ISRCTN15067672 https://doi.org/10.1186/ISRCTN15067672

A randomised multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and removing as many visible tumors as possible by surgery or other means versus chemotherapy alone

Submission date	Recruitment status	[_] Prospectively registered
27/01/2020	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/02/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
03/10/2025	Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-chemotherapy-with-other-treatments-for-bowel-cancer-that-has-spread-orchestra

Contact information

Type(s)
Scientific

Contact name
Dr Lotte Bakkerus

ORCID ID
https://orcid.org/0000-0002-7168-3799

Contact details
Geert Grooteplein Zuid 10
Department Medical Oncology
Route 452
Nijmegen
Netherlands
6525 GA
+31 (0)6 21000287
Lotte.bakkerus@radboudumc.nl

Additional identifiers

ClinicalTrials.gov (NCT)
NCT01792934

Clinical Trials Information System (CTIS)
2011-005003-32

Integrated Research Application System (IRAS)
255338

Central Portfolio Management System (CPMS)
43762

Study information

Scientific Title
A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone

Acronym
ORCHESTRA

Study objectives
Colorectal cancer is the third most common malignancy worldwide and the second leading cause of cancer death in the United Kingdom. In both early stage and metastatic disease, curative treatment is only possible with complete resection of the tumor. In recent years, resection of single organ metastases has improved survival in patients with limited metastatic colorectal cancer. Besides surgical resection, several techniques have become available for local treatment of metastases, including radiofrequency ablation, stereotactic ablative radiotherapy and transarterial chemoembolization. Local treatment of metastases of patients with metastatic colorectal cancer is often technically feasible, but effects on survival and quality of life have not been studied in patients with multi-organ metastatic colorectal cancer. The standard treatment of multi-organ metastasized colorectal cancer is systemic chemotherapy. This study is a randomized multicenter clinical trial for patients with multi-organ metastatic colorectal cancer, comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone. It is hypothesized that adding tumor debulking to chemotherapy will increase overall survival with at least six months.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/11/2019, North East – Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Address: Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; Tel: +44 (0)207 1048084; Email: nrescommittee.northeast-tyneandwearsouth@nhs.net), ref: 19/NE /0261

Primary study design

Interventional

Study design
Randomised; Interventional; Design type: Treatment, Radiotherapy, Surgery

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multi-organ, colorectal cancer metastases

Interventions
All patients will receive 3 cycles of chemotherapy with the XELOX regimen (capecitabine and oxaliplatin; 3-week cycle) or 4 cycles of FOLFOX regimen (5-FU and oxaliplatin; 2-week cycle) with or without bevacizumab. A baseline CT or 18F-FDG-PET-CT will be performed no more than 28 days prior to the first dose of chemotherapeutic treatment. After 3 or 4 cycles of XELOX or FOLFOX respectively, a second CT or 18F-FDG-PET-CT will be made and response rates will be evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). When required for assessing response rates, an MRI scan will be performed. Patients who show clinical benefit, defined as stable disease or response to therapy, will be randomized in one of the two study arms, arm A and arm B. Patients with progressive disease are not eligible study participation and will be treated according to best clinical practice, including all treatment modalities.

A CT or 18F-FDG-PET-CT, laboratory analysis, tumor markers and quality of life and multidimensional fatigue inventory questionnaires will be obtained at baseline, after 3 or 4 cycles of chemotherapy and subsequently every three months will be done.

Patients included in study arm A will continue to receive XELOX or FOLFOX therapy with or without bevacizumab until disease progression or unacceptable therapy-related toxicity. After 6 cycles of XELOX or FOLFOX, capecitabine monotherapy is also allowed. In case of unacceptable toxicity of oxaliplatin, capecitabine monotherapy may be considered before 6 cycles of XELOX or FOLFOX. When patients show progressive disease, they will be treated with second line therapy according to best clinical practice. Palliative local treatment options are accepted for a single progressive metastasis or for symptomatic metastases.

Patients in study arm B will be treated with 1 additional cycle of XELOX or FOLFOX without bevacizumab and additional local treatment in case of >30% response rates. Preferred local treatment will be surgical resection of the tumor lesions. Technically unresectable tumor lesions will be treated within 4 weeks by any form of other local treatment i.e. RFA, (DEBIRI-)TACE or SABR, depending on best clinical judgment and depending on the metastatic site. After local treatment, patients will receive 8 to12 additional cycles of XELOX or corresponding FOLFOX therapy with or without bevacizumab. After a total of 6 cycles of XELOX or FOLFOX, monotherapy with capecitabine is allowed. In case of unacceptable toxicity XELOX or FOLFOX therapy will be withheld. In case of unacceptable toxicity of oxaliplatin, monotherapy with capecitabine may be considered.

Patients in study arm B with stable disease will receive 3 additional cycles of XELOX or 4 cycles of FOLFOX with or without bevacizumab, whereafter response rates will be reevaluated. When these patients show a response or stable disease at this reevaluation they will be subjected to 1 additional cycle of XELOX or FOLFOX without bevacizumab and local treatment as described above. After local treatment, patients will receive 4 to 8 additional cycles of XELOX or

corresponding FOLFOX therapy with or without bevacizumab. In case of unacceptable toxicity XELOX or FOLFOX therapy will be withheld. In case of unacceptable toxicity of oxaliplatin, capecitabine monotherapy may be considered. Patients with progressive disease will be treated according to best clinical practice, including all treatment modalities. It is recommended to continue treatment until disease progression or unacceptable toxicity. However, continuation of any treatment schedule after 6 months in absence of disease progression or unacceptable toxicity is at the discretion of the investigator.

After local treatment, patients in study arm B will receive additional cycles of XELOX or corresponding FOLFOX therapy with or without bevacizumab to complete a minimum of 8 cycles of XELOX (or a corresponding 12 cycles of FOLFOX) or until disease progression or unacceptable toxicity. Patients with progressive disease will be treated according to best clinical practice, including all treatment modalities.

The primary endpoint of the study is overall survival. The study will be successful if at least a 6-month OS benefit is demonstrated in the experimental arm. In this randomized controlled trial the ratio of experimental versus control arm is 1:1. Using the log-rank test this trial will have 80% power to show this difference in OS with a 5% type I error rate (two-sided) when a minimum of 382 patients are enrolled with a follow-up time of 24 months.

Intervention Type
Mixed

Primary outcome(s)
Overall survival (OS), counting from the date of study inclusion to the date of death of the patient

Key secondary outcome(s)
1. Progression-free survival measured using the inclusion date and the progression date. Progression measured using RECIST 1.1 scoring system for each CT scan at baseline, randomization (after 3 or 4 cycles of chemotherapy) and every 3 months until progressive disease
2. Safety and efficacy of additional local treatment measured using scoring of Serious Adverse Events using the CTCAE version 4 and Clavien Dindo scoring systems when a SAE occurred
3. Quality of life measured using the validated EORTC QLQ CR29 and C30 questionaires at baseline, randomization (after 3 or 4 cycles of chemotherapy) and every 3 months until progressive disease

Completion date
01/07/2025

Eligibility

Key inclusion criteria
1. Patients with CRC metastases in ≥ 2 different organs and
1.1. >3 extrahepatic metastases or
1.2. >5 hepatic metastases not located to one lobe or
1.3. ≥1 hepatic metastases and either positive para-aortal lymph nodes or celiac lymph nodes or adrenal metastases or pleural carcinomatosis or peritoneal carcinomatosis
1.4. The primary tumor is excluded as metastatic site
2. Feasible radical tumor debulking. Incomplete tumor debulking is allowed only if at least 80%

of metastases can be treated
3. Age >= 18 years
4. WHO performance status 0 – 1
5. Life expectancy of at least 12 weeks
6. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Prior (neo-)adjuvant chemotherapy for < 6 months after last treatment and first detection of extrahepatic metastases, except for neoadjuvant capecitabin in the context of chemoradiation for rectal carcinoma
2. Candidates for HIPEC
3. Patients with liver metastases only
4. Evidence of brain metastases
5. History of other prior malignancy except for adequately treated basal cell or squamous cell skin cancer or in-situ carcinoma of any organ. Patients with other malignancies are eligible if they have remained disease free for at least 5 years
6. History of cardiac disease:
6.1. Congestive heart failure >NYHA class 2
6.2. Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening)
6.3. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
7. Uncontrolled hypertension. Blood pressure must be ≤160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 3 separate measurements on at least 2 separate days
8. Uncontrolled infections (> grade 2 NCI-CTC version 4.0)
9. Pregnant or breastfeeding women. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, and diaphragm) or intrauterine device during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised.
10. Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug
11. Concomitant chronic use of dexamethasone, anti-convulsants and anti-arrhythmic drugs

other than digoxin or beta blockers
12. Severe allergy for contrast media not controlled with premedication
13. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results
14. Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study

Date of first enrolment
01/05/2013

Date of final enrolment
01/07/2023

Locations

Countries of recruitment
United Kingdom

England

Netherlands

Study participating centre
University Hospital Southampton NHS Foundation Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Royal Liverpool University Hospital
Prescot Street

Liverpool
United Kingdom
L7 8XP

Study participating centre
Hampshire Hospitals NHS Foundation Trust
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Sponsor information

Organisation
Radboud University Medical Centre Nijmegen (Netherlands)

Funder(s)

Funder type
Charity

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

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		05/06/2024	04/03/2025	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version v3	01/10/2019	07/02/2020	No	Yes
Plain English results			03/10/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes