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

Submission date
26/04/2016

Recruitment status
No longer recruiting

Registration date
11/05/2016

Overall study status
Ongoing

Last Edited
20/11/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Current plain English summary:
Background and study aims
Cytoreductive surgery with HIPEC is a curative intent treatment for patients with operable colorectal peritoneal metastases without other metastases (isolated colorectal peritoneal metastases). The addition of chemo-immunotherapy before and after CRS-HIPEC could have potential benefits. It may eliminate invisible cancer cells that have already spread elsewhere in the body. Furthermore, chemo-immunotherapy before CRS-HIPEC may downsize the peritoneal metastases so that they are easier to remove completely. Chemotherapy after CRS-HIPEC may help to stop the cancer from coming back by eliminating invisible cancer cells that may have been left behind in the body. Chemo-immunotherapy before and after CRS-HIPEC also has potential drawbacks. It may cause side effects and it prolongs and intensifies the treatment period. In other operable cancers (stomach, oesophagus, ovaries, rectum), chemo-immunotherapy before and/or after surgery is standard care, since high-quality research showed that it significantly improves the long-term outcomes of patients. Doctors expect that chemo-immunotherapy before and after CRS-HIPEC also significantly improves the long-term outcomes of patients with operable isolated colorectal peritoneal metastases. However, to date, this has never been investigated. Therefore, this is the first study that investigates whether chemo-immunotherapy before and after CRS-HIPEC truly improves the long-term outcomes of patients with operable colorectal peritoneal metastases as compared to the current standard care in the Netherlands: CRS-HIPEC alone.

Who can participate?
Patients with operable isolated colorectal peritoneal metastases who qualify for CRS-HIPEC.

What does the study involve?
Patients are randomly allocated into two groups. One group receives CRS-HIPEC alone (control group). The other group receives CRS-HIPEC with chemo-immunotherapy before and after CRS-HIPEC (experimental group). Patients in both groups are followed for short-term outcomes and long-term outcomes. Additionally, patients in both groups regularly receive questionnaires about their quality of life, work, and use of health care.

What are the possible benefits and risks of participating?
Doctors hypothesise that patients in the experimental arm have favourable long-term outcomes than patients in the control arm. This potential benefit needs to be weighed against the potential burden/risks of the experimental arm: side effects of the chemo-immunotherapy and a prolonged and intensified treatment period that could interfere with the quality of life.

Where is the study run from?
Eight Dutch and one Belgian tertiary referral hospitals for the surgical treatment of colorectal peritoneal metastases:
Catharina Hospital, Eindhoven, Netherlands
Erasmus University Medical Centre, Rotterdam, Netherlands
Amsterdam University Medical Centre, Location VUMC, Amsterdam, Netherlands
St. Antonius Hospital, Nieuwegein, Netherlands
Netherlands Cancer Institute, Amsterdam, Netherlands
University Medical Centre Groningen, Groningen, Netherlands
Radboud University Medical Centre, Nijmegen, Netherlands
University Medical Centre Utrecht, Utrecht, Netherlands
Ziekenhuis Oost-Limburg, Genk, Belgium

When is the study starting and how long is it expected to run for?
June 2017 to June 2029. November 2024 (first analysis of primary outcome) and April 2029 (last visit of last patient)

Who is funding the study?
Dutch Cancer Society (KWF Kankerbestrijding), Amsterdam, Netherlands
Catharina Research Fund (Catharina Onderzoeksfonds), Eindhoven, Netherlands
Hoffman-La Roche, Basel, Switzerland

Who is the main contact?
Dr. Koen Rovers
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Previous plain English summary:
Background and study aims
Cancer of the colon or rectum may spread (metastasise) to the peritoneum, the thin layer of tissue that lines the abdomen. Doctors treat these metastases by combining surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), which involves filling the abdominal (peritoneal) cavity with chemotherapy drugs that have been heated. Many patients also receive chemotherapy before and after surgery with HIPEC. This has several advantages. It may make the metastases in the peritoneum smaller before surgery so that they are easier to remove completely. Furthermore, it may eliminate any cancer that has already spread elsewhere in the body. Chemotherapy after surgery may help to stop the cancer from coming back by eliminating invisible cancer cells that may have been left behind in the body. Chemotherapy before and after surgery with HIPEC also has potential disadvantages. It may cause side effects, which may be so severe that they decrease quality of life or make surgery impossible. Furthermore, doctors are still not sure if chemotherapy is effective against metastases in the peritoneum. If not, the metastases in the peritoneum will only grow during chemotherapy. Nowadays, many doctors do not agree about whether to give chemotherapy before and after surgery with HIPEC, because the potential advantages and disadvantages have never been properly investigated. Therefore, this study aims to find out whether chemotherapy before and after surgery with HIPEC is of benefit for patients with colon or rectal cancer with peritoneal metastases.

Who can participate?
Patients aged 18 years and over with colon or rectal cancer and metastases in the peritoneum, who are candidates for surgery with HIPEC. This is determined by the treating doctor.

What does the study involve?
Participants are randomly allocated into two groups. One group receives surgery with HIPEC without chemotherapy (the standard treatment). The other group receives surgery with HIPEC with chemotherapy before and after surgery (the experimental treatment). Additionally, participants in both groups are asked to fill in questionnaires about their quality of life and health care costs.

What are the possible benefits and risks of participating?
The experimental treatment may lead to an increased life expectancy and an increased chance of being cured. These possible benefits have to be weighed against the most important risks of the experimental treatment, which are side effects that make surgery impossible and/or decrease quality of life.

Where is the study run from?
1. Antoni van Leeuwenhoek Hospital – Netherlands Cancer Institute (Amsterdam, the Netherlands)
2. Catharina Hospital (Eindhoven, the Netherlands)
3. Erasmus Medical Centre (Rotterdam, the Netherlands)
4. Medical Spectrum Twente (Enschede, the Netherlands)
5. Radboud University Medical Centre (Nijmegen, the Netherlands)
6. Sint Antonius Hospital (Nieuwegein, the Netherlands)
7. University Medical Centre Groningen (Groningen, the Netherlands)
8. University Medical Centre Utrecht (Utrecht, the Netherlands)
9. VU University Medical Centre (Amsterdam, the Netherlands).

When is the study starting and how long is it expected to run for?
June 2017 to June 2029

Who is funding the study?
1. Dutch Cancer Society
2. Roche Netherlands B.V.

Who is the main contact?
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Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02758951

Clinical Trials Information System (CTIS)
2016-001865-99

Protocol serial number
NL57644.100.16

Study information

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

Acronym
CAIRO6

Study objectives
Current hypothesis as of 11/01/2019:
Patients with isolated resectable colorectal peritoneal metastases have a 3-year overall survival of 50% after treatment with upfront cytoreductive surgery with HIPEC alone (control arm), and a 3-year overall survival of 65% after treatment with perioperative systemic therapy and cytoreductive surgery with HIPEC (experimental arm)

Hypothesis as of 04/05/2017:
Perioperative systemic therapy and surgery with HIPEC results in improved overall survival compared to surgery with HIPEC alone.

Previous hypothesis:
Perioperative systemic therapy and cytoreductive surgery with HIPEC will result in an overall survival benefit compared to cytoreductive surgery and HIPEC alone in patients with peritoneal metastases of colorectal cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
MEC-U (Medical Research Ethics Committees United), Nieuwegein, the Netherlands, 22/12/2016, ref: R15.056

Primary study design

Interventional

Study design
Open-label parallel-group multicentre randomized controlled Phase II-III trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Current condition as of 11/01/2019:
Isolated resectable colorectal peritoneal metastases

Previous condition:
Colorectal cancer with isolated peritoneal metastases

Interventions
Current interventions as of 20/11/2024:
At the discretion of the treating medical oncologist, perioperative systemic therapy consists of either:
1. Four three-weekly neoadjuvant and adjuvant cycles of CAPOX (130 mg/m2 body-surface area [BSA] of oxaliplatin, intravenously [IV] on day 1; 1000 mg/m2 BSA of capecitabine, orally twice daily on days 1-14), with bevacizumab (7.5 mg/kg body weight, IV on day 1) added to the first three neoadjuvant cycles, or;
2. Six two-weekly neoadjuvant and adjuvant cycles of FOLFOX (85 mg/m2 BSA of oxaliplatin, IV on day 1; 400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2), with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles, or;
3. Six two-weekly neoadjuvant cycles of FOLFIRI (180 mg/m2 BSA of irinotecan, IV on day 1; 400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) and either four three-weekly (capecitabine (1000 mg/m2 BSA, orally twice daily on days 1-14) or six two-weekly (400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) adjuvant cycles of fluoropyrimidine monotherapy, with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles.

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

CRS-HIPEC is performed according to the Dutch protocol in all study centres (Kuijpers, Ann Surg Oncol, 2013). Until the publication of the PRODIGE7 trial (Quenet, Lancet Oncol, 2021), the choice of HIPEC medication (oxaliplatin or mitomycin C) has been left to the discretion of the treating physician, since neither one has a favourable safety or efficacy until then (Hompes, J Surg Oncol, 2014; van Eden, Eur J Surg Oncol, 2018). After the publication of the PRODIGE7 trial in 2021, oxaliplatin-based HIPEC was omitted in all centres (and therefore automatically omitted

in the present study), and all centres switched to mitomycin C-based HIPEC. In the control arm, CRS-HIPEC should be performed within six weeks after randomisation. In the experimental arm, CRS-HIPEC should be performed within six weeks after completion of neoadjuvant systemic therapy, and at least six weeks after the last administration of bevacizumab in order to minimise the risk of bevacizumab-related postoperative complications (Hompes, Eur J Surg Oncol, 2011).

Previous interventions as of 11/01/2019 to 20/11/2024:
At the discretion of the treating medical oncologist, perioperative systemic therapy consists of either:
1. Four three-weekly neoadjuvant and adjuvant cycles of CAPOX (130 mg/m2 body-surface area [BSA] of oxaliplatin, intravenously [IV] on day 1; 1000 mg/m2 BSA of capecitabine, orally twice daily on days 1-14), with bevacizumab (7.5 mg/kg body weight, IV on day 1) added to the first three neoadjuvant cycles, or;
2. Six two-weekly neoadjuvant and adjuvant cycles of FOLFOX (85 mg/m2 BSA of oxaliplatin, IV on day 1; 400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2), with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles, or;
3. Six two-weekly neoadjuvant cycles of FOLFIRI (180 mg/m2 BSA of irinotecan, IV on day 1; 400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) and either four three-weekly (capecitabine (1000 mg/m2 BSA, orally twice daily on days 1-14) or six two-weekly (400 mg/m2 BSA of leucovorin, IV on day 1; 400/2400 mg/m2 BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) adjuvant cycles of fluoropyrimidine monotherapy, with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles.

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

CRS-HIPEC is performed according to the Dutch protocol in all study centres (Kuijpers, Ann Surg Oncol, 2013). The choice of HIPEC medication (oxaliplatin or mitomycin C) is left to the discretion of the treating physician, since neither one has a favourable safety or efficacy (Hompes, J Surg Oncol, 2014; van Eden, Eur J Surg Oncol, 2018). In the control arm, CRS-HIPEC should be performed within six weeks after randomisation. In the experimental arm, CRS-HIPEC should be performed within six weeks after completion of neoadjuvant systemic therapy, and at least six weeks after the last administration of bevacizumab in order to minimise the risk of bevacizumab-related postoperative complications (Hompes, Eur J Surg Oncol, 2011).

Interventions as of 04/05/2017:
Experimental arm: Perioperative systemic therapy:
1. Neoadjuvant systemic therapy: combination chemotherapy plus bevacizumab for three 3-weekly (CAPOX + bevacizumab) or four 2-weekly (FOLFOX + bevacizumab) cycles, followed by restaging. In case of systemic disease progression (e.g. liver or lung metastases), the best possible palliative treatment is offered. In case of stable or responsive disease, one 3-weekly (CAPOX) or two 2-weekly (FOLFOX) neoadjuvant cycles of combination chemotherapy without bevacizumab are administered.

2. Cytoreductive surgery with HIPEC.
3. Adjuvant systemic therapy: Only in case of a sufficiently good clinical condition and stable or responsive disease upon neoadjuvant treatment, adjuvant combination chemotherapy is intentionally administered according to the neoadjuvant regimen without bevacizumab for four 3-weekly cycles (CAPOX) or six 2-weekly cycles (FOLFOX).

Control arm:
1. Cytoreductive surgery with HIPEC

Previous interventions from 02/09/2016 to 04/05/2017:
Experimental arm:
1. Patients in the experimental arm will receive 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 and unresectable disease, the best possible palliative treatment will be offered. In case of progressive but resectable disease, patients will undergo explorative laparotomy and subsequent cytoreductive surgery with HIPEC at least 6 weeks after the last cycle of bevacizumab is administered. In case of responsive or stable disease, one 3-weekly (CAPOX) or two 2-weekly (FOLFOX) neoadjuvant cycles of combination chemotherapy without bevacizumab will be administered. Subsequently, not earlier than 3 weeks after the last day of the last cycle of combination chemotherapy, explorative laparotomy and subsequent cytoreductive surgery with HIPEC will be performed.
2. Cytoreductive surgery with HIPEC.
3. Adjuvant systemic therapy: Only in patients with stable disease or response upon neoadjuvant treatment, adjuvant combination chemotherapy will be given according to the neoadjuvant regimen, but without bevacizumab, for four 3-weekly cycles (CAPOX) or six 2-weekly cycles (FOLFOX).

Control arm:
1. Cytoreductive surgery with HIPEC

Original interventions:
Experimental arm:
1. Neoadjuvant systemic therapy: Combination chemotherapy with the addition of bevacizumab for three 3-weekly (CAPOX + Bevacizumab) or four 2-weekly (FOLFOX + BEV) cycles, followed by restaging with thoracoabdominal CT-scan. In case of progressive disease, the best possible treatment will be offered. In case of responsive or stable disease, one 3-weekly (CAPOX) or two 2-weekly (FOLFOX) additional cycles of combination chemotherapy alone will be administered.
2. Cytoreductive surgery and HIPEC.
3. Adjuvant systemic therapy: Combination chemotherapy for four 3-weekly (CAPOX) or six 2-weekly (FOLFOX) cycles.

Control arm:
1. Cytoreductive surgery and HIPEC

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)

Drug names as of 11/01/2019: 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan, bevacizumab Previous drug names: 5-fluorouracil, capecitabine, leucovorin, oxaliplatin, bevacizumab

Primary outcome(s)

Current primary outcome measures as of 20/11/2024:
Phase II study:

1. The feasibility of accrual, based on the total accrual rate, the accrual rate in each study centre, and screening failures;
2. The feasibility of perioperative systemic therapy, based on the number of patients that:
2.1. Undergo complete CRS-HIPEC (primary)
2.2. Start and complete neoadjuvant systemic therapy, with or without dose reductions
2.3. Start and complete adjuvant systemic therapy, with or without dose reductions;
3. The safety of perioperative systemic therapy, based on the number of patients with:
3.1. Clavien-Dindo grade 3 or higher postoperative morbidity up to three months postoperatively (primary)
3.2. Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 2 or higher systemic therapy-related toxicity up to one month after the last administration of systemic therapy
3.3. Clavien-Dindo grade 2 postoperative morbidity up to three months after CRS-HIPEC
4. The tolerance of perioperative systemic therapy, based on patient-reported outcomes extracted from EQ-5D-5L, QLQ-C30, and QLQ-CR29 during study treatment;
5. The radiological and pathological response of colorectal PM to neoadjuvant systemic therapy, based on a central review of thoracoabdominal CT and resected specimens during CRS-HIPEC, respectively. Classifications are not defined a prior.

Phase III study:
The primary outcome that is compared between both arms is overall survival, defined as the time between randomisation and death (time point: three years after randomisation).

Previous primary outcome measures as of 11/01/2019 to 20/11/2024:
Phase II study:
1. The feasibility of accrual, based on the total accrual rate, the accrual rate in each study centre, and screening failures (time point: not applicable).
2. The feasibility of perioperative systemic therapy, based on the number of patients that:
2.1. Start/complete neoadjuvant systemic therapy with/without dose reductions
2.2. Are scheduled for CRS-HIPEC
2.3. Undergo complete CRS-HIPEC
2.4. Start/complete adjuvant systemic therapy with/without dose reductions (time point: nine months after randomisation).
3. The safety of perioperative systemic therapy, based on the number of patients with:
3.1. Systemic therapy related toxicity, defined as grade ≥2 according to CTCAE v4.0, up to one month after the last administration of systemic therapy
3.2. Postoperative morbidity, defined as grade ≥2 according to Clavien-Dindo, up to three months after CRS-HIPEC (time points: nine months after randomisation).
4. The tolerance of perioperative systemic therapy, based on health-related quality of life extracted from EQ-5D-5L, QLQ-C30, and QLQ-CR29 during study treatment (time point: nine months after randomisation).
5. The radiological response of colorectal PM to neoadjuvant systemic therapy, based on central review of thoracoabdominal CT during neoadjuvant systemic therapy (time point: three months after randomisation). Classifications are not defined a priori.
6. The histological response of colorectal PM to neoadjuvant systemic therapy, based on central

review of resected specimens during CRS-HIPEC (time point: four months after randomisation). Classifications are not defined a priori.

Phase III study:
Overall survival, defined as the time between randomisation and death (time point: three years after randomisation).

Primary outcome measures as of 04/05/2017:
Phase II study (n=80):
1. Both arms: number of patients who undergo a complete or near-complete cytoreduction (CC0 or CC1)
2. Both arms: major postoperative complications 90 days after surgery with HIPEC (Clavien-Dindo III-V)

Phase III study (n=358):
1. Both arms: number of patients alive three years after randomisation

Primary outcome measures from 02/09/2016 to 04/05/2017:
1. Primary outcome of the phase II study (n=80): major postoperative complications, defined as Clavien-Dindo grade III-V, at 90 days postoperatively
2. Primary outcome of the phase III study (n=340): overall survival after 3-years follow-up

Original primary outcome measures:
1. Primary outcome of the phase II study (n=80): major morbidity, defined as Clavien-Dindo grade III-V, at 90 days post-op
2. Primary outcome of the phase III study (n=340): 3-year overall survival (regular oncological follow-up at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post-op)

Key secondary outcome(s)

Current secondary outcome measures as of 20/11/2024:
Secondary outcomes in both arms are:
1. Progression-free survival, defined as the time between randomisation and physician-determined disease progression before CRS-HIPEC, CRS-HIPEC in case of unresectable disease or incomplete CRS, physician-determined recurrence after CRS-HIPEC, or death due to any cause;
2. The proportion of patients undergoing macroscopic complete CRS-HIPEC;
3. The peritoneal cancer index during explorative laparotomy;
4. The proportion of patients with a bowel anastomosis during CRS-HIPEC;
5. The proportion of patients with an ostomy formation during CRS-HIPEC;
6. The operating time of CRS-HIPEC;
7. Days between CRS-HIPEC and initial discharge;
8. The proportion of patients with Clavien-Dindo grade ≥3, grade ≥4, and grade 5 postoperative morbidity (including a description of adverse events) up to 90 days after CRS-HIPEC;
9. The proportion of patients with readmissions within 90 days after CRS-HIPEC;
10. Disease-free survival, defined as the time between macroscopic complete CRS-HIPEC and physician-determined recurrence or death;
11. Patient-reported outcomes (PROs) extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different points in time
12. Costs extracted from questionnaires (iMTA PCQ, iMTA MCQ) at different points in time

Secondary outcomes in the experimental arm are:
1. The proportion of patients with CTCAE grade ≥3, grade ≥4, and grade 5 systemic therapy-related toxicity (including a description of adverse events) up to 30 days after the last

administration of systemic therapy;
2. The proportion of patients with an objective radiological response of colorectal PM to neoadjuvant systemic therapy, determined by a central review of thoracoabdominal CTs before and after neoadjuvant treatment by two radiologists blinded for clinical outcomes. The radiological response is assessed according to standard RECIST criteria and the radiological PCI. Response according to radiological PCI is classified as complete response (i.e. disappearance of all peritoneal lesions), partial response (i.e. ≥30% decrease of PCI), stable disease (i.e. <30% decrease or <20% increase of PCI), progressive disease (i.e. ≥20% increase of PCI), or non-evaluable. When in situ, the primary tumour is not included in response assessment according to the radiological PCI.
3. The proportion of patients with an objective pathological response of colorectal PM to neoadjuvant systemic therapy, determined by a central review of resected specimens during CRS-HIPEC by two pathologists blinded for clinical outcomes. Pathological response is assessed using the peritoneal regression grading score (PRGS) and the standard Mandard tumour regression grading (TRG).

Previous secondary outcome measures as of 11/01/2019 to 20/11/2024:
Both arms:
1. Progression-free survival, defined as the time between randomisation and disease progression before CRS-HIPEC, CRS-HIPEC in case of unresectable disease, radiological proof of recurrence, or death (time point: three years after randomisation).
2. Disease-free survival, defined as the time between CRS-HIPEC and radiological proof of recurrence or death (time point: three years after randomisation).
3. Health-related quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) before study treatment, after completion of neoadjuvant systemic therapy (experimental arm), every three months after CRS-HIPEC until one year postoperatively, and every six months thereafter until five years after randomisation (time pint: three years after randomisation).
4. Costs, extracted from questionnaires (iMTA Productivity Cost Questionnaire, iMTA Medical Consumption Questionnaire) before study treatment, after completion of neoadjuvant systemic therapy (experimental arm), every three months after CRS-HIPEC until one year postoperatively, and every six months thereafter until five years after randomisation (time pint: three years after randomisation);.
5. Surgical characteristics, e.g. PCI, intraoperative complications, operating time, resections, completeness of cytoreduction, hospital stay (time point: four months after randomisation).
6. She number of patients with major postoperative morbidity, defined as grade ≥3 according to Clavien-Dindo, up to three months after CRS-HIPEC (time point: nine months after randomisation).

Experimental arm:
1. The number of patients with major systemic therapy related toxicity, defined as grade ≥3 according to CTCAE v4.0, up to one month after the last administration of systemic therapy (time point: nine months after randomisation).
2. The number of patients with an objective radiological response of colorectal PM to neoadjuvant systemic therapy, determined by central review of thoracoabdominal CT (time point: three months after randomisation). Classifications are determined after exploration of the radiological response in the phase II study.
3. The number of patients with an objective histological response of colorectal PM to neoadjuvant systemic therapy, determined by central review of resected specimens during CRS-HIPEC (time point: four months after randomisation). Classifications are determined after exploration of the histological response in the phase II study.

Secondary outcome measures as of 04/05/2017:
Phase II study (n=80):
1. Both arms: minor postoperative complications 90 days after surgery with HIPEC (Clavien-Dindo II)
2. Experimental arm: moderate/severe systemic therapy related toxicity until one month after the last administration of systemic therapy (CTCAE II-V)

Phase III study (n=358):
1. Both arms: number of patients without disease progression one and three years after randomisation.
2. Both arms: number of patients alive five years after randomisation
3. Both arms: extent of peritoneal disease during surgery (PCI score)
4. Both arms: number of complete or near complete cytoreductions (CC0 or CC1)
5. Both arms: procedure-related characteristics of surgery with HIPEC (e.g. blood loss, operating time)
6. Both arms: major postoperative complications 90 days after surgery with HIPEC (Clavien-Dindo III-V)
7. Both arms: quality of life (EQ-5D, EORTC QLQ-C30, EORTC QLQ-CR29)
8. Both arms: cost-effectiveness (iMTA Medical Consumption Questionnaire, iMTA Productivity Cost Questionnaire)
9. Experimental arm: severe systemic therapy related toxicity until one month after the last administration of systemic therapy (CTCAE III-V)
10. Experimental arm: radiological response to neoadjuvant systemic therapy
11. Experimental arm: pathological response to neoadjuvant systemic therapy

Previous secondary outcome measures from 02/09/2016 to 04/05/2017:
1.Secondary outcome of the phase II study (n=80):
1.1 feasibility of randomisation, defined as inclusion of 80 patients 1 year after the start of accrual at the last participating centre.
1.2 Minor postoperative complications, defined as Clavien-Dindo grade II, at 90 days postoperatively.
1.3 Systemic therapy related toxicity, defined as NCICTCAE v4.0 grade II-V.
2. Secondary outcomes of the phase III study (n=340):
2.1. 5-year overall survival
2.2. 3-year and 5-year disease-free survival
2.3. Procedure-related characteristics of cytoreductive surgery with HIPEC (i.e. operating time, blood loss)
2.4. Peritoneal Cancer Index (PCI) at start of cytoreductive surgery.
2.5. Completeness of Cytoreduction (CC) Score directly after cytoreductive surgery
2.6. Severe postoperative complications, defined as Clavien-Dindo ≥3 at 90 days postoperatively
2.7. Postoperative mortality at 90 days postoperatively.
2.8. Hospital stay, until 12 months postoperatively.
2.9. Quality of life (EQ5D questionnaire, EORTC QLQ C30 questionnaire, EORTC QLQ CR29 questionnaire) at inclusion, and 3, 6, 12, 24, 36 and 60 months postoperatively.
2.10. Cost-effectiveness (iMTA Productivity Cost Questionnaire, iMTA Medical Consumption Questionnaire) at inclusion, and 3, 6, 12, 24, 36 and 60 months postoperatively.
2.11. Severe systemic therapy related toxicity (NCICTCAE v4.0 grade 3-5) of neoadjuvant combination chemotherapy with bevacizumab (experimental arm)
2.12. Severe systemic therapy related toxicity (NCICTCAE v4.0 grade 3-5) of adjuvant combination chemotherapy (experimental arm)
2.13. Number of patients with disease progression, stable disease, or responsive disease to neoadjuvant combination chemotherapy/bevacizumab.

Original secondary outcome measures:
1. Secondary outcome of the phase II study (n=80): feasibility of randomisation, defined as inclusion of 80 patients in 1 year after the start of accrual at the last participating centre
2. Secondary outcomes of the phase III study (n=340):
2.1. 5-year overall survival (regular oncological follow-up at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post-op)
2.2. 3-year and 5-year disease-free survival (regular oncological follow-up at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post-op)
2.3. Procedure-related characteristics of CRS + HIPEC (i.e. operating time, blood loss)
2.4. Peritoneal Cancer Index (PCI) Score during diagnostic laparoscopy and directly after laparotomy
2.5. Completeness of Cytoreduction (CC) Score directly after cytoreductive surgery
2.6. Treatment-related severe postoperative complications, defined as Clavien-Dindo ≥3 (in-hospital, 30-day, 90-day)
2.7. Treatment-related postoperative complications, defined as Clavien-Dindo <3 (in-hospital, 30-day, 90-day)
2.8. Treatment-related mortality (in-hospital, 30-day, 90-day)
2.9. ICU stay and hospital stay
2.10. Quality of life (EQ5D questionnaire, EORTC QLQ C30 questionnaire, EORTC QLQ CR29 questionnaire) at 6, 12, 36 and 60 months post-op
2.11. Cost-effectiveness (iMTA Productivity Cost Questionnaire, iMTA Medical Consumption Questionnaire) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57 and 60 months post-op
2.12. % of patients able to complete their full neoadjuvant treatment, and reasons for not completing and/or dose reduction (experimental arm)
2.13. % of patients able to complete their full adjuvant treatment, and reasons for not completing and/or dose reduction (experimental arm)
2.14. Treatment-related toxicity of neoadjuvant systemic treatment (experimental arm)
2.15. Treatment-related toxicity of adjuvant systemic treatment (experimental arm)
2.16. % of patient eligible for CRS + HIPEC after neoadjuvant treatment (experimental arm)
2.17. Overall survival in patients with progressive disease during neoadjuvant therapy (experimental arm) at 3 and 5 years after diagnosis with PMCRC
2.18. Morphological tumour response to neoadjuvant systemic therapy (experimental arm) after 3 (CAPOX + Bevacizumab) or 4 (FOLFOC + Bevacizumab) courses of neoadjuvant systemic therapy
2.19. Pathological tumour response to neoadjuvant systemic therapy (experimental arm) (Mandard score)

Completion date
01/06/2029

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 20/11/2024:
1. A World Health Organisation (WHO) performance status of ≤1
2. Histological or cytological proof of peritoneal metastases of a non-appendiceal colorectal adenocarcinoma with ≤50% of the tumour cells being signet ring cells
3. Resectable disease determined by a diagnostic laparoscopy/laparotomy in combination with abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI); only in

patients in whom diagnostic laparoscopy or laparotomy is considered not feasible or valuable (e. g. due to known adhesions impeding adequate PCI scoring), it is also allowed to determine resectability by CT or MRI only (provided that the colorectal peritoneal metastases are histologically or cytologically proven)
4. No evidence of systemic colorectal metastases within three months prior to enrolment
5. No systemic therapy for colorectal cancer within six months prior to enrolment
6. No contraindications for CRS-HIPEC
7. No previous CRS-HIPEC
8. No concurrent malignancies that interfere with the planned study treatment or the prognosis of resected colorectal peritoneal metastases.

Importantly, enrolment is allowed for patients with radiologically non-measurable disease. The diagnostic laparoscopy/laparotomy may be performed in a referring centre, provided that the peritoneal cancer index (PCI) is appropriately scored and documented before enrolment.

Previous participant inclusion criteria as of 11/01/2019 to 20/11/2024:
1. A World Health Organisation (WHO) performance status of ≤1
2. Histological or cytological proof of peritoneal metastases of a non-appendiceal colorectal adenocarcinoma with ≤50% of the tumour cells being signet ring cells
3. Resectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy/laparotomy
4. No evidence of systemic colorectal metastases within three months prior to enrolment
5. No systemic therapy for colorectal cancer within six months prior to enrolment
6. No contraindications for CRS-HIPEC
7. No previous CRS-HIPEC
8. No concurrent malignancies that interfere with the planned study treatment or the prognosis of resected colorectal peritoneal metastases.

Importantly, enrolment is allowed for patients with radiologically non-measurable disease. The diagnostic laparoscopy/laparotomy may be performed in a referring centre, provided that the peritoneal cancer index (PCI) is appropriately scored and documented before enrolment.

Inclusion participant criteria as of 04/05/2017:
1. PCI score ≤20 and CC-0 or CC-1 achievable, determined by adequate preoperative work-up
2. Histological confirmation of non-appendiceal colorectal cancer with non-signet histology in peritoneal deposits or ascites
3. 18 years or older
4. WHO performance score 0-1
5. Adequate clinical condition to undergo cytoreductive surgery with HIPEC and/or neoadjuvant combination chemotherapy with bevacizumab within 4 weeks after randomisation
6. Adequate organ functions: normal bone marrow function (Hb ≥6.0 mmol/L, absolute neutrophil count ≥1.5 x 109/L, platelet count ≥100 x 109/L), renal function (serum creatinine ≤1. 5 x ULN and creatinine clearance [Cockroft formula] ≥30 ml/min), determined <3 months prior to randomisation;
7. No known bleeding diathesis or coagulopathy
8. Written informed consent
9. Able and willing to adhere to follow-up

Previous participant inclusion criteria:
1. Peritoneal Cancer Index (PCI) score ≤20, determined by diagnostic staging laparoscopy
2. Achievability of complete cytoreduction, determined by diagnostic staging laparoscopy
3. Pathological confirmation of non-signet adenocarcinoma in peritoneal deposits or ascites

4. 18 years or older
5. WHO performance score 0-1
6. Adequate clinical condition to undergo CRS + HIPEC and neoadjuvant systemic therapy within 4 and 3 weeks after staging laparoscopy, respectively
7. Neutrophil count of at least 3.000/mm3, platelet count of at least 100,000/mm3 (<3 months before inclusion)
8. No bleeding diathesis or coagulopathy
9. Normal creatinine or creatinine clearance, determined by the MDRD-formula, of at least 50 ml /min (<3 months before inclusion)
10. Written informed consent
11. Expected adequacy of follow-up

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
358

Key exclusion criteria
Current participant exclusion criteria as of 20/11/2024:
Patients are excluded in case of any comorbidity or condition that prevents safe administration of the planned perioperative systemic therapy, determined by the treating medical oncologist, e. g.:
1. Inadequate bone marrow, renal, or liver functions (e.g. haemoglobin <6.0 mmol/L, neutrophils <1.5 x 109/L, platelets <100 x 109/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml /min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);
2. Previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan;
3. Dehydropyrimidine dehydrogenase deficiency;
4. Serious active infections;
5. Severe diarrhoea;
6. Stomatitis or ulceration in the mouth or gastrointestinal tract;
7. Recent major cardiovascular events;
8. Unstable or uncompensated respiratory or cardiac disease;
9. Bleeding diathesis or coagulopathy;
10. Pregnancy or lactation.

Previous exclusion criteria as of 11/01/2019 to 20/11/2024:
1. Inadequate bone marrow, renal, or liver functions (e.g. haemoglobin <6.0 mmol/L, neutrophils <1.5 x 109/L, platelets <100 x 109/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml

/min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);
2. Previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan;
3. Dehydropyrimidine dehydrogenase deficiency;
4. Serious active infections;
5. Severe diarrhoea;
6. Stomatitis or ulceration in the mouth or gastrointestinal tract;
7. Recent major cardiovascular events;
8. Unstable or uncompensated respiratory or cardiac disease;
9. Bleeding diathesis or coagulopathy;
10. Pregnancy or lactation.

Exclusion criteria as of 04/05/2017:
1. Signet ring cell histology (>50% of the cells have signet ring cell histology) of the primary tumour
2. Systemic metastases (i.e. liver, lung)
3. Known pregnancy or lactation, wish for pregnancy, and not willing to use contraceptives
4. Known unstable or uncompensated respiratory or cardiac disease
5. Serious active infections
6. Adjuvant chemotherapy after primary resection of colorectal cancer within 6 months prior to randomisation;
7. Any condition not allowing the safe administration of the planned systemic treatment (bevacizumab, 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan)
8. Stomatitis, ulceration in the mouth or gastrointestinal tract
9. Severe diarrhoea
10. Known pernicious anaemia or other anaemias due to vitamin B12 deficiency
11. Known previous peripheral sensory neuropathy with functional impairment after previous use of oxaliplatin
12. Impaired liver function (serum bilirubin ≤2 x ULN, serum transaminases ≤5 x ULN), assessment only if indicated

Previous exclusion criteria from 02/09/2016 to 04/05/2017:
1. Signet ring cell histology (>50% of the cells have signet ring cell histology) of the primary tumour
2. Systemic metastases (i.e. liver, lung)
3. Known pregnancy or lactation
4. Known unstable or uncompensated respiratory or cardiac disease
5. Serious active infections
6. Adjuvant chemotherapy after primary resection of colorectal cancer used within 6 months prior to randomisation
7. Any condition not allowing the safe administration of the planned systemic treatment (bevacizumab, 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, irinotecan)
8. Stomatitis, ulceration in the mouth or gastrointestinal tract
9. Severe diarrhoea
10. Known pernicious anaemia or other anaemias due to vitamin B12 deficiency
11. Known previous peripheral sensory neuropathy with functional impairment after previous use of oxaliplatin.
12. Impaired liver function (serum bilirubin ≤2 x ULN, serum transaminases ≤5 x ULN), assessment only if indicated
13. Known dihydropyrimidine dehydrogenase deficiency, determined by dihydropyrimidine dehydrogenase genotyping

Original exclusion criteria:
1. Signet ring cell histology (>50% of the cells have signet ring cell histology) of the primary tumour
2. Pregnant or lactating women
3. Unstable or uncompensated respiratory or cardiac disease
4. Serious active infections
5. Other concurrent chemotherapy used within 6 months prior to inclusion
6. Any condition not allowing the safe administration of the planned systemic treatment (bevacizumab, fluorouracil, folinic acid, capecitabine or oxaliplatin/irinotecan)
7. Stomatitis, ulceration in the mouth or gastrointestinal tract
8. Severe diarrhoea
9. Severe hepatic and/or renal dysfunction
10. Plasma bilirubin concentrations greater than 85 µmol/L

Date of first enrolment
01/06/2017

Date of final enrolment
29/04/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
Catharina Hospital
PO Box 1350
Eindhoven
Netherlands
5602 ZA

Study participating centre
Ziekenhuis Oost-Limburg
Synaps Park 1
Genk
Belgium
3600

Study participating centre
VU University Medical Centre
PO Box 7057

Amsterdam
Netherlands
1007 MB

Study participating centre
Antoni van Leeuwenhoek Hospital
PO Box 90203
Amsterdam
Netherlands
1006 BE

Study participating centre
Erasmus University Medical Centre
PO Box 2040
Rotterdam
Netherlands
3000 CA

Study participating centre
University Medical Centre Groningen
PO Box 30001
Groningen
Netherlands
9700 RB

Study participating centre
University Medical Centre Utrecht
PO Box 85500
Utrecht
Netherlands
3508 GA

Study participating centre
Radboud University Medical Center
PO Box 9101
Nijmegen
Netherlands
6500 HB

Study participating centre
Sint Antonius Hospital
PO Box 2500
Nieuwegein
Netherlands
3430 EM

Study participating centre
Netherlands Cancer Institute
PO Box 90203
Amsterdam
Netherlands
1006 BE

Sponsor information

Organisation
Catharina Hospital (Netherlands)

ROR
https://ror.org/01qavk531

Funder(s)

Funder type
Other

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Funder Name
KWF Kankerbestrijding

Alternative Name(s)
Dutch Cancer Society, Dutch Cancer Society (KWF Kankerbestrijding), KWF, DCS

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 11/01/2019:
Participant-level datasets and statistical codes will become available upon reasonable request

Previous IPD sharing statement:
The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	25/04/2019	29/04/2019	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes