that combines cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).[6] Ever since, a large number of phase II and two phase III studies have showed an improved survival of CRS + HIPEC with or without systemic therapy in comparison with systemic therapy alone.[7-19] Nowadays, this treatment modality is increasingly used worldwide and offers the only chance of long-term survival or even cure in selected patients with PMCRC.[20-22] Theoretically, patients are suitable for CRS + HIPEC if they have a good clinical condition, limited peritoneal disease, and no evidence of distant metastases on abdominal and thoracic CT-scan.

1.2 Standard of care

1.2.1 CRS + HIPEC

According to the Dutch guideline for treatment of colorectal cancer, patients with PMCRC are candidate for CRS + HIPEC if:

- Peritoneal dissemination does not exceed 5 out of 7 defined abdominal regions.
- There are no distant metastases detected by abdominal/thoracic CT scan.

In clinical practice, the abdominal region score is nowadays replaced by the more reliable and informative Peritoneal Cancer Index (PCI) score (***Figure 1***). Patients with a PCI score ≤20 are potential candidates for CRS + HIPEC. In the Netherlands, CRS + HIPEC is performed by a median laparotomy form xyphoid to the pubic bone, with careful visual and manual inspection of the abdominal cavity. If technically possible, resection of all macroscopically visible tumour is accomplished by performing both visceral and peritoneal resections, which is referred to as complete cytoreduction, or CC-0 (***Figure 2***). Residual tumour after CRS is classified as CC-1 or CC-2 depending on the thickness of remnant lesions of ≤2.5 mm or >2.5 mm, respectively. If a CC-0 or CC-1 is achieved, HIPEC is perfused through the abdominal cavity. If a CC-2 or CC-3 remains, HIPEC is not administered and palliative care will be offered to the patient. Analysis of the Dutch CRS + HIPEC experience revealed a median hospital stay of 16 days (95% CI 13-22) after the CRS + HIPEC procedure.[23] Major morbidity was present in 33% of the patients, of which anastomotic leakage, abscess and fistula were the most commonly observed. Postoperative mortality rate was 3%.

1.2.2 Perioperative systemic therapy

Perioperative systemic therapy, either neoadjuvant or adjuvant, is not standard of care for patients who undergo CRS + HIPEC for PMCRC in the Netherlands. The Dutch guideline states that adjuvant

systemic therapy could be considered, whereas no recommendations on the use of neoadjuvant systemic therapy are provided.[24]

1.3 Motivation for intervention

1.3.1 Background

Conventional systemic treatment strategies for PMCRC traditionally resulted in disappointing overall survival.[4,5,25] However, improved overall survival of patients with PMCRC has been reported with modern chemotherapy and targeted agents[26-31], which is similar to findings in other entities of metastatic colorectal cancer.[32-35] Between 1995 and 2014, the increasing use of both systemic therapy and CRS + HIPEC doubled overall survival in patients with PMCRC in the Netherlands.[32,36,37] Furthermore, the multidisciplinary approach led to combined treatment strategies with the use of perioperative systemic therapy, either neoadjuvant or adjuvant, in patients who undergo CRS + HIPEC for PMCRC. However, in the absence of prospective evidence, there is a worldwide controversy on the timing, efficacy, and risks of systemic therapy in this setting.[38]

Therefore, a recently conducted systematic review evaluated the evidence on systemic therapy as adjunct to CRS + HIPEC for PMCRC, with respect to overall and postoperative complications.[39] In this review, studies were included if they reported on the influence of neoadjuvant, adjuvant, or perioperative systemic therapy on overall survival or postoperative complications in patients who underwent CRS + (H)IPEC for PMCRC. Studies were excluded if detailed information about systemic therapy regimens was not provided, if CRS was performed without (H)IPEC, or in case of peritoneal metastases of other primary malignancies. As a result, 13 observational studies were included, of which five studies investigated the association between neoadjuvant systemic therapy and overall survival (***Table 1***)[40-44], three studies analysed the effect of tumour response to neoadjuvant systemic therapy on overall survival (***Table 2***)[40,41,45], four studies assessed the association between adjuvant

systemic therapy and overall survival (***Table 3***)[46-49], and another five studies investigated the influence of neoadjuvant systemic therapy on major postoperative complications (***Table 4***).[42-44,50,51] Systemic chemotherapy regimens were classified as 'single agent chemotherapy' if they only consisted of 5-FU with or without leucovorin (LV), as 'combination chemotherapy' if they consisted of either 5-FU/LV or capecitabine with oxaliplatin (FOLFOX, CAPOX) or irinotecan (CAPIRI, FOLFIRI), or as 'combination chemotherapy with targeted therapy' if they consisted of combination chemotherapy with targeted agents such as bevacizumab, cetuximab or panitumumab. Based on findings of this systematic review, the rationale for perioperative systemic therapy, neoadjuvant and adjuvant, will be discussed in sections 1.3.2 and 1.3.3, respectively.

1.3.2 Neoadjuvant systemic therapy

Peritoneal metastases traditionally appeared to be less responsive to systemic therapy compared to systemic CRC liver or lung metastases.[52,53] This may possibly be due to a lack of vascularisation of peritoneal lesions, resulting in a lower penetration of systemic therapy.[54] However, major and even complete pathological responses to neoadjuvant systemic therapy have been reported in included studies in the review by Rovers *et al* (***Table 2***).[39,41,45] Besides this observation, other arguments that support the use of neoadjuvant systemic therapy are preoperative tumour downsizing, potential elimination of clinically undetectable systemic metastases, and prediction of biological behaviour and chemotherapy sensitivity of the tumour, enabling better patient selection for CRS + HIPEC. These potential benefits are supported by the findings of Ceelen *et al*, Passot *et al*, and Devilee *et al*, who all revealed a survival benefit of patients who received neoadjuvant systemic therapy (***Table 1***).[40,42,44] Interestingly, the study population of Devilee *et al* only consisted of patients with a stable or major/complete response to neoadjuvant systemic therapy (***Table 1***).[42,44] The high survival rates in this group support the potential use of response to neoadjuvant systemic therapy as a selection tool for CRS + HIPEC. Numerous other studies reported on the association between neoadjuvant systemic therapy and overall survival in patients undergoing CRS + HIPEC.[9,21,46,55-70] However, none of these

studies provided detailed information on neoadjuvant systemic therapy regimens, and some studies included patients with PM of different primary malignancies without providing subgroup analyses for PMCRC.[9,59,62,64,67-69] Therefore, results of these studies are difficult to interpret. The observational nature of all studies reporting on neoadjuvant systemic therapy and overall survival unavoidably resulted in selection bias. It is not clear from these studies which patients received neoadjuvant systemic therapy and for what reason, and whether they were consecutive series. As a result, baseline imbalance in disease extent and patient condition may have influenced survival results. Nothing is known about survival outcomes in patients who do not qualify for CRS + HIPEC due to disease progression while on neoadjuvant systemic therapy. To eliminate selection bias and baseline imbalances, a prospective intention-to-treat study should be performed, with randomisation of patients with potentially resectable PMCRC to neoadjuvant systemic therapy and CRS + HIPEC in one arm, and upfront CRS + HIPEC alone in the other arm. The positive effect of neoadjuvant systemic therapy in the majority of studies included in the review by Rovers *et al* supports such a study.[39]

With regard to targeted agents in the neoadjuvant setting, two studies (Ceelen *et al*; Passot *et al*) demonstrated a survival benefit of adding intravenous (IV) bevacizumab to combination chemotherapy regimens (***Table 1***).[41,42] This finding is supported by studies in patients with unresectable metastasised colorectal cancer.[71,72] Specifically for peritoneal disease, it should be mentioned that the inhibition of vascular endothelial growth factor (VEGF) by bevacizumab is known for its central role in tumour associated angiogenesis and formation of ascites.[73] Therefore, interference with VEGF may be an important aspect of new therapeutic strategies against PM.[74] Bevacizumab, an inhibitor of VEGF, is thought to lower the interstitial fluid pressure in the tumour by vascular normalisation, which may result in improved delivery of intraperitoneal chemotherapy.[75,76] Through these mechanisms, bevacizumab may result in downstaging of intraperitoneal tumour load, thereby possibly leading to improved outcome by increasing the likelihood of achieving a complete cytoreduction. These potential benefits have been confirmed by recent preclinical studies, in which

VEGF inhibitors reduced interstitial fluid pressure, increased intraperitoneal chemotherapy drug penetration, and reduced tumour growth and ascites.[77,78] A clinical study confirmed that neoadjuvant intravenous bevacizumab was associated with lower intraperitoneal VEGF levels during surgery, which was associated with improved survival in another clinical study.[79,80] The potential survival benefit of neoadjuvant systemic therapy with bevacizumab should be weighed against the probability of a higher postoperative complication rate after CRS + HIPEC. However, the majority of the studies included in the review by Rovers *et al,* as well as other studies not providing detailed information on neoadjuvant systemic therapy regimens, suggest that neoadjuvant systemic therapy does not increase the operative risks (***Table 4***).[42-44,51,81-94] By contrast, Eveno *et al* showed that addition of bevacizumab to systemic therapy may increase grade III-V postoperative complications in patients who undergo CRS + HIPEC for PMCRC (***Table 4***).[50] The anti-angiogenic effect of bevacizumab, together with its long half-life, may interfere with wound and anastomotic healing, as is shown in preclinical studies.[95-98] A recent clinical study demonstrated a higher postoperative complication rate in patients with low preoperative IV VEGF levels.[79] However, clinical studies did not demonstrate increased postoperative complications in patients receiving neoadjuvant intravenous bevacizumab for major cancer surgery, especially if a time to surgery of 5-6 weeks is respected.[99--111] In conclusion, addition of bevacizumab to neoadjuvant combination chemotherapy may result in improved oncological outcome, but there is no consensus on the safety of bevacizumab in patients undergoing CRS + HIPEC. Therefore, its potential benefit and safety should both be subject of a future prospective study.

The lack of evidence does not allow for definitive conclusion regarding neoadjuvant systemic therapy in this setting. Therefore, it is not considered standard of care in the Dutch guideline for the treatment of colorectal cancer. As a result, patients in the control arm of this study do not receive neoadjuvant systemic therapy. With all evidence taken into account, and all limitations kept in mind, there is a potential benefit of a neoadjuvant treatment strategy that includes neoadjuvant

combination chemotherapy with bevacizumab, whereas there is no consensus on its safety prior to CRS + HIPEC. Therefore, patients receive neoadjuvant combination chemotherapy with bevacizumab in the experimental arm of this study.

1.3.3 Adjuvant systemic therapy

In the review by Rovers *et al,* three observational studies (Glehen *et al*; Nikolic *et al*; Maillet *et al*) did not demonstrate a significant overall survival benefit for patients receiving adjuvant systemic therapy compared to patients that did not (***Table 3***).[47-49] The oldest and largest study by Glehen *et al* initially revealed a univariable and multivariable survival benefit for patients receiving adjuvant systemic therapy. [46] However, after exclusion of patients who died of postoperative complications, the authors could not demonstrate a significant survival benefit anymore. Many observational studies assessed the influence of adjuvant systemic therapy on overall survival in PMCRC patients who undergo CRS + (H)IPEC without providing information on systemic therapy regimens, showing both positive[40,42,55,56,63,112,113] and negative[21,57,66,68,114] results. These studies do not allow for any conclusions, since patients with postoperative mortality or morbidity were not excluded. This may have led to a selection bias, since patients in good clinical condition after surgery are more likely to receive adjuvant systemic therapy, while patients with major morbidity from surgery are less likely to receive adjuvant systemic therapy, and are known to have impaired overall survival.[115] The most recent study by Maillet *et al*, which was the only study that excluded postoperative deaths and used modern chemotherapy regimens did not show an overall survival benefit of adjuvant systemic therapy compared to surveillance only.[49] With regard to targeted agents in the adjuvant setting, several studies revealed no survival benefit of adjuvant targeted therapy in addition to combination chemotherapy after resection of stage III colon cancer and colorectal liver metastases.[116-119] Therefore, adjuvant targeted therapy should not be standard of care after CRS + HIPEC for PMCRC.

Despite the lack of evidence that supports the use of adjuvant systemic therapy, this has been standard of care for PMCRC patients ever since the results of the randomised study by Verwaal *et al*, in which adjuvant 5-fluorouracil was administered after CRS + HIPEC, were published.[7] However, this study was not designed to assess any benefit of adjuvant systemic therapy. Subsequently, adjuvant combination chemotherapy became standard of care in stage III CRC.[120-122], and administration of adjuvant combination chemotherapy was extrapolated to patients who undergo CRS + HIPEC for PMCRC. However, extrapolation of evidence in patients undergoing resection for early stage colorectal cancer to patients undergoing resection for colorectal cancer metastases is questionable. The results from observational studies in this systematic review (***Table 3***), as well as the fact that adjuvant systemic therapy is associated with morbidity and even mortality[120], strongly questions its position as standard of care after CRS + HIPEC. Taking these arguments together, the Dutch Peritoneal Oncology group recently (March, 2016) organised an expert meeting, in which it was concluded that adjuvant systemic therapy can no longer be considered as standard of care after CRS + HIPEC for PMCRC in the absence of high-quality evidence.

In the CAIRO5 study, patients with colorectal liver metastases who undergo surgery after response to neoadjuvant systemic therapy, receive perioperative systemic therapy for a total duration of 6 months, with the chemotherapy schedule being continued postoperatively according to the preoperative schedule.[123] In patients who respond to neoadjuvant treatment, adjuvant systemic therapy in the same regimen may be of value by treating systemic micro-metastases. In the few observational studies that showed a survival benefit for adjuvant systemic therapy after surgery for PMCRC all administered adjuvant systemic therapy to patients who responded to neoadjuvant systemic therapy.[42,55,56,112] Again, the evidence is hardly interpretable, but this observation supports the continuation of adjuvant combination chemotherapy in patients with PMCRC that responded or revealed stable disease upon neoadjuvant combination chemotherapy, if they are in sufficiently good condition.

Taken together, adjuvant systemic therapy should not be considered standard of care in all patients who undergo CRS + HIPEC for PMCRC, since high-quality evidence and clear recommendations in the Dutch guideline for colorectal cancer are not available. Therefore, the control group does not receive adjuvant systemic therapy. However, in patients who responded to neoadjuvant combination chemotherapy, adjuvant chemotherapy to a total of 6 months may be of benefit by treating systemic micro-metastases. Therefore, in the experimental arm, only patients with stable or responsive disease to neoadjuvant combination chemotherapy receive adjuvant systemic therapy, whereas patients with peritoneal disease progression but resectable disease receive surveillance. In the absence of literature that reveals a benefit of adjuvant targeted therapy, only adjuvant combination chemotherapy will be administered.

1.3.4 Motivation for this study

Unlike in potentially resectable colorectal liver metastases[32-35], the low quality evidence available in PMCRC still leads to a worldwide controversy on the indication, effectiveness, timing, and risks of perioperative systemic therapy in patients undergoing CRS + HIPEC for PMCRC, with countries and hospitals adopting different treatment strategies. Since overall survival of patients with PMCRC in the Netherlands has dramatically improved due to increasing use of both CRS + HIPEC and systemic therapy[36], it is now time to create consensus regarding combined treatment strategies. As explained in sections 1.3.2 and 1.3.3, a perioperative treatment strategy including neoadjuvant (+ adjuvant) combination chemotherapy with neoadjuvant bevacizumab suggests improved oncological outcome and better patient selection. Therefore, the present study will prospectively evaluate the potential beneficial effect of this treatment strategy.

1.3.5 Blood collection for future translational research purposes

To date, nothing is known about the mechanism of how peritoneal metastases respond to systemic therapy. Furthermore, it is still unknown how to measure response of peritoneal metastases to neoadjuvant systemic therapy. This study provides an exceptional and unique opportunity to study the effect of systemic therapy on peritoneal metastases on a translational level. Examples of questions that our research group want to answer are:

- Is there an effect of systemic therapy on peritoneal metastases? And, if yes:
- Is it possible to predict in which patients peritoneal metastases respond to systemic therapy?
- Is it possible to measure the effect/response? And how?
- Is it possible to measure the effect in an early phase of treatment?
- Is it possible to predict the effect before start of systemic treatment?

To answer these important questions in the future, it is essential to routinely collect blood at pre-specified timepoints in patients in the experimental arm as well as the control arm, who may serve as a comparator. It is of upmost importance that these blood collections are performed in such a way that they (1) are able to answer future translational research questions, and (2) do not lead to discomfort in the included patients. Therefore, we carefully chose the timepoints of additional blood collections. All blood collections are performed when a patient already undergoes a venapunction for baseline registration, study treatment, postoperative hospital stay after CRS + HIPEC, or follow-up.

Blood that is collected for translational research purposes is centrally stored in the laboratory of the Antoni van Leeuwenhoek Hospital, which provides financial support for the logistics of the central storage as well as the possibility to perform analyses (e.g. circulating tumour DNA).[124] Later, research proposals on these blood samples can be submitted to the CAIRO6 collaborative group. Then, additional funding is requested. The additional blood collections are described in more detail in section 3.5.5.

1.3.6 Tissue collection for future translational research purposes

Several clinical risk factors have already been identified for the prognosis after CRS + HIPEC. However, there are still patients with very early disease recurrence after CRS + HIPEC, which is undesirable given the intensity of the treatment. Other patients remain disease free for >5 years.

This is potentially explained by several molecular and genetic subtypes of colorectal cancer that have a strong influence on prognosis, thereby leading to prognostic heterogeneity.[125,126] Ideally, these histological and genetic factors are included in prognostic decision making models to predict prognosis and identify the best treatment for each individual patient with PMCRC.
To provide more insights in these molecular, genetic, and histological features, it is essential to routinely collect tissue of the primary tumour and peritoneal metastases at pre-specified timepoints in patients in the experimental arm as well as the control arm, who may serve as a comparator. With these tissues, future translational research questions may be answered in order to improve and personalize the treatment of PMCRC. Again, it is of upmost importance that this tissue collection does not lead to discomfort in included patients.

The pre-specified timepoints include:

1. Primary tumour tissue during primary tumour resection or during CRS + HIPEC;
2. Tissue collection during diagnostic laparoscopy before start of neoadjuvant treatment (experimental arm);
3. Tissue collection during CRS + HIPEC;
4. Tissue collection of recurrent disease after CRS + HIPEC;

Regarding bullet 1, approximately half of the patients are estimated to have their primary tumour in situ during CRS + HIPEC. In these patients, tissue collection of the primary tumour is part of the standard pathological procedure, thereby not leading to additional discomfort of the patient. In the other half, the primary tumour was removed before inclusion in the study. Primary tumour tissue of these patients is stored in the PALGA network or the 'Prospectief Landelijk CRC Cohort' (PLCRC) network. At inclusion, patients are asked for permission to collect their primary tumour tissue through these networks for future translational research purposes. If patients do not give permissions for this tissue collection, they can still participate in the study.

Regarding bullet 2, this diagnostic laparoscopy is outside the study protocol. It is performed in many, but not all patients (e.g. not in patients who underwent a recent laparotomy), to estimate whether their PMCRC is potentially eligible for CRS + HIPEC. Tissue collection during this laparoscopy is part of the standard pathological procedure, thereby not leading to additional discomfort of the patient. Since we aim to use the collected tissue for future translational research purposes within the CAIRO6 study population, patients have to give permission for this tissue collection. However, patients are asked for participation in the CAIRO6 study after this diagnostic laparoscopy. Therefore, not all

patients who undergo this diagnostic laparoscopy eventually decide to participate in the CAIRO6 study. Nevertheless, we decided to consider the tissue collection during diagnostic laparoscopy as 'related to the CAIRO6 study', even though it is before potential study inclusion. Therefore, we developed an additional patient information and informed consent form, which may be presented to patients before they undergo a diagnostic laparoscopy. This patient information only contains information about the tissue collection for future translational research purposes, while it contains only very little information on the CAIRO6 study, since we do not want to influence the voluntary decision of the patient about whether to participate in the CAIRO6 study after diagnostic laparoscopy.

Regarding bullet 3, this tissue collection is part of the standard pathological procedure during CRS + HIPEC, thereby not leading to additional discomfort of the patient. Regarding bullet 4, this tissue collection is only performed if it is indicated according to standard of care. No additional efforts are taken to collect tissue from recurrent disease outside standard of care, given the potential discomfort for the patient.

All collected tissue is stored at the pathology departments of the participating sites. Later, research proposals on these tissue samples can be submitted to the CAIRO6 collaborative group. Then, additional funding is requested and the tissue samples are sent for central pathology review. The additional tissue collections are described in more detail in section 3.5.6.

2. OBJECTIVES

2.1 Primary objective(s)

Primary objectives of the phase II study are the safety of neoadjuvant combination chemotherapy with bevacizumab, as well as the feasibility of randomisation. The primary objective of the subsequent phase III study is to compare overall survival of CRS + HIPEC with perioperative systemic therapy versus upfront CRS + HIPEC alone.

2.2 Secondary objectives

Secondary objectives of the phase II-III study are:

- To compare progression-free survival between CRS + HIPEC with perioperative systemic therapy versus upfront CRS + HIPEC alone;
- To compare procedure related characteristics of CRS + HIPEC after neoadjuvant systemic therapy vs. upfront CRS + HIPEC alone (i.e. blood loss, operating time, number of resections);
- To compare the PCI score (***Figure 1***) and completeness of cytoreduction (***Figure 2***) of CRS + HIPEC after neoadjuvant systemic therapy vs. upfront CRS + HIPEC;
- To compare minor and major postoperative complications of CRS + HIPEC after neoadjuvant systemic therapy vs. upfront CRS + HIPEC alone;
- To compare quality of life and cost-effectiveness of CRS + HIPEC with perioperative systemic therapy vs. upfront CRS + HIPEC alone;
- To determine the number of patients with disease progression, stable disease, and responsive disease upon neoadjuvant systemic therapy (experimental arm);
- To compare survival of patients with disease progression, stable disease, and responsive disease upon neoadjuvant systemic therapy (experimental arm);

- To determine systemic therapy-related morbidity and toxicity of perioperative systemic therapy (experimental arm);
- To routinely collect blood and tissue for future translational research purposes.

3. STUDY DESIGN

This study is a sequential phase II-III randomised controlled multicentre study conducted in the Netherlands, with an estimated inclusion period of 4-5 years and a follow-up of 5 years. The general flow chart of this study can be found in ***Figure 3.*** assessment schedules can be found in ***Table 5*** (experimental arm) and ***Table 6*** (control arm)***.*** The general flowchart and assessment schedule are globally explained in sections 3.1 to 3.5. The phase II-III design is further explained in section 3.6.

3.1 Adequate preoperative work-up

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

If a patient is referred to a HIPEC centre, the completeness of preoperative work-up is determined. Preoperative work-up consists of primary tumour histology, radiologic imaging to detect systemic metastases, and the assessment of the extent of peritoneal disease (PCI) and its potential resectability (CC score). Non-signet histology must be pathologically confirmed in peritoneal deposits or ascites. Regarding radiological findings, CT-imaging of both abdomen and thorax must be done no longer than 4 weeks prior to visit to the surgical outpatient clinic in the HIPEC centre. With regard to assessment of disease extent, criteria for an adequate PCI score during laparotomy or laparoscopy in the referral centre are:

- PCI score adequately determined according to ***Figure 1***, which includes exploration of all relevant areas (mesentery of the small bowel, right and left subdiaphragmatic space, lesser and greater omentum, right and left paracolic gutter, pelvic space including Douglas pouch, anterior abdominal wall). Furthermore, the potential resectability should be determined (CC-O or CC-1).

- PCI score determined not earlier than 3 weeks prior to visit to the surgical outpatient clinics in the HIPEC centre.

According to criteria described above, preoperative work-up will be judged at the surgical outpatient clinics in the HIPEC centre as complete or incomplete. In case of incomplete preoperative work-up regarding tumour histology, either the referral centre will be contacted by the treating physician for additional pathological information, or additional biopsies of peritoneal deposits or ascites will be done in the HIPEC centre. In case of incomplete radiologic imaging, CT-abdomen/CT-thorax will be performed in the HIPEC centre. In case of incomplete preoperative work-up regarding assessment of PCI and resectability, a diagnostic laparoscopy will be performed in the HIPEC centre, which is standard of care in the Netherlands. Ideally, a diagnostic laparoscopy is performed prior to potential inclusion in every patient. Unfortunately, this is not always possible, for example duo to a recent laparotomy. To keep the study pragmatic, the diagnostic laparoscopy was not included in the study protocol.

After complete preoperative work-up is performed, patients may be considered for inclusion:

- If they do not have signet ring cells in >50% of cells.
- If they do not have systemic metastases on CT-abdomen and CT-thorax.
- if they have a PCI score of ≤ 20.
- if (nearly) complete resection of all PMCRC seems possible (CC-0 or CC-1).
- if resection of PMCRC on the small bowel does not result in short bowel syndrome (< 1 m remaining length of small bowel).

3.2 Inclusion of patients

Eligibility of all potentially eligible patients must be discussed with the coordinating investigator prior to the informed consent and registration procedures. The coordinating investigator records all

communication regarding potentially eligible patients and takes responsibility for being reachable during office hours.

3.2.1 Informed consent procedure

All potential study candidates are written and orally informed by their treating physician or research nurse about the aims and rationale of the study, the possible adverse events, the procedures and possible hazards to which they are exposed, and the mechanism of treatment allocation. They are informed about the strict confidentiality of their patient 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. Patients are asked to give permission to provide their contact details (address, phone number, e-mail address) only to the coordinating investigator, and only in order to send quality of life and health care cost questionnaires with Research Manager (http://deresearchmanager.nl/nl/home/) or by mail (section 8.3.2). The paper-based study description contains contact details of the coordinating investigator, in case patients have further questions. After a sufficient period of time, patients are asked if they want to participate in the study. If patients want to participate, the written informed consent form must be signed in twofold and personally dated by both the patient and (preferably) the research nurse or the treating physician. Documented informed consent must be obtained for all patients included in the study before they are registered to the study.

As described in section 1.3.5, a separate informed consent procedure for tissue collection for future translational research purposes takes places before the diagnostic laparoscopy, which is outside the study protocol. This informed consent procedure is performed by the treating physician or research nurse. During this informed consent procedure, the patient will be written and orally informed about

the future translational research purpose of tissue collection during diagnostic laparoscopy. At this time, patients are only very briefly informed about the CAIRO6 study, since we do not want to influence the voluntary decision about whether to participate in the CAIRO6 study after diagnostic laparoscopy.

3.2.2 Randomisation, stratification, and treatment allocation.

Patients who signed informed consent are registered and randomised by the coordinating investigator. Randomisation is performed by a central automatic randomisation tool, with stratification for:

- PCI (<10 vs ≥10)
- Metachronous vs synchronous PMCRC
- Previous adjuvant systemic therapy: yes vs. no
- Intraperitoneal mitomycin C or oxaliplatin

Results of the randomisation and treatment assignment will be communicated to the treating physician and the coordinating investigator. The allocation is not blinded to the patient or outcome assessor. After randomisation and treatment allocation, the treating physician informs the patient about the arm he or she has been randomised to, and arranges an appointment with the medical oncologist (experimental arm), or plans CRS + HIPEC (control arm). Randomised patients are assigned a random subject number. A log of the assigned subject numbers is maintained by each site.

3.3 Patients randomised to the control arm

In the control arm, explorative laparotomy intentionally followed by CRS and HIPEC are performed preferably within 4 weeks but no longer than 6 weeks after randomisation. No perioperative systemic therapy, either neoadjuvant or adjuvant, is administered.

3.4 Patients randomised to the experimental arm

3.4.1 Neoadjuvant systemic therapy

A detailed flow-chart of patients randomised to the experimental arm is provided in ***Figure 4.*** In the experimental arm, patients are referred to the medical oncologist within 2 weeks, and combination chemotherapy plus bevacizumab starts within 4 weeks after randomisation. Counselling, policy and follow-up with regard to the neoadjuvant and adjuvant systemic therapy are performed by treating physicians in participating centres.

Neoadjuvant systemic therapy consists of four three-weekly cycles of CAPOX or six two-weekly cycles of FOLFOX with the addition of bevacizumab. These regimens are considered equally effective, but have different potential adverse events and require different logistics. Based on these differences, the treating physician decides which regimen is the most suitable for each individual patient. In case of (previous) unacceptable toxicity (physician's discretion) to oxaliplatin, neoadjuvant CAPOX or FOLFOX may be continued as FOLFIRI. Restaging with thoraco-abdominal CT-scan is performed after three or four cycles of CAPOX + bevacizumab or FOLFOX + bevacizumab, respectively. Subsequently, suitability for CRS + HIPEC is discussed in multidisciplinary team meetings in the HIPEC centres. Generally, suitability for CRS + HIPEC is assessed by applying in and exclusion criteria for participating in the study, which means:

- If a patient has progressive systemic disease (e.g. lung or liver metastases) upon neoadjuvant systemic therapy, and therefore does not qualify for CRS + HIPEC anymore, the best palliative treatment is offered according to the Dutch guideline.[24]
- If a patient has progressive peritoneal disease without progressive systemic disease, and complete cytoreduction is still considered feasible based on imaging, no further systemic therapy is administered, and explorative laparotomy intentionally followed by CRS and HIPEC (PCI ≤20, CC0/1 feasible) is performed as soon as the clinical condition of the patient allows the procedure, but not earlier than six weeks after the last day of administration of bevacizumab.
- If a patient has stable or responsive disease, neoadjuvant treatment is continued with either one cycle of CAPOX or 2 cycles of FOLFOX, both without bevacizumab. Explorative laparotomy intentionally followed by CRS and HIPEC is performed as soon as clinical condition allows, but not earlier than three weeks after the last day of the last cycle of either CAPOX or FOLFOX and 6 weeks after the last administration of bevacizumab. If clinical condition does not allow laparotomy at that time, laparotomy may be delayed and the time of delay must be registered.

3.4.2 Adjuvant systemic therapy

Only in patients with a CC0-1 cytoreduction, stable/responsive disease to neoadjuvant systemic therapy, and sufficiently good clinical condition, adjuvant combination chemotherapy is started preferably within 6, but not later than 12 weeks after CRS + HIPEC. The same chemotherapy schedule as the neoadjuvant regimen is administered, but without bevacizumab, thereby resulting in either four three-weekly cycles of CAPOX or six two-weekly cycles of FOLFOX. In case of unacceptable toxicity to oxaliplatin during adjuvant treatment, adjuvant FOLFOX or CAPOX may be continued as 5-FU or capecitabine monotherapy.

3.5 All patients

3.5.1 Baseline characteristics

Baseline tumour and patient characteristics are obtained in every patient. Primary tumour location and histology is registered according to the International Classification of Diseases for Oncology (ICD-O).[127] T-stage and N-stage are based on the TNM Classification of Malignant Tumours, v7.0.[128] In case the primary tumour is still in situ, clinical TNM stage is used for baseline registration, and pathological TNM staging is determined after CRS + HIPEC. If the primary tumour is removed in the referring hospital, pathological TNM stage will be used for baseline registration. If the referring hospital provided incomplete baseline data, the treating physician obtains necessary data from the referring hospital. Blood of all patients is drawn at baseline, which is according to standard care.

3.5.2 CRS + HIPEC and postoperative period

After a median laparotomy, PCI score and achievability of complete cytoreduction are determined by the operating surgeon after careful inspection of the abdominal cavity. In case of unresectable disease, no surgical procedure other than with palliative intent, if indicated, is performed. In case of resectable disease, cytoreductive surgery with removal of all visible tumour nodules and resection of involved organs, is performed. If a complete cytoreduction, defined as CC0-1, is achieved, HIPEC is performed. If there is an incomplete cytoreduction (CC-2), no HIPEC is performed. In all patients who undergo explorative laparotomy, the PCI-score, performed visceral/peritoneal resections, completeness of cytoreduction score, operating time and blood loss are documented by the treating physician directly after the procedure. After completion of CRS + HIPEC, all postoperative complications, reoperation rates, ICU stay and hospital stay are registered at 3 months follow-up.

3.5.3 Follow-up

Patients are seen on routine oncological follow-up at 3, 6, 12, 18, 24, 36, 48, and 60 months postoperatively, which is according to standard of care.[24] According to standard care, a thoraco-abdominal CT-scan is performed at 6 12, 24, 36, 48 and 60 months follow-up. Disease and survival status are registered during follow-up. Patients with progressive unresectable systemic disease after CT-restaging are also seen on routine oncological follow-up at 3, 6, 12, 18, 24, 36, 48, and 60 months after CT-restaging.

3.5.4 Quality of life and health care costs

Patients are asked to fill in EQ-5D-5L, EORTC QLQ-C30, CR-29, iMTA Medical Consumption Questionnaire, and iMTA Productivity Costs Questionnaire: at inclusion and 3, 6, 12, 24, 36, and 60 months after CRS + HIPEC or CT-restaging (in case of progressive systemic disease upon neoadjuvant systemic therapy).

3.5.5 Blood sample collection

All additional blood samples for translational research purposes are collected during a venapunction that patients already have to undergo. The additional blood collection includes two additional Streck® tubes (10 ml each) and one additional EDTA® tube (10 ml), which are not harmful to patients. In the experimental arm, the timepoints of this additional blood collection are: after inclusion, at start of the second cycle of neoadjuvant systemic therapy, one day prior to CRS + HIPEC, 7 days after CRS + HIPEC, at the start of the second cycle of adjuvant systemic therapy, and during all follow-up appointments until disease recurrence. In the control arm, these moments are: after inclusion, one day prior to CRS + HIPEC, 7 days after CRS + HIPEC, and during all follow-up appointments until disease recurrence. According to already existing logistics in the CAIRO5 study, blood is sent to the laboratory of the Antoni van Leeuwenhoek Hospital, where it is processed and stored for future analyses.

3.5.6 Tissue sample collection

To analyse DNA, RNA, and proteins in future translational research, both paraffin embedded and snap frozen tissue is necessary. Tissue samples may be collected during diagnostic laparoscopy, during CRS + HIPEC, and during disease recurrence. Tissue samples are stored at the pathology department of the participating hospitals. Later, central pathology review is performed on collected tissues.

Diagnostic laparoscopy

During diagnostic laparoscopy, the aim is to at least biopsy three peritoneal laesions, preferably the largest ones. Of each laesion, the aims is that one pieces is snap frozen and one piece is embedded in paraffin. Afterwards, the remaining laesion is marked with a suture and its size is measured and documented.

CRS + HIPEC

During CRS + HIPEC, the marked laesion(s) is/are measured in size, and thereafter removed. Again, the aim is that one piece of each laesion is snap frozen and one piece is embedded in paraffin. In case the primary tumour is still in situ during CRS + HIPEC (estimated: 50%), this goes directly to the pathology lab, in which the aim is that three pieces of tumour tissue are snap frozen and three are embedded in paraffin.

Recurrent disease

In approximately 40% of cases of recurrent disease, the recurrence is suspected by an increase in tumour markers without a clearly visible or accessible laesion on imaging techniques. In these patients, it is undesirable to obtain tumour tissue. Therefore, this will not be routinely collected in these patients. However, if recurrent disease is diagnosed during surgery, tissue samples of the recurrent tumour are collected. Again, the aim is that one piece of this biopsy is snap frozen and one piece is embedded in paraffin.

3.5.7 Assessment schedule

An assessment schedule of the experimental arm is demonstrated in ***Table 5.*** An assessment schedule of the control arm is demonstrated in **Table 6.**

3.6 Sequential Phase II – III study design

The first 80 patients will be included as part of an initial randomised phase II study. In these patients, feasibility of randomisation and safety of neoadjuvant combination chemotherapy with bevacizumab is investigated. Randomisation is considered feasible if 80 patients one year after the start of accrual of the last participating HIPEC centre are included. The phase II study is defined as unsafe if >7 patients more suffer major postoperative complications (Clavien-Dindo grade III-V[129]) in the experimental arm compared to the control arm, or if >20/40 patients in the experimental arm do not undergo CRS + HIPEC due to disease progression or impaired clinical condition.

When the initial 80 patients of the phase II study are included, inclusion is stopped until all patients completed their 3 months follow-up. Subsequently, safety and feasibility analyses are performed. If feasibility and safety criteria of the phase II study have been met, the study continues as a phase III study in which an additional 278 patients will be included as described above. If randomisation is not feasible and/or neoadjuvant combination chemotherapy/bevacizumab is associated with unacceptable rates of postoperative complications or disease progression according to the predefined criteria, the included patients enter regular follow-up and further inclusion is stopped.

In the phase II study, neoadjuvant and adjuvant systemic therapy, as well as CRS + HIPEC and follow-up take place in the 9 participating HIPEC centres. In the subsequent phase III study, neoadjuvant systemic therapy, adjuvant systemic therapy and follow-up may also take place in referring hospitals in the Netherlands, whereas CRS + HIPEC and the postoperative hospital admission will of course still be performed in a HIPEC centre.

The sequential phase II – III study design has previously been used with success in the FOXTROT study, which investigated the feasibility of preoperative chemotherapy for locally advanced colon cancer in a phase II study before proceeding to the phase III study.[130]

4. STUDY POPULATION

4.1 Population

All patients with non-signet cell synchronous or metachronous PMCRC, without systemic metastases, who are candidate for CRS + HIPEC (PCI score ≤20, CC0/1 seems feasible), are considered for inclusion. These patients may be diagnosed with PMCRC in or referred to one of the 9 HIPEC centres in the Netherlands. In 2016, 420 patients received CRS + HIPEC in the Netherlands, which may increase in the next few years. Synchronous and metachronous PMCRC are defined as a first diagnosis of PMCRC earlier or later than 6 months after initial diagnosis with CRC, respectively. PMCRC should be diagnosed either by histologic or cytological confirmation after laparotomy/laparoscopy or cytological confirmation obtained from CT proven malignant ascites. The primary tumour may be previously resected or still be in place.

4.2 Inclusion criteria

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

- PCI score ≤20 and CC-0 or CC-1 achievable, determined as described in section 3.1.
- Histological confirmation of colorectal cancer with non-signet histology in peritoneal deposits or ascites.
- 18 years or older.
- WHO performance score 0-1.
- Adequate clinical condition to undergo CRS + HIPEC and neoadjuvant combination chemotherapy with bevacizumab within 4 weeks after randomisation.
- Adequate organ functions: normal bone marrow function (Hb ≥6.0 mmol/L, absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L), renal function (serum

creatinine ≤1.5 x ULN and creatinine clearance [Cockroft formula] ≥30 ml/min), determined <3 months prior to randomisation.

- No known bleeding diathesis or coagulopathy.
- Written informed consent.
- Able and willing to adhere to follow-up.

4.3 Exclusion criteria

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

- Signet ring cell histology (>50% of the cells have signet ring cell histology) of the primary tumour.
- Systemic metastases (i.e. liver, lung)
- Known pregnancy or lactation, wish for pregnancy, and not willing to use contraceptives.
- Known unstable or uncompensated respiratory or cardiac disease.
- Serious active infections.
- Adjuvant chemotherapy after primary resection of colorectal cancer within 6 months prior to randomisation.
- Any condition not allowing the safe administration of the planned systemic treatment (bevacizumab, 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan).
- Stomatitis, ulceration in the mouth or gastrointestinal tract.
- Severe diarrhoea.
- Known pernicious anaemia or other anaemias due to vitamin B12 deficiency.
- Known previous peripheral sensory neuropathy with functional impairment after previous use of oxaliplatin.

- Impaired liver function (serum bilirubin ≤2 x ULN, serum transaminases ≤5 x ULN), assessment only if indicated.

4.4 Sample size calculation phase II - III study

If feasibility and safety criteria of the phase II study have been met, the total inclusion of the total phase II-III study is based on a superiority design for the primary endpoint. Nowadays, the expected 3-year overall survival after CRS + HIPEC alone is 50%.[44] It is our hypothesis that the experimental treatment results in a 15% absolute improvement of 3-year overall survival if analysed according to the intention-to-treat principle. With a two-sided alpha of 0.05, a sample size of 179 patients per group, or 358 patients in total, is needed for a log-rank test to detect such difference with a power of 80%. A drop-out rate of 5% is expected and included in this sample size. The Data Safety Monitoring Board and the METC will be notified if the drop-out rate exceeds this percentage.

The total number of 80 patients in the phase II study is primarily based on an anticipated total inclusion period of 4 years for the whole study group. If we have proven to be able to include 80 one year after all participating centres started accrual, it is likely that we are able to finish inclusion in the 3 years thereafter, considering that inclusion rates often slightly improve beyond the first year.

5. TREATMENT OF SUBJECTS

An assessment schedule is provided in ***Table 5***. A flow-chart with a detailed overview of different systemic therapy regimens, and preferred regimens in case of toxicity, is provided in ***Figure 5***.

5.1 Neoadjuvant systemic therapy

5.1.1 CAPOX + Bevacizumab

CAPOX consists of capecitabine and oxaliplatin. CAPOX + bevacizumab is administered according to standard schedule:

- Day 1: Administration of bevacizumab (7.5 mg/kg in 15-30 minutes IV) followed by oxaliplatin (130 mg/m^2 in 120 minutes IV).
- Day 1-14: Administration of capecitabine (1000 mg/m^2, twice daily, orally).
- Day 15 - 21: Rest days.

This regimen is initially administered for a total of 3 cycles as neoadjuvant systemic therapy. In case of stable disease or response after 3 cycles, a 4th cycle of neoadjuvant CAPOX without bevacizumab is administered. In case of unacceptable (previous) toxicity (physician's discretion) to oxaliplatin, neoadjuvant CAPOX may be continued as neoadjuvant FOLFIRI (section 5.1.2).

5.1.2 FOLFOX + Bevacizumab

FOLFOX consists of 5-FU, leucovorin and oxaliplatin. FOLFOX + bevacizumab is administered according to the following schedule:

- Day 1: bevacizumab (5 mg/kg in 15-30 minutes IV), followed by oxaliplatin (85 mg/m^2 IV) together with leucovorin (400 mg/m^2 in 120 minutes IV), followed by bolus 5-FU (400 mg/m^2 within 4 minutes IV), followed by continuous infusion of 5-fluorouracil (2400 mg/m^2) in 46 hours.
- Day 3 - 14: Rest days.

This regimen is initially administered for a total of 4 cycles as neoadjuvant systemic therapy. In case of stable disease or response after 4 cycles, a 5th and 6th cycle of neoadjuvant FOLFOX without bevacizumab is administered. In patients with unacceptable (previous) toxicity (physician's discretion) to oxaliplatin, a neoadjuvant regimen containing FOLFIRI + bevacizumab may be used according to the following schedule:

- Day 1: bevacizumab (5 mg/kg in 15-30 minutes IV), followed by irinotecan (180 mg/m^2 in 60 minutes IV) together with leucovorin (400 mg/m^2 in 120 minutes IV), followed by bolus 5FU (400 mg/m^2 within 4 minutes IV), followed by continuous infusion of 5-fluorouracil (2400 mg/m^2) in 46 hours.
- Day 3 – 14: Rest days.

This regimen is initially administered for a total of 4 cycles as neoadjuvant systemic therapy. In case of stable or responsive disease after 4 cycles, a 5th and 6th cycle of neoadjuvant FOLFIRI without bevacizumab is administered.

5.2 CRS + HIPEC

Patients with stable or responsive disease while on neoadjuvant systemic therapy will be scheduled for this procedure not earlier than three weeks after the last day of the last cycle of neoadjuvant combination chemotherapy and not earlier than 6 weeks after the last day of administration of

bevacizumab. Patients with progressive peritoneal disease upon neoadjuvant systemic therapy are scheduled for this procedure not earlier than 6 weeks after the last day of administration of bevacizumab.

CRS + HIPEC is performed as outlined below:

- Median laparotomy from xyphoid process to pubic bone.
- Visual and manual abdominal exploration and assessment of the PCI score.
- Removal of all visible tumour in the abdominal cavity (CC-0), or debulking with a residual tumour thickness of less than 2.5 mm (CC-1). If necessary, involved organs such as bowel segments, uterus, ovaries, stomach or spleen are resected together with omentum (always) and involved parts of the peritoneum.
- If a CC-0 or a CC-1 is achieved, HIPEC will be performed with mitomycin C or oxaliplatin, according to the preference of the treating hospital.
- Only in case of HIPEC with oxaliplatin, 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) are administered intravenously prior to HIPEC to potentiate oxaliplatin activity.
- The abdominal wall is then retracted using a Colosseum approach with positioning of inflow and outflow catheters in the abdominal cavity.
- The abdominal cavity is filled with Dianeal© peritoneal dialysis solution (Baxter, peritoneal dialysis solutions, USA; Glucose 1.36 mg/100ml) and the solution is heated to 42°C with a minimal flow of 2L/min.
- In case a hospital uses oxaliplatin, oxaliplatin at a dose of 460 mg/m^2 is added to the circuit in a single dose in 30 minutes. In case a hospital uses mitomycin C, mitomycin C at a dose of 35mg/m^2 is added to the circuit and administered in three doses: 50% at the start of perfusion, 25% after 30 minutes and 25% after 60 minutes, after which another 30 minutes of perfusion follow. In both chemotherapeutic agents, the abdomen is agitated throughout

the infusion to allow homogeneous exposure of the peritoneal surfaces to the heated chemotherapy.

- After completion of perfusion, the perfusion fluids are aspirated and collected together with all used materials following the local protocol of chemotherapy waste collection and disposal.
- Reconstruction with bowel anastomoses if indicated.
- Placement of abdominal drains according to local treatment protocol.
- Closure of the abdomen.
- Formation of ostomy if indicated.
- All body excretions are collected as chemotherapy-contaminated as long as the patient is admitted, for up to 48 hours (mitomycin C) or 5 days (oxaliplatin).

5.3 Adjuvant systemic therapy

Adjuvant combination chemotherapy is administered at the same dose and schedule as the neoadjuvant treatment (section 5.1), but without bevacizumab. CAPOX and FOLFOX are administered in four 3- weekly cycles and six 2-weekly cycles, respectively. In case of unacceptable toxicity to oxaliplatin, adjuvant systemic therapy may be continued according to medical oncologist's discretion as monotherapy with 5-fluorouracil or capecitabine in the same schedules as described in section 5.1, but without oxaliplatin.

5.4 Handling of toxicity, dose modifications

Toxicity is graded according to NCICTCAE v4.0. Dose modifications and handling of toxicity should be performed according to local treatment protocols. Best supportive care for treatment-related symptoms (i.e. nausea) is offered by the treating medical oncologist according to local treatment protocols to all patients in this study.

6. INVESTIGATIONAL PRODUCT(S)

6.1 Name and description of investigational products

Investigational products used in this study are outlined below:

- 5-fluorouracil (synonyms: 5-FU, fluorouracil, L01BC02)
- Leucovorin (synonyms: calcium folinate, V03AF03)
- Capecitabine (synonyms: Xeloda, L01BC06)
- Oxaliplatin (synonyms: L01XA03)
- Irinotecan (synonyms: L01XX19)
- Bevacizumab (synonyms: Avastin, L01XC07)

6.2 Summary of findings from (clinical) studies and potential risks and benefits.

All investigational products are registered and widely used for the treatment of metastatic colorectal cancer. All relevant findings from (non-)clinical studies can be found in the Summary of Product Characteristics (SPC) and the patient instructions:

- 5-fluorouracil: http://db.cbg-meb.nl/IB-teksten/h22303.pdf and http://db.cbg-meb.nl/Bijsluiters/h22303.pdf
- Leucovorin: http://db.cbg-meb.nl/IB-teksten/h15828.pdf and http://db.cbg-meb.nl/Bijsluiters/h15828.pdf
- Capecitabine: http://db.cbg-meb.nl/IB-teksten/h109444.pdf and http://db.cbg-meb.nl/Bijsluiters/h109444.pdf
- Oxaliplatin: http://db.cbg-meb.nl/IB-teksten/h32774.pdf and http://db.cbg-meb.nl/Bijsluiters/h32774.pdf

- Irinotecan: http://db.cbg-meb.nl/IB-teksten/h22820.pdf and http://db.cbg-meb.nl/Bijsluiters/h22820.pdf
- Bevacizumab: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf

6.3 Route of administration and dosage

The routes of administration and dosages of the investigational products are provided in section 5.1 and 5.3.

6.4 Labelling

Since CAPOX/FOLFOX + bevacizumab are standard of care for stage IV CRC (also including PMCRC) according to the Dutch guideline,[24] these products are considered insured care and not considered study medication. Therefore, the investigational products are not labelled. The pharmacy prepares the investigational products regularly and the preparation sources are retained.

7. NON INVESTIGATIONAL PRODUCTS

CRS + HIPEC is the non-investigational product used in this study. This non investigational product is standard of care for patients with resectable PMCRC without distant metastases.[24] CRS + HIPEC will be performed as described in section 5.2.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameters

The primary endpoints of the phase II study are:

- The number of randomised patients one year after the start of accrual at the last participating HIPEC centre.
- The number of patients who undergo CRS + HIPEC.
- Major postoperative complications (Clavien-Dindo Grade III-V)

The primary endpoint of the phase III study is 3-year overall survival measured from date of randomisation.

8.1.2 Secondary study parameters

The secondary endpoint of the phase II study are systemic therapy related toxicity according to NCICTCAE v4.0 (grade II-V) and minor postoperative complications (Clavien-Dindo Grade II).

Secondary endpoints of the phase III study are:

- Median and 5-year overall survival measured from date of randomisation.
- Median, 1-year and 3-year progression-free survival measured from date of randomisation.
- Procedure related characteristics of CRS + HIPEC (i.e. operating time, blood loss, PCI score, CC-score)
- In-hospital, 30-day, and 90-day major postoperative complications (Clavien-Dindo ≥3).
- Hospital stay.
- Quality of life.

- Cost-effectiveness
- % of patients planned and able to complete the neoadjuvant systemic treatment, and reasons for not completing and/or dose reduction (experimental arm).
- % of patients planned and able to complete the adjuvant systemic treatment, and reasons for not completing and/or dose reduction (experimental arm).
- Severe systemic therapy related toxicity of neoadjuvant and adjuvant systemic therapy, defined as NCICTCA v4.0 grade III-V (experimental arm).
- Number of patients with disease progression, stable disease, or responsive disease to neoadjuvant systemic therapy (experimental arm).

8.2 Randomisation, stratification, and treatment allocation

The procedures of randomisation, stratification, and treatment allocation are described in section 3.2.

8.3 Study procedures

8.3.1 Primary study parameters

In the phase II study, the number of randomised patients is determined 1 year after the start of accrual at the last participating centre. Major postoperative complications are registered in the patient file by local treating physicians, and registered in the CRF by local data managers according to Clavien-Dindo (Grade III-V).

In the phase III study, survival status is registered by treating physicians in the patient file, and registered by local data managers in the CRF.

8.3.2 Secondary study parameters

In the phase II study, minor postoperative complications are registered according to Clavien-Dindo (Grade II) at 90 days postoperatively. Information on toxicity (NCICTCAE v4.0 grade ≥2) of perioperative systemic therapy is registered in the patient file by the treating physician, and registered by the local data manager in the CRF after CT-restaging or, in case of stable or responsive disease to neoadjuvant systemic therapy, prior to CRS + HIPEC. Information on toxicity (NCICTCAE v4.0 grade ≥2) of adjuvant systemic therapy is registered in the patient file by the treating physician, and registered by the local data manager in the CRF.

Study procedures of secondary outcome parameters of the phase III study are outlined below:

- Median, 1-year and 3-year progression-free survival.

  Disease progression is measured from randomisation and defined as 1) date of confirmed disease progression upon neoadjuvant systemic therapy, 2) date of surgery in case of unresectable disease after explorative laparotomy or CC-2 disease after cytoreductive surgery, or 3) date of recurrence in case of recurrent disease after CRS + HIPEC. Disease recurrence and patterns of recurrence are registered by the treating physician in the patient file during routine oncological follow-up at 3, 6, 12, 18, 24, 36, 48, and 60 months after CRS/HIPEC, and registered in the CRF by the local data manager.

- Procedure related characteristics of CRS + HIPEC.

  Directly after CRS + HIPEC, information with respect to procedure related characteristics (i.e. intraoperative blood, operation time, etcetera) is registered by the operating surgeon or surgical registrar in the patient file, and registered by the local datamanager in the CRF.

- PCI score.

  The PCI-score is determined by the operating surgeon directly after explorative laparotomy, and documented in the patient file directly after CRS. Subsequently, the local datamanager documents the PCI in the CRF.

- Completeness of cytoreduction score (CC-score).

  The CC-score is determined and documented in the patient file by the operating surgeon directly after CRS, and recorded in the CRF by the local datamanager. The CC-score is classified as CC-0 (no residual tumour), CC-1 (residual tumour <2.5mm), CC-2 (residual tumour >2.5mm).

- In-hospital, 30-day and 90-day major postoperative complications (Clavien-Dindo ≥3).

  Major postoperative complications (Clavien-Dindo Grade III-V) are registered at 3 months follow-up by the treating physician in the patient file, and registered in the CRF by the local data manager. Between CRS + HIPEC and 3 months postoperatively, all medical or surgical interventions and/or reoperations or any procedure to treat a major postoperative complication are collected.

- In hospital mortality, 30-day mortality, and 90-day mortality.

  Postoperative mortality is registered at 3 months follow-up by the treating physician in the patient file, and registered in the CRF by the local data manager.

- ICU stay, and hospital stay.

  Hospital stay is registered at 3 months follow up, and if the patient is still admitted, again at 6 and up to 12 months follow-up. All hospital admission days will be added up.

- Quality of life.

  Generic and cancer-specific quality of life assessments are assessed with EQ-5D-5L, EORTC QLQ-C30 and CR-29 questionnaires: at inclusion, and at 3, 6, 12, 24, 36, and 60 months follow-up. According to the patients preference, the questionnaires are sent by the coordinating investigator either online or to the patients' home addresses accompanied by a return envelope provided with postage stamps and the address of the Catharina Ziekenhuis. The Research Manager (http://deresearchmanager.nl/nl/home/), an ISO 27001 compliant secured web-based portal, is used by the coordinating investigator for the online questionnaires. Patients have to register with a unique token and verification of their e-mailaddress. Subsequently, patients are able to fill in the questionnaire in the Research Manager environment in order to avoid e-mails with patient data.

- Cost-effectiveness.

  For the purpose of economic evaluation, the iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire, adapted to the current study setting and target population, are used at 3, 6, 12, 24, 36 and 60 months during follow-up. According to the patients preference, the questionnaires are sent by the coordinating investigator either online or to the patients' home addresses accompanied by a return envelope provided with postage stamps and the address of the Catharina Ziekenhuis. The Research Manager (http://deresearchmanager.nl/nl/home/), an ISO 27001 compliant secured web-based portal, will be used by the coordinating investigator for the online questionnaires. Patients have to register with a unique token and verification of their e-mailaddress. Subsequently, patients are able to fill in the questionnaire in the Research Manager environment in order to avoid e-mails with patient data.

- % of patients able to complete their full neoadjuvant treatment, and reasons for not completing and/or dose reduction (experimental arm).

  Information on completeness of neoadjuvant systemic therapy, and reasons for not completing and/or dose reduction, are registered by the treating physician in the patient file in the CRF by the local data manager.

- % of patients able to complete their full adjuvant treatment, and reasons for not completing and/or dose reduction (experimental arm).

  Information on completeness of adjuvant systemic therapy, and reasons for not completing and/or dose reduction, are registered by the treating physician in the patient file at 6 months follow-up, and registered by the local datamanager in the CRF.

- Severe systemic therapy related toxicity of neoadjuvant combination chemotherapy with bevacizumab (NCICTCAE v4.0 grade ≥3) (experimental arm).

  Information on toxicity of neoadjuvant combination chemotherapy/bevacizumab (NCICTCAE v4.0 grade ≥3) is registered by the treating physician in the patient file during neoadjuvant treatment, and in the CRF by the local data manager.

- Severe systemic therapy related toxicity of adjuvant combination chemotherapy (NCICTCAE v4.0 grade ≥3) (experimental arm).

  Information on toxicity of adjuvant combination chemotherapy (NCICTCAE v4.0 grade ≥3) is registered by the treating physician in the patient file at 6 months follow-up, and registered by the local datamanager in the CRF.

- Number of patients with disease progression, stable disease, or responsive disease to neoadjuvant combination chemotherapy/bevacizumab (experimental arm).

Based on standard of care, CT-restaging is performed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[131] Morphological response is divided into four groups: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The number and location of locoregional and systemic metastases is documented.

8.3.3 Other study parameters

Age, gender, WHO performance status, ASA score, tumour topography, tumour histology, TNM stage, and tumour differentiation are all documented during registration. Tumour location and histology are registered according to the International Classification of Diseases for Oncology (ICD-O).[127] T-stage and N-stage are based on the TNM Classification of Malignant Tumours, v7.0.[133] In case of missing baseline characteristics, referring hospitals may be contacted by the treating physician to obtain the additional necessary information. In case the primary tumour is still in situ, clinical tumour characteristics (i.e. TNM) are used for baseline registration, and pathological tumour characteristics (i.e. TNM) are determined after CRS + HIPEC.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time and for any reason if they wish to do so without any consequences. Reason for withdrawal or early termination are documented and no further study treatments are performed after the subject has withdrawn. The investigators can decide to withdraw a subject from the study intervention if he/she fails to comply with the study requirements or if the investigator feels it is in the best interest of the subject to discontinue participation. Follow-up of these patients will be completed according to the protocol.

8.5 Replacement of individual subjects after withdrawal

Potential withdrawal of an individual subject is included in the drop-out rate of 5%.

8.6 Follow-up of subjects withdrawn from treatment

Patients who are randomised and not able to receive the study treatment according to this study protocol receive follow-up according to the protocol, and are analysed according to the intention-to-treat principle.

8.7 Premature termination of the study

This study may be prematurely terminated for the following reasons. First, the study may be terminated if less than 80 patients are randomised in the phase II study one year after the last participating centre started accrual. If accrual of 80 patients was successful, there are two reasons for terminating the study after 80 patients completed their 3 months follow-up: 1) if less than 50% (20/40) of included patients in the experimental arm proceed to CRS + HIPEC due to bad clinical condition, systemic toxicity, or disease progression 2) if >7 patients more suffer major morbidity (Clavien-Dindo grade III-V) in the experimental arm compared to the control arm.

During the subsequent phase III study, the study will be terminated, after 160 and 240 patients completed their 3 months follow-up (inclusion is not stopped), if:

- a difference of major postoperative complication rate (Clavien-Dindo grade III-V) of >20% more is observed in favour of either the experimental arm or the control arm.
- <50% of the patients in the experimental arm received CRS + HIPEC.

This makes it impossible to recruit new patients or to continue the treatment of patients already recruited for medical or ethical reasons. The clinical investigation in an individual patient will be terminated in case of:

1. Insufficient compliance.
2. A patient's request.
3. Investigators request because of the onset of life-threatening adverse events.
4. Changes in health status incompatible with continued participation in the clinical investigation, as judged by the clinical investigator.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject 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 will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The coordinating investigator will take care that all subjects 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 subject during the study, whether or not related to systemic therapy or CRS + HIPEC. Therefore, all AEs are reported in the CRF. In the phase II study, all AEs with a severity degree of ≥2 are recorded. In the phase III study, all AEs with a severity degree of ≥3 are recorded. The time window for AE reporting is from randomisation until 30 days after the last administration of systemic therapy or 90 days after CRS + HIPEC.

9.2.2 Serious adverse events (SAEs)

A serious adverse event 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.

The hospital admission prior to CRS + HIPEC or a hospital admission for administration of systemic therapy will not be considered as serious adverse event. Local investigators report all SAEs to the coordinating investigator without undue delay and within 24 hours after obtaining knowledge of the events. The coordinating investigator reports the 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 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 the serious adverse events. The time window for SAE reporting is from randomisation until 30 days after the last administration of systemic therapy or 90 days after CRS + HIPEC.

A predefined list of (S)AEs that is reported every six months instead of individually using the CCMO-module *ToetsingOnline* is outlined below:

- (S)AE's related to and occurring while patients are on combination chemotherapy and/or bevacizumab.
- (S)AE's occurring within 90 days after CRS + HIPEC.
- (S)AE's that are classified by the steering group as 'not related to the trial'.

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 perioperative systemic therapy, 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 the Summary of Product Characteristics (SPC).

Local investigators report all SUSARs to the coordinating investigator. The coordinating investigator reports the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical study that was assessed by the METC;
- SUSARs that have arisen in other clinical studies of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical study 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 *ToetsingOnline* is sufficient as notification to the competent authority. The coordinating investigator reports 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 sponsor has 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. Information on all SUSARs with a severity degree of ≥2 (phase II) or ≥3 (phase III) is recorded in the CRF.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the coordinating investigator submits, 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 subjects, 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

The clinical course of each event is followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause. (S)AEs which occur between CRS + HIPEC and 90 days postoperatively (control arm) are followed up to resolution to determine the final outcome. (S)AEs which occur between randomisation and the 1 month after the last day of adjuvant systemic therapy (experimental arm) are followed up to resolution to determine the final outcome. 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 Safety Monitoring Board (DSMB)

A central DSMB consisting of an experienced medical oncologist, surgeon, and a statistician who are not involved in the study is installed to monitor quality and patient safety in this multicentre study with regard to patient accrual, safety of neoadjuvant systemic therapy, and number of patients who proceed to CRS + HIPEC. All relevant data, including a full description of local treatments which have been performed in each individual patient, all serious adverse events and patient withdrawal specified per participating hospital is made available to the DSMB by the coordinating investigator. The DSMB reviews the safety data, reports their findings to the principal investigators and advise on study continuation after **40** (+/- ½ year after start of accrual at the last participating centre), **80** (+/- 1 year)**, 160** (+/- 2 years)**,** and **240** (+/- 3 years) patients are included. The principal investigators submits these reports to the ethics committee along with all relevant data. Cessation of the study is warranted if criteria for termination as described in section 8.7 have been met. As for the rest, the DSMB counsels the principal investigators on study continuation or cancellation based on their expertise. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB is not followed.

There are a few topics that will be closely monitored by the DSMB. Firstly, treatment related morbidity and toxicity of combination chemotherapy and bevacizumab, as well as the number of patients who proceed to CRS + HIPEC in the experimental arm. Secondly, severe postoperative complications (Clavien–Dindo ≥3) will be closely evaluated in both the experimental and control arm. Finally, survival distributions between different treatment arms will be evaluated after 160 and 240 patients are included.

10. STATISTICAL ANALYSIS

All statistical analyses are performed 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 (standard deviation), median ([interquartile] range), depending on distribution. All survival outcomes are measured from date of randomisation. All multivariable regression analyses and Cox proportional hazard analyses adjust for variables (i.e. gender, age, TNM, tumour differentiation, tumour histology, etcetera) having a significant or near-significant (*p*<.10) influence on the respective outcome parameter on univariable analysis. All results of multivariable regression analysis are reported as odds ratios with 95% confidence intervals. All results of Cox proportional hazard regression analysis are reported as hazard ratios with 95% confidence intervals.

10.1 Primary study parameters

In the phase II study, major postoperative complications and the number of patients who undergo CRS + HIPEC are both presented as *n* (%), and compared between both arms by using Chi-square test of Fisher's exact test. Multivariable regression analysis is performed to analyse the influence of treatment arm on postoperative complications, adjusted for important clinical variables.

In the phase III study, 3-year overall survival is presented as *n* (%), and compared between both arms by using Kaplan Meier survival analysis with log-rank test. The primary analysis is performed on an intention-to-treat basis, whereby patients are analysed according to the treatment group to which they were randomised regardless of whether they complied with this treatment. Secondary analyses are performed according to per-protocol-principle, in which survival distributions of different treatment scenarios (***Figure 3***) are compared by using Kaplan Meier survival analysis with log-rank test. Cox proportional hazard analysis is performed to analyse the influence of treatment arm on

overall survival, adjusted for important clinical variables. Subgroup per-protocol analyses will be performed for different treatment scenarios (***Figure 3***).

10.2 Secondary study parameters

- Median survival, 5-year overall survival

  Median survival is presented in months, with range and 95% confidence intervals. 5-year overall survival is presented as *n* (%). Median and 5-year overall survival are compared between both arms by using Kaplan Meier survival analysis with log-rank test. Cox proportional hazard analysis is performed to analyse the influence of treatment arm on overall survival, with adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses will be performed for different treatment scenarios (Figure 3).

- 1-year and 3-year progression-free survival

  1-year and 3-year disease free survival are presented as *n* (%), and compared between both arms by using Kaplan Meier survival analysis with log-rank test. Median progression-free survival is presented in months with range and 95% confidence intervals. Cox proportional hazard analysis is performed to analyse the influence of treatment arm on progression-free survival, with adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses will be performed for different treatment scenarios (***Figure 3).***

- Procedure related characteristics of CRS + HIPEC.

  Procedure related characteristics may be presented as continuous variable (i.e. operating time in minutes, blood loss in ml) or as binary/categorical variable (i.e. bleeding yes vs. no). Continuous variables are compared between both arms using independent sample t-test or

Mann Whitney U test. Binary and categorical variables are compared between both arms by using Chi-square test of Fisher's exact test. Multivariable regression analyses are performed to analyse the influence of treatment arm on procedure related characteristics, with adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses are performed for different treatment scenarios (***Figure 3***).

- PCI score (***Figure 1***).

  PCI score is presented as continuous variable, and compared between both arms by using independent sample t-test or Mann Whitney U test. Multivariable regression analyses is performed to analyse the influence of treatment arm on the PCI score, with adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses are performed for different treatment scenarios (***Figure 3***).

- CC-score (***Figure 2***).

  CC-score is presented as categorical variable (CC-0, CC-1, or CC-2), and compared between both study arms by using Chi-square test or Fisher's exact test. Multivariable regression analyses is performed to analyse the influence of treatment arm on CC-score, with adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses are performed for different treatment scenarios (***Figure 3***).

- In-hospital, 30-day, and 90-day major postoperative complications and mortality.

  Postoperative complications and postoperative mortality are presented as binary variables (yes vs. no), and compared between both study arms by using Chi-square test or Fisher's exact test. Multivariable regression analyses is performed to analyse the influence of treatment arm on both postoperative complications and postoperative mortality, with

adjustment for significantly important clinical variables in univariable analysis. Subgroup per-protocol analyses are performed for different treatment scenarios (***Figure 3***).

- Hospital stay.

  Hospital stay is presented as continuous variable, and compared between both study arms by using independent sample t-test or Mann Whitney U test.

- Quality of life.

  Quality of life data are graphically presented across all time points and analysed by using a repeated measures analysis of variance.

- Cost-effectiveness and cost-utility.

  The iMTA Medical Consumption Questionnaire and iMTA Productivity Costs Questionnaire are used to obtain information about used health care resources of included patients. 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.[132] 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.

- Treatment related toxicity of combination chemotherapy/bevacizumab (experimental arm).

  Toxicity is presented as categorical variable (no toxicity, moderate toxicity, severe toxicity), and compared between different treatment regimens (i.e. CAPOX, FOLFOX, etc.) by using Chi square test or Fisher's exact test. Multivariable regression analyses is performed to analyse the influence of treatment regimen, as well as other significantly important clinical variables on univariable analysis, on toxicity.

- Number of patients with disease progression, stable disease, or responsive disease to neoadjuvant combination chemotherapy/bevacizumab (experimental arm).

  Response to neoadjuvant systemic therapy is presented as categorical variable (progressive disease, stable disease, partial response, complete response), and compared between different treatment regimens (i.e. CAPOX, FOLFOX, etc.) by using Chi square test or Fisher's exact test. Multivariable regression analyses is performed to analyse the influence of treatment regimen, as well as other significantly important clinical variables on univariable analysis, on response to neoadjuvant systemic therapy.

10.3 Other study parameters

Baseline characteristics may be presented as continuous variables (e.g. age), or as continuous variables (e.g. tumour histology, tumour differentiation, TNM stage, tumour topography, gender, WHO performance score, ASA score, etcetera). Continuous variables are compared between both

arms by using independent sample t-test or Mann Whitney U test. Binary and categorical variables are compared between both arms by using Chi-square test of Fisher's exact test. As described above, baseline characteristics may be incorporated in both Cox proportional hazard regression analysis and multivariable regression analysis if they have a significant influence on the respective outcome parameters in univariable analyses.

10.4 Interim analyses

After inclusion of the 80thpatient (end of phase II), the inclusion will be stopped until all patients completed their 3 months follow-up. Both major postoperative complications and number of patients undergoing CRS + HIPEC will be expressed as categorical variable, presented as *n* (%). Criteria for premature termination after the phase II study are defined in section 8.7.

If the study proceeds to the phase III trial, additional interim analyses will be performed after 160 and 240 patients. Since safety criteria have already been met in the phase II study, inclusion will not be stopped at interim analyses in the phase III study. Major postoperative complications, number of patients undergoing CRS + HIPEC and survival will be determined and compared between both arms by using Chi Square and log-rank test. After all interim analyses, the DSMB will be established to advice whether to stop or not to stop. Criteria for premature termination of the study after inclusion of 160 and 240 patients are defined in section 8.7.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study is conducted according to the principles of the Declaration of Helsinki (Fortaleza, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Written informed consent is obtained as described in 3.1. Regarding ethical considerations, the information offered to the patients at least contains the following:

- A statement that the study involves research.
- A full explanation of the procedures to be followed.
- A full explanation of the nature, expected duration, and purpose of the study.
- A description of any reasonable foreseeable risks or discomfort to the patient.
- A description of any benefits that may reasonably be expected.
- A statement that patient data will be handled with care and confidentiality.
- A statement that participation is voluntary.
- A statement that refusal to participate will involve no penalty or loss to benefits to which the patients is otherwise entitled.
- A statement that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care.

11.3 Objection by minors or incapacitated subjects

Minors and incapacitated subjects are not eligible for the study.

11.4 Benefits and risks assessment in both arms

11.4.1 Experimental arm

In the experimental arm, potential risks of this study are treatment related toxicity of combination chemotherapy and bevacizumab. Furthermore, there is a chance of not undergoing CRS + HIPEC due to disease progression upon neoadjuvant systemic therapy.

Regarding treatment related toxicity, this risk is outweighed by the potential survival benefit due to downstaging of intraperitoneal tumour load, limiting the extensiveness of cytoreductive surgery and increasing the chance of a complete cytoreduction. Since the extent of intraperitoneal tumour load and completeness of cytoreduction are the most important prognostic factors for survival, the experimental treatment in this study may have a significant survival benefit.

Patients in this arm may not undergo CRS + HIPEC due to disease progression. However, since patients with disease progression during neoadjuvant systemic therapy are unlikely to benefit from CRS + HIPEC, neoadjuvant systemic therapy may result in improved patient selection and prohibits futile and potentially harmful CRS + HIPEC to patients with progressive disease while on neoadjuvant treatment, since these patients are not likely to benefit from upfront CRS + HIPEC. Therefore, this may actually not considered to be a risk of the experimental treatment strategy.

11.4.2 Control arm

In the control arm, patients are not exposed to combination chemotherapy and bevacizumab, potentially reducing the risk of systemic therapy related toxicity. However, survival may be impaired in these patients, since they don’t have the potential advantages of preoperative tumour downstaging with less extensive cytoreductive surgery.

Furthermore, in the control arm, patients with aggressive tumour biology also undergo CRS + HIPEC. If these patients were allocated to the experimental arm, they may have revealed disease progression while on neoadjuvant systemic therapy. Patients with aggressive tumour biology may be more likely to develop early recurrence after CRS + HIPEC. Given the relatively high morbidity of CRS + HIPEC, CRS + HIPEC should ideally not be performed in patients with very early recurrence, since potential postoperative morbidity after CRS + HIPEC may significantly impair the quality of the last part of life in these patients.

11.5 Compensation for injury

The Catharina Ziekenhuis has taken out the compulsory insurance, in accordance with legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of July, 2015). This insurance provides cover for damage to research subjects through injury or death caused by the study:

- €650.000,- for death or injury for each subject who participates in the research;
- €5.000.000,- for death or injury for all subjects who participate in the research;
- €7.500.000, - for the total damage incurred by the organisation for all damage disclosed by scientific research for the Catharina Ziekenhuis as ''Sponsor'' in the meaning of said Act in each year of insurance coverage.

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

Enrolled patients do not receive any incentives or compensation through participation in this study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Every randomised patient is assigned a study number. Communication occurs only with this number. The full name and birth date of the patient are recorded solely on the informed consent form. Execution of local data management, central data management, and monitoring is performed and/or supported by the Netherlands Comprehensive Cancer Centre (IKNL). Their experience with continuous data monitoring and data collection based on high quality CRFs guarantees complete and timely recording, handling and storage of data and documents.

This study is monitored based on the recommendations as described in the brochure "Kwaliteitsborging mensgebonden onderzoek 2.0", published in October 2012 by the Dutch Federation of University Medical Centres (NFU). The monitor plan is based on the judgement of the principle investigators that the study treatment carries a moderate risk for the participating patients. During the phase II study, all participating centres are monitored twice. A new monitor plan is conducted after obtaining monitor reports from the phase II study. The trial is monitored by independent, qualified, and experienced monitors of the IKNL clinical research department. A comprehensive description of the aspects and frequency of monitoring can be found in a separate monitoring plan.

12.2 Amendments

Amendments are changes made to the study after a favourable opinion by the accredited METC has been given. All amendments are notified to the METC that gave a favourable opinion. 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 subjects of the study;

- the scientific value of the study;
- the conduct or management of the study; or
- the quality or safety of any intervention used in the study.

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 are recorded and filed by the sponsor.

12.3 Annual progress report

The coordinating investigator submits a summary of the progress of the study to the accredited METC once a year. Information is provided on the date of inclusion of the first subject, number of subjects included and number of subjects that have completed the study, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.4 Temporary halt and (prematurely) end of study report

The accredited METC and the competent authority are notified of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the accredited METC and the competent authority are notified within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the a final study report with the results of the study is submitted, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.5 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the study on the basis of their participation in it. The publication policy and criteria for authorship are extensively described in the Clinical Trial Agreements between the sponsor and the participating sites.

The results of study are submitted for publication to peer-reviewed scientific journals. Besides the group of principal investigators and the coordinating investigator, authorship is granted to physicians of each HIPEC centre or referring hospital depening on the number of included patients (see Clinical Trial Agreement). Manuscripts will be offered for publication on behalf of the CAIRO6 study group. In all publications and presentations, the Dutch Peritoneal Oncology Group (DPOG) and the Dutch Colorectal Cancer Group (DCCG), as well as all participating centres with the local investigators, are acknowledged. In case the number of authors exceeds the maximum number of authors allowed by a journal, authors other than the principal investigators and the coordinating investigator will be listed in a ''List of Collaborators''. A study protocol with all involved researchers is submitted to BioMed Central Cancer.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Since all investigational products are registered for metastatic colorectal cancer, this specific section is kept short. Potential risks of the experimental arm are:

1. Treatment related toxicity of combination chemotherapy with bevacizumab in the experimental arm.
2. Patients in the experimental arm do not proceed to CRS + HIPEC due to disease progression or toxicity.
3. Higher postoperative complication rate in the experimental arm.

13.2 Measures to reduce the risks

First, our phase II – phase III study design allows for an early detection of all potential issues of concern, since this study will be terminated in the following situations:

1. If less than 50% (20/40) patients in the experimental arm proceed to CRS + HIPEC due to systemic toxicity or disease progression.
2. if >7 patients more suffer major morbidity (Clavien-Dindo grade III-V) in the experimental arm compared to the control arm.

These potential risks are actively monitored by the DSMB (section 9.5). Furthermore, the principal investigators feel the remaining risks are acceptable for the subjects participating in the study.

With regard to potential issue of concern 1 (section 13.1), we expect the treatment related toxicity to be outweighed against the potential survival benefit in the experimental arm. Furthermore, medical oncologists in the Netherlands have extensive experience in oxaliplatin-based treatment of

metastatic colorectal cancer since this drug is registered for this indication for many years. Therefore, toxicity is treated according to standardised treatment protocols. Furthermore, in case of toxicity to oxaliplatin, systemic therapy can be continued as FOLFIRI, CAPIRI, 5-FU or capecitabine.

With regard to potential issue of concern 2 (section 13.1), patients with disease progression during neoadjuvant systemic therapy are unlikely to benefit from CRS + HIPEC. Therefore, neoadjuvant combination chemotherapy with bevacizumab may result in improved patient selection and prohibits futile and potentially harmful CRS + HIPEC to patients with progressive disease while on neoadjuvant treatment, since these patients are not likely to benefit from the procedure.

With regard to potential issue of concern 3 (section 13.1), CRS + HIPEC is performed not earlier than 6 weeks after the last administration of bevacizumab. Furthermore, the last neoadjuvant systemic therapy cycle consists of combination chemotherapy alone. Bevacizumab can be safely used in major cancer surgery if a time to surgery of 5-6 weeks after the last administration is respected.[111] The potential survival benefit of bevacizumab, especially in peritoneal metastases, is likely to outweigh the potential higher risk of postoperative complications.[41,44]

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