Participant Information Sheet (PIS)

ORCHESTRA trial

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

Dear Sir/Madame

Unfortunately you were recently diagnosed with metastatic bowel cancer for which, due to the extensive nature of the disease, there are currently no curative treatment options available. The standard treatment in this situation is chemotherapy which is intended to increase your survival time. However, in an effort to improve therapy we are investigating whether it is worthwhile to combine the standard chemotherapy with additional tumor debulking by local treatment of the metastases. Debulking means that as many visible tumors as possible are removed by surgery or other means. This is already being done in patients with limited disease. However, it is unknown whether patients with metastases in several organs would benefit from this form of treatment.

With respect to this aspect we would like to kindly request whether you would be willing to participate in the ORCHESTRA trial.

Aim
Our goal is to evaluate the benefit of tumor debulking on survival time in patients with multi organ metastatic bowel cancer when added to the standard chemotherapy, compared to chemotherapy alone.

Research population
Participation in this study is limited to patients with bowel cancer that have metastases in 2 or more organs and are about to start chemotherapy. Tumor debulking of at least 80% should be feasible. A team of specialists, who have experience with the local treatment of metastases, will decide whether it is feasible to treat 80% on a patient by patient basis. In addition, there should not be any other important underlying medical issues, which will be determined by a physical examination, a heart tracing (ECG) as well as blood and urine tests. These examinations are part of standard of care.

In total, it is the aim to recruit 478 patients in hospitals both in the Netherlands and in the United Kingdom for participation in this trial.

Recruitment
You have been informed about the study by your medical oncologist or surgeon. The study team examined in detail whether you are eligible to participate in the study. If you have received this letter and information it's because you are potentially eligible for the study. You now have the time to review all the information. You will be called by the study team so that you can still ask questions and you can then say whether you are interested in participating in this study. If you are interested in the trial, you will receive an appointment for an enrollment visit in the hospital where any remaining questions are answered. At the end of this visit you can sign this information sheet with which you give permission for research-related procedures. A copy of this document is given to the you, and copies are placed in the hospital records, the research records, and filed with the Clinical Research Office.

You are entirely free to decide whether you want to take part in this trial. Take your time to make this decision. Whatever you decide, it will not influence the standard of care you will receive from the treating physician or nursing staff. At any time during the trial, you can decide to end your participation within the trial without effecting your overall

treatment. In addition, if your treating physician decides that it is in your best interest to end your trial participation prematurely, he/she will discuss this with you. If you agree to participate, your general practitioner will be informed.

What's involved?
If you decide to participate within the trial your treatment would initially start with standard chemotherapy to treat the tumor. Your treating physician will decide whether is this will be CAPOX or FOLFOX. This treatment is part of standard of care. More information on the chemotherapy can be found in appendix A.

After 3 courses of CAPOX or 4 courses of FOLFOX a (PET) CT scan, or a MRI scan when required, will be performed. This is also standard of care. If your disease has progressed despite the chemotherapy, you will receive treatment with a different chemotherapy regimen; however, this would mean you would no longer be able to take part in the study.

If your disease has remained stable or responded to chemotherapy, you will be randomised (decided by the trial) into one of two groups. This random selection will decide whether you will receive the additional tumor debulking treatment, or if you will continue with the standard chemotherapy alone. A flow chart of the study design can be found in appendix B.

If you are randomised to receive additional tumor debulking, a team of specialists will decide how the metastases should be treated on an individual basis. This team will consist of a surgeon, a radiotherapist, a radiologist and an oncologist. Potential additional treatments may include either surgery, radiation therapy or local treatment of the tumour by a technique called ablation or local administration of chemotherapy into the tumour (called transarterial chemoembolisation). All debulking procedures are used sometimes but not routinely in this setting. The procedures are not experimental treatments themselves. There is already many years of experience with these different types of local treatments of metastases, but normally these procedures would not be performed in patients with multi-organ metastatic colorectal cancer. Details on these treatments can be found in appendix C.

What would taking part mean to you?
If you decide to participate in the trial, it will be necessary to collect all kinds of information on your disease and current quality of life. To screen for additional medical issues, your medical history and medications that you take will be reviewed. Furthermore, physical examination, a heart tracing and blood and urine tests will be performed. This is all part of standard care. If your CT scan was performed more than 4 weeks before the start of the chemotherapy, a new one will be made. This would in many circumstances be normal standard of care but not invariably.
Next, we ask you to complete 3 short questionnaires on quality of life before the treatment is started, after 3 cycles of chemotherapy and every 3 months thereafter. This study related procedure does not belong to standard of care.
A complete overview of all the study related procedures can be found in appendix D.

What are possible adverse events?
Patients respond differently to the administration of chemotherapy. Therefore, adverse events are difficult to predict. Before you start the chemotherapy your oncologist and nurse will give you thorough information on the possible side effects of the chemotherapy and give you instructions on what to do and whom to contact if you experience side effects. As mentioned before, chemotherapy treatment is part of the routine care. Possible adverse events of chemotherapy are also part of standard care and could therefore also occur if you receive standard treatment outside this clinical trial. More information about chemotherapy and its possible side effects can be found in appendix A.
If you are randomised to receive additional tumor debulking, it is important to realize that there is ample experience with the different treatments, however, despite the fact that these treatments are considered to be safe, each treatment can cause side effects or

complications. With every surgery, there is a small risk that you could die from the intervention. Also, surgical intervention, ablation or embolization techniques can be painfull where infections or bleeding can occur. You could also develop fever, nausea or vomiting. The possible risks of (extra) radiation in this study are described below per study arm:

Patients in standard arm:

If you take part in this study you may be required to undergo an addition PET-CT or CT scan which you would not require if you did not take part in the trial. This scan uses ionising radiation to form images of your body. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. In patients with your current clinical condition, the chance of this happening to you is very small.

Patients in experimental arm: (no radiotherapy)

If you take part in this study you will have CT guided procedures which will be extra to those that you would have if you did not take part in the trial. These procedures use ionising radiation to form images of your body. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. In patients with your current clinical condition, the chance of this happening to you is very small.

Patients in experimental arm: (with radiotherapy)

You are undergoing radiotherapy as part of your care. If you take part in this study the radiotherapy you receive may be different to standard radiotherapy. The total radiation dose you receive will be substantial due to the contribution from radiotherapy treatment. You will have additional examinations which will be extra to those scans that you would have if you did not take part in this study. These procedures use ionising radiation to form images of your body. The radiation dose from these additional procedures will be very small compared to the dose from the radiotherapy treatment you receive.

Since the various debulking procedures do not belong to standard care but are only given as part of the study, the different debulking procedures give additional risks compared to standard care. More information on all possible adverse events can be found in appendix C.

What are the possible benefits and disadvantages of taking part?

In both study arms you will receive chemotherapy in accordance with the current guidelines. There are indications that tumor debulking could lead to a survival benefit. We do not know if this applies to you. Depending on the type of local treatment that you will have, you will be admitted to hospital for several days. You might experience complications from the local treatments (see appendix C).

This study requires you to undergo a series of CT scans to follow the progress of your treatment. The vast majority of these scans would be considered normal care, and would be performed even if you did not take part in the study. The main risk of x-rays is that a cancer may occur many years after the exposure. It is considered that for a patient with your medical condition this represents a very small risk. Many hospitals routinely use this number of CT scans. During most CT scans, intravenous contrast agent is administered. There is a very small risk of an allergic reaction and kidney problems from the contrast agent.

Pregnancy and breast feeding

Women who are pregnant or breast feeding can not take part in this study, because participation will most probably pose risks to the (unborn) child. Patients and/or their partners are required to use effective birth control during the entire course of therapy. Please note that before inclusion in the trial, pregnancy will be excluded by means of a urine test.

Privacy

All the data that are collected during the course of the trial will be handled confidentially. The data will be documented on separate trial forms that include only your trial participation number, and not your name or other personal data. The results will be coded before being analyzed.

Radboud University Medical Center in the Netherlands is the sponsor for this study based

in the Netherlands. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Radboud University Medical Center will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

The [NHS/other site] will collect information from you and your medical records for this research study in accordance with our instructions. [NHS/other site] will use your name, [NHS number] and contact details [add other identifiers] to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Radboud University Medical Center and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [NHS site] will pass these details to Radboud University Medical Center along with the information collected from you and your medical records. The only people in Radboud University Medical Center who will have access to information that identifies you will be people who need to contact you to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, [NHS number] or contact details.

[NHS/ other site] will keep identifiable information about you from this study for 15 years after the study has finished.

Reimbursement
You can only receive a travel allowance for hospital visits that were only intended for study purposes. For standard care procedures such as chemotherapy treatment or CT scans, you cannot receive travel reimbursement from the study.

Insurance
The sponsor is making no arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises. Further information and the contact details of the insurance can be found in appendix F.

The sponsor and organizer of the trial is the Radboud University Medical Center in the Netherlands.
Contact information sponsor:
Principal investigator Radboud University Medical Center:
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Trialcoordinator:
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Approval Medical Research Ethics Committee
An NHS research ethics committee has reviewed the application of the trial and has given its full approval for the conduction of this research.

Informed Consent
If you decide to participate in this trial, we will ask you to sign an informed consent form (See Appendix G). By signing you confirm that you are considering trial participation. You still have the right to end participation for any reason that might be relevant to you. The physician will counter-sign the form, confirming that he/she informed you about the trial, handed you the patient information (including appendices) and is willing to answer any questions you might have.

The results of the trial will be published in a peer reviewed scientific journal. This document will be made available to the general public on the Southampton CTUs website. It will also be brought to the attention of Macmillan Cancer Support, an independent patient advisory group. If you want to know the results at the end of the trial, please contact your treating oncologist or the Macmillan Cancer Support group.

Thank you very much for reading this information sheet.

On behalf of Prof. H.M.W. Verheul MD PhD, medical oncologist and Ms L. Bakkerus MD.

Appendices

A. Chemotherapy Treatment
B. Flow chart of study design
C. Local Treatment Options
D. Study related procedures
E. Insurance
F. Local contact details
G. Informed Consent Form

Appendix A: Chemotherapy treatment

The chemotherapy is standard of care in accordance with the treatment guidelines.

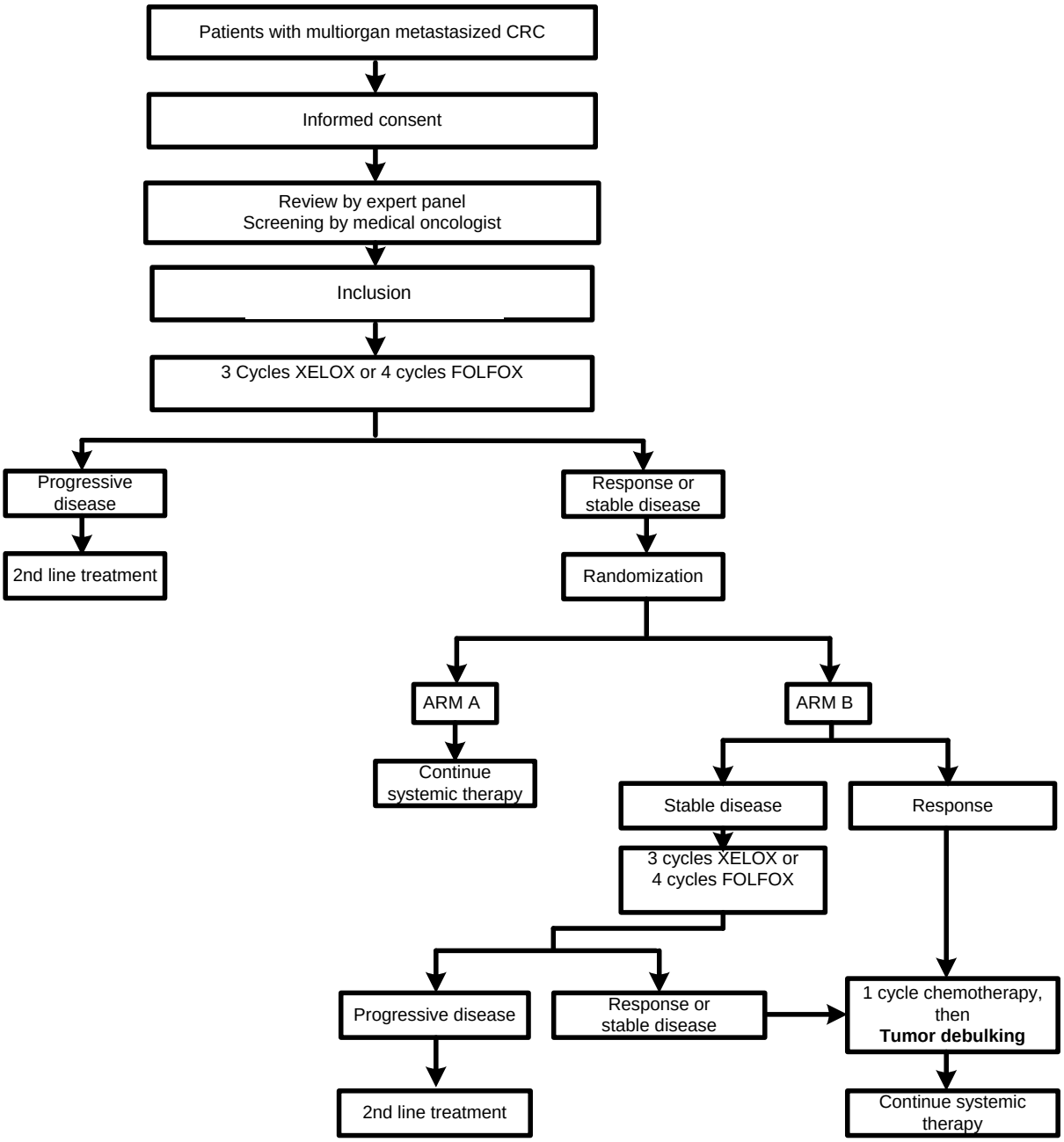
The chemotherapy can consist of CAPOX (xeloda and oxalipatin) or FOLFOX (5-FU and oxaliplatin). Your treating physician will decide whether this will be CAPOX or FOLFOX.

CAPOX: Oxaliplatin will be administered via an intravenous catheter. You will receive this infusion every first day of a 3-week cycle. You will take the Xeloda tablets twice a day, on days 1-14 of the 3-week cycle. This means that after the last dose of Xeloda, you have a week of rest before the next cycle begins.

FOLFOX: FOLFOX treatment consists of 3 medications. Two chemotherapeutic agents (5-FU and oxaliplatin) combined with folinic acid, which enhances the effect of the 5-FU. All agents will be administered via an intravenous catheter, either peripherally or via a Port-a Cath. This takes 3 days for which you will either be admitted to hospital or receive a portable infusion pump, according to local practice. FOLFOX is administered in 2-week cycles.

Patients can experience different side effects of the anti-tumor treatment. Before you start the treatment, your oncologist and nurse will give you thorough information on the possible side effects and will give you instructions on what to do and whom to contact if you experience side effects. It is important to follow those instructions. You should contact your doctor if you want to start new medication, also if you can buy them without prescription, because they could interact with the chemotherapy.

Appendix B: Flowchart study design



Appendix C: Local treatment modalities

Preferably, metastases will be surgically resected. If not possible, radiotherapy or ablative or embolization techniques will be applied.

Surgical Resection:
The surgeon will discuss with you which metastases will be resected. The planned procedure will depend on the localization of the metastases. During the operation you will be anesthetized. With every operation, there is a risk of bleeding, infection and a small risk of not surviving the 90 days after the procedure. This is in common with any major surgical procedure.

Ablation
The metastases can be treated by ablation techniques like radiofrequency ablation or microwave ablation. This means that during a short period of time extreme heating of the lesion occurs, which will cause the tumor cells to die. The procedure can be combined with an operation (open procedure) or through the skin (closed procedure).The procedures will be performed under anesthesia. The lesions are closely monitored before and during the procedure using ultrasound and CT scan. You will be admitted to hospital for a few days for observation and recovery. Typically after 3 days, you can develop fever, muscle ache, nausea of vomiting due to the ablation. This usually resolves within 10 days. With the procedure there is also a risk of bleeding or infection.

Radiation
Local radiation of metastases is also called stereotactic radiotherapy. It means that radiation is delivered to the metastases from a lot of different angles, causing a high dose of radiation in the metastases, and a low dose in the healthy surrounding tissue. The amount of radiation sessions depends on the localization. The radiotherapist will discuss the treatment plan with you. You will get extra CT scans for localization purposes. It is also possible that a FDG-PET-CT scan or a MRI scan is needed for the planning of the stereotactic radiotherapy. Selected patients may require additional investigations such as pulmonary function testing or a renogram, prior to stereotactic radiotherapy. Radiation usually has limited side effects, the skin can turn red and itchy. You should avoid sun exposure of the skin that was in the field of radiation.
Radiation treatment can result in damage to the surrounding normal tissues which can lead to an increased risk of developing a second cancer. In patients with your current clinical condition, the chance of this happening to you is very small. This can be discussed in more detail with your clinical team.

Embolization techniques
Transarterial chemoembolization (TACE) is a treatment where spheres filled with a chemotherapeutic agent are inserted in the blood vessels of the tumor. The spheres cause occlusion of the blood supply (and thereby oxygen and nutrients supply), causing the tumor cells to die. For optimal treatment planning you will receive a CT-angiography and portal venous phase CT of the upper abdomen before the TACE procedure. You will usually be admitted to hospital for a few days. The procedure can be painful and you can experience nausea and vomiting or develop a fever. Possible complications include bleeding and infection.

Appendix D: Study procedures

	Baseline	After 1 cycle of chemotherapy (CAPOX/FOLFOX)	After 3/4[1] cycles of chemotherapy (CAPOX/FOLFOX)	Follow-up phase at least every 3 months
Week	-4 to 0	2 or 3	8 or 9	
Medical history[6]	X		X	x
Physical examination [6]	X		X	x
Standard laboratory analysis[2, 6]	X		X	x
Standard urinalysis[3, 6]	X			
Heart tracing[6]	X			
CT or PET-CT[4, 6]	X		X	x
Tumor marker[6]	X	X	X	x
Quality of life questionnaires[7]	X		X	X[5]

[1]After 3 cycles of CAPOX chemotherapy or again after additional 3 cycles of CAPOX chemotherapy in case of stable disease for patients included in the experimental study arm. For FOLFOX chemotherapy after 4 cycles or additional 4 cycles of FOLFOX chemotherapy in case of stable disease for patients included in the experimental study arm.
[2] -7 days to 0
[3]Urinalysis: including pregnancy test in fertile female patients (-7 days to 0).
[4]Sometimes supplemented with an MRI scan if necessary.
[5]The first year of follow-up, then annually
[6]Part of standard of care
[7]Excess to normal standard of care

Appendix F: Contact details

Local Principal Investigator
Name
Function
Address
Tel/fax

Outside office hours:

Coordinating center
Principal Investigator: H.M.W. Verheul MD PhD, Professor of medical oncology
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