EXtended **C**riteri**A** treatment for **LI**ver metastases with heavy tumour **BUR**den

Protocol Identification Number: EXCALIBUR

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SIGNATURE PAGE

Title **EX**tended **C**riteri**A** treatment for **LI**ver Metastases with heavy tumour **BUR**den

Protocol ID no: **EXCALIBUR**

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I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Kristoffer Lassen	MD,PhD	PI		
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PROTOCOL SYNOPSIS

Protocol title: **EX**tended **C**riteri**A** treatment for **LI**ver Metastases with heavy tumour **BUR**den

Sponsor	Oslo university Hospital
Phase and study type	Phase II, Randomized controlled trial
Investigational Medical Product (IMP) (including active comparator and placebo) :	Fluorodeoxyuridine or floxuridine (FUDR, Fresenius Kabi, LLC, USA)
Centers:	Oslo University Hospital
Study Period:	Estimated date of first patient enrolled: February 2021 Anticipated recruitment period: 3 years Estimated date of last patient completed: October 2033
Treatment Duration:	24 weeks (6 cycles of 4 weeks)
Follow-up:	10 years
Objectives	Main study objective: To improve treatment outcome for patients with a heavy burden of colorectal liver metastases and progression on 1st line chemotherapy. Key secondary objectives: To establish whether the favourable results obtained by use of hepatic artery infusion chemotherapy can be replicated outside of US single centre series.
Endpoints:	Overall Survival (OS) at two years Secondary endpoints: Progression-free survival, overall survival at 5 years, resection/transplantation rate, quality of life.
Study Design:	Three-armed, two-sided, open label, parallel-group, single center, phase II trial.

Main Inclusion Criteria:	– Multiple colorectal liver metastases (6 or more metastases) – Progression on 1st line chemotherapy
Main Exclusion Criteria	– Extensive extrahepatic disease
Sample Size:	45 patients
Efficacy Assessments:	Overall survival, progression-free survival and resection rate
Safety Assessments:	Major adverse events/side-effects from chemotherapy and major complications following surgery.
Other Assessments:	Health economy assessment, quality-of-life

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List of Abbreviations and Definitions of Terms

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria (for cancer trials only)
CTCAE	Common Terminology Criteria for Adverse Event (for cancer trials only)
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (includes active comparator and placebo)
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 Background – Disease

Colorectal cancer (CRC) is the second most frequent malignant disease in Norway (Cancer in Norway 2017). About 50% of the patients will have metastatic disease at time of diagnosis or develop metastatic disease later on. Liver metastases are the most frequent site of metastatic disease. Liver resection is considered the only curative treatment option in CRC patients with liver metastases, however only about 20% of the patients are candidates for liver resection. The treatment option for the majority of the patients is palliative chemotherapy with median overall survival from start of chemotherapy of about 2 years and 10-12 months from starting second line chemotherapy.

1.2 Liver resections for Colorectal Liver metastases (CRLM)

While high-quality data (randomized trials) are lacking, it is generally accepted that the only curative treatment for colorectal liver metastases (CRLM) is surgery. Liver resections are generally well tolerated and safe [1], but some patients recur early and probably have limited or no benefit from surgery. These are hard to identify upfront. Even following three decades of systematic liver surgery for CRLM, there is a lack of robust prognostic scoring systems that have sufficient

discriminatory power to serve as selectors for surgery or non-operative treatment [2, 3]. Even among patients with very poor prognostic scores, there are some who will survive five years following surgery [4], and even without surgery [5]. Over the decades, the definition of resectability/un-resectability has been steadily modified. Today, any configuration of metastases can be deemed resectable as long as a resection will leave behind a working liver volume of at least 20-30 % of the estimated total liver volume with a functioning arterial inflow, portal venous inflow, draining bile duct and draining hepatic vein.

1.3 The grey zone

As resections are generally well tolerated and adequate prognostication is wanting, there is a tendency to offer resections to patients who have borderline resectable CRLM or who exhibit other non-favourable traits like large or multiple metastases. For patients who have early recurrence of disease, such resections represent a net loss of quality-of-life and an unwanted expenditure for society. Exploring the optimal treatment modality for patients in this grey zone, i.e. with uncertain benefit from surgery, is important to avoid unnecessary resections and providing the optimal treatment for patients in a critical situation.

1.4 Systemic chemotherapy for CRLM

Palliative chemotherapy is in general the only treatment option for the vast majority of non-resectable patients. The expected median overall survival (OS) from start of first line chemotherapy is about 2 years and the 5 years OS is about 10%, although, longer median OS has been obtained in selected patients with good performance status (ECOG 0-1), no (K)RAS or BRAF mutations and left-sided tumors [6-10]. OS from start of second line chemotherapy is 10-12 months [11].

1.5 Liver transplant for CRLM

Liver transplantation (LTX) has emerged as a possible solution for some patients with unresectable CRLM who otherwise have good prognosis based on available scorings systems [12, 13]. In patients with non-resectable liver only metastases we have previously shown 5 year OS of 56% compared to 9% in a similar cohort of patients starting first line chemotherapy [6], but due to lack of donor organs this will never become the backbone of any treatment modality for a disease as prevalent as CRLM. However, LTX is probably the best treatment option in highly selected patients with non-resectable CRLM liver only disease.

1.6 Hepatic artery infusion (HAI) chemotherapy for CRLM

The biological rationale for intra-arterial chemotherapy is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumors. Hepatic Artery Infusion (HAI) of a cytotoxic drug floxuridine (FUDR) that has a very high first-pass extraction (ca 95 %) in the liver has shown promising results in selected series for several decades [14-16]. It was developed at Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA) but is currently unavailable in the European Union, because floxuridine is not registered. HAI has however not gained foothold as a standard treatment option for CRLM, and most publications stem from a very few centres. The reasons for this lack of dissemination are unknown but could well be related to the complexity of the treatment algorithm and the lack of modern randomized trials. In Europe several centers in The Nederlands have recently started the HAI treatment procedure as adjuvant treatment in CRC patients who have received liver resection. (Buisman FE et al. Ann. Surg. Oncol. 2019 26: 4599-4607. Of the 20 patients included in the study in The Nederlands two patients had Clavien-Dindo complication grade III with reoperation due to replacement of a pump with slow flow-rate and a flipped pump. The treatment administered both at MSKCC and the two centers in The Nederlands consist of 0.12 mg FUDR/kg/day + 35.000 IE heparin + 25 mg dexamethasnone in a total volume of 35ml NaCL administered as a continue infusion for 14 days with dose reduction if liver function is affected (Table 2). At day 15 the pump is emtied and refiled with a low dose heparin solution for continuous infusion to avoid coagulation of the catheter. A new cycle is started at day 29. The HAI treatment has been combined with both oxaliplatin and irinotecan regimens combined with 5-FU as systemic chemotherapy [14,16,17] .HAI has also been

combined with systemic gemcitabine-oxaliplatin regimen in patients with non-resectable intrahepatic cholangiocarcinoma[18]

In the study by D'Angelica in non-resectable CRC patients the response rate was 76%, median overall survival was 38 months and 23 of 49 patients became resectable and received a liver resection. Patients having a liver resection had a 3 year overall survival of 80%. In the study by Pak 33 of 64 non-resectable CRC patients received a liver resection with 5 year overall survival of 36%. These results are better compared to what has been reported by systemic chemotherapy only with median overall survival of about 24 months in most studies. Optimal treatment for patients with CRLM in the grey zone is therefore not yet defined and there is a definte need for further studies.
To optimize treatment for patients with a large tumour burden and borderline resectability, we will compare three treatment modalities in a randomized controlled trial in patients that have progressive disease on 1st line of chemotherapy treatment.

1.7 Rationale for the Study and Purpose

The target population for this study will be patients who based on traditional preoperative criteria have a very dismal prognosis. They will – according to the inclusion criteria – have a large tumour burden and have shown progression on 1st line systemic chemotherapy treatment. Based on previous trials, only 30 % of this patient group will be alive after two years. These patients have today only one treatment modality available: 2nd line systemic chemotherapy. Response can, however, only be expected in a small minority of these patients. As of today, they are not acceptable for inclusion into any of the liver transplant protocols, and hepatic aretery infusion (HAI) chemotherapy treatment is not offered in Norway (or any other European country, save the Netherlands, as far as we know).

With such a dismal outcome for these patients, an alternative modality that has the potential to improve survival is highly warranted. While transplantation has such a potential, the access to donor organs will allways limit the real-life use of such a treatment and the inclusion of a transplant group in this trial is primarily for proof-of-principle reasons: to benchmark what we have reason to believe is the optimal treatment.

The use of HAI chemotherapy with FUDR has some inherent risks. A laparotomy is necessary to apply the catheter and intra hepatic infusion of FUDR has been reported to cause biliary inflammation and necrosis in a small fraction of the patients. The risk for the latter is however significantly reduced by concommittant steroid infusion. The experiences published from the MSKCC (se further) does however suggest that the drug has few systemic side effects as the first-pass effect in the liver is close to complete, i.e. there is minimal release of active drug into the systemic circulation.

The IMP for use in this protocol does not have a marketing authorization in Europa. The institution that has pioneered the HAI treatment in CRC is Memorial Sloan Kettering Hospital (MSKCC) in New York and the dose is identical to the dose that used in several studies from MSKCC [14,16] and The Nederlands[17].

1.8 Research hypothesis

In patients with large tumour burden and/or borderline resectability of colorectal liver metastases and progression on 1st line systemic chemotherapy, overall survival following systemic therapy combined with hepatic artery infusion chemotherapy (HAI), or liver transplantation, is better than following conventional systemic chemotherapy alone.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

The objectives and endpoints of the study are listed in Table 1 below. The primary endpoint is Overall survival at 2 years after randomization. Safety and toxicity grade 3-5 toxicity will be reported.

Table 1 Objectives and related endpoint:

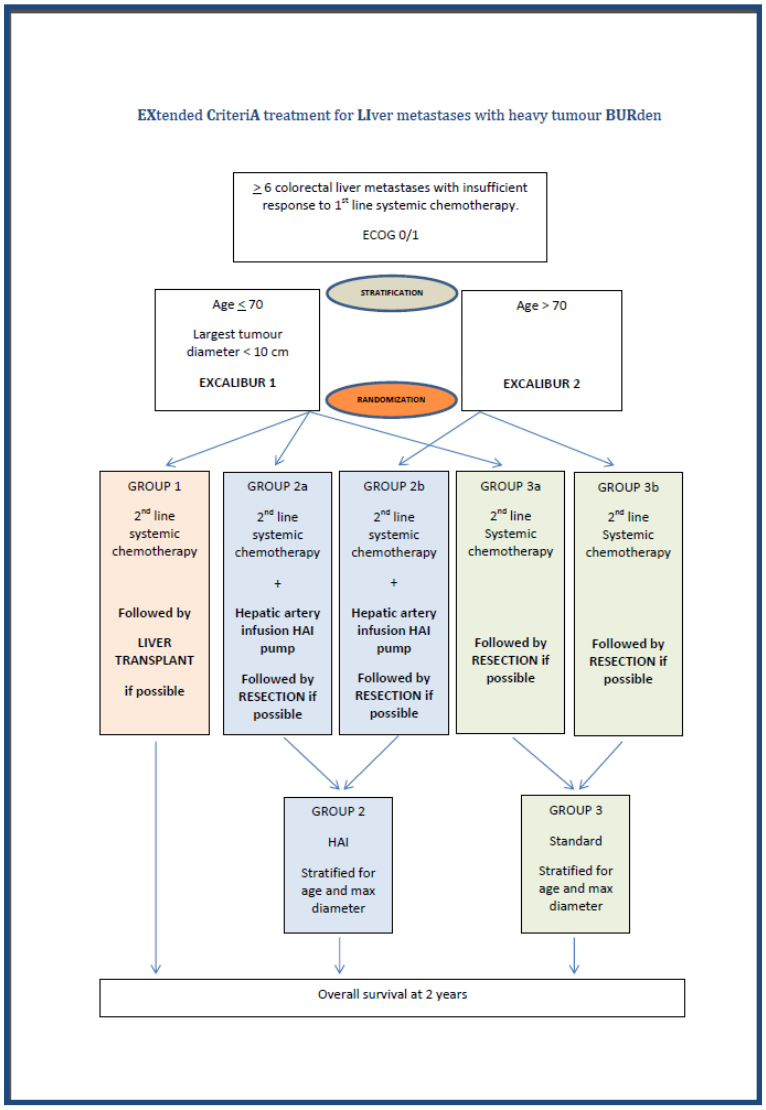
Objectives	Endpoints	Assessment
Primary: Overall survival	Overall survival at 2 years after randomization	Medical records
Secondary: 1. Efficacy	Overall survival (OS), at 5- and 10-years after randomization.	Medical records
Radiological response to treatment	Response rate	CT/MRI-scans RECIST 1.1
2. Efficacy	Resection rate	Medical records
3. Efficacy	Number of patients randomized til HAI receiving HAI-treatment	
4. Efficacy	Quality of life	EORTC QoL C30
Safety all patients	Adverse events in patients receiving chemotherapy	NCI-CTC 5.0 grade III-V toxicity
Safety in patients receiving resection/transplantation.	Major surgical complications	Accordion Grade III - VI
Exploratory	Molecular analyses related to disease-free and overall survival	Biobank stored blood and tumour tissue
	Progression free survival (PFS). (PFS will be calculated both with and without sensoring patients receiving resection or transplantation at time of resection/transplantation) Disease free survival after liver resection/transplantation in the different treatment arms	CT/MRI-scans RECIST 1.1

3 OVERALL STUDY DESIGN/OVERVIEW OF DESIGN

EXCALIBUR is a phase II study.

Excalibur 1 is a three-armed RCT comparing 2nd line systemic chemotherapy to liver transplant and to HAI. Because of the transplant arm, this sub-trial has somewhat stricter inclusion criteria.

Excalibur 2 is a two-armed RCT conducted within the same framework as *Excalibur* 1, but without the transplant arm, and with somewhat wider inclusion criteria (see figure). For analysis, the HAI arm and the systemic chemotherapy arm of *Excalibur* 1 and 2 will be directly comparable (stratified for age and primary tumour resected/in situ) and hence boost numbers for this comparison.



Study period:

Estimated date of first patient enrolled: February 2021

Anticipated recruitment period: 3 years

Estimated date of last patient completed: November 2024

Treatment duration: up to 2 years

- HAI (intervention group 2) and Systemic therapy (control arm, group 3): Until progression or resection, up to two years
- Transplant (intervention group 1): Until transplant or until removal from list.

Follow-up for outcomes: 10 years

4 STUDY POPULATION

4.1 Selection of Study Population

Patients may be referred to OUS from all surgical or oncological departments in Norway. Systemic chemotherapy will be administered according to standard procedure at the local oncological departments. Administration of HAI-treatment will be performed at OUS. Liver resection and liver transplantation will be performed at OUS.

Palliative systemic 2nd line chemotherapy is standard of care for patients eligible for inclusion in this study. Liver transplantation is not considered standard treatment option for CRC patients neither in Norway nor internationally. Documented benefit of liver resection has not been established in this cohort of CRC patients. If HAI-treatment improves survival in this cohort of patients has not been well documented. Patients included in this study may have the benefit of extended overall survival compared to standard palliative chemotherapy only, although liver transplantation or liver resection may result in serious complications in a small fraction og patients.

4.2 Number of Patients

Forty-five patients will be included in this trial.

4.3 Inclusion and exclusion criteria

4.3.1 Inclusion *Excalibur* 1 and 2

Included patients must fulfil the following criteria

1. Primary histology:
   a. Verified adenocarcinoma in colon/rectum, radically resected with adequate margins/pre-operative treatment
2. Liver metastases:
   a. Six or more liver metastases that have progression (or insufficient response on 1st line chemotherapy, including toxicity). and are hence planned for 2nd line chemotherapy
3. If a history of confirmed extra hepatic metastatic lesion or local relapse, this must have been successfully treated more than 2 years ago without a new relapse.

4. Chemotherapy
   a. Planned for 2nd line chemotherapy.
   b. If patients are switched to 2nd line chemotherapy, randomization can only be allowed prior to first evaluation on 2nd line chemotherapy regimen.

5. The patient
   a. Good performance status, ECOG 0 or 1.
   b. Satisfactory blood tests: Hb >10g/dl, neutrophiles >1.0 (after any G-CSF), TRC >75, Bilirubin<1.5 x upper normal level, ASAT, ALAT<5 x upper normal level, Creatinine <1.25 x upper normal level. Albumin above lower normal level.
   c. Women of childbearing potential (WOCBP) must have a confirmed menstrual cycle and a negative highly sensitive pregnancy test prior to inclusion, or two negative pregnancy tests two weeks apart
   d. WOCBP must agree to use a highly effective method of contraception (see section 6.1.2) for the entire period of exposure to the IMP in the trial, plus for one menstrual cycle/30 days after the last exposure due to the genotoxic potential of the IMP
   e. Men that may have sexual relations with a WOCBP during the trial must agree to use a condom during intercourse for the entire period of exposure plus for one sperm cycle / 90 days after the last exposure due to the genotoxic potential of the IMP

6. Signed informed consent and expected cooperation of the patients for treatment and follow up must be obtained and documented according to GCP, and national/local regulations.

Exclusion Criteria Excalibur 1 and 2

Any of the following criteria will exclude participation in the trial:

1. Arterial anatomy not suited for HAI pump-line insertion.
2. Liver metastatic ingrowth to the diaphragm determined by CT-scan and/or MRI/or ultrasound
3. Previous bone or CNS metastatic disease.

4. Non-curable pulmonary or peritoneal metastases, non-regional lymph-nodes, or local recurrence on PET/CT scan, and on CT or MRI thorax/abdomen/pelvis dated within 6 weeks prior to the trial hospital MDT meeting.
5. Patients with known intolerance or allergy to any ingredient of the IMP to be used as standard therapy for that patient must be excluded
6. Breastfeeding women must be excluded
7. Patients with a psychiatric condition that makes participation in the trial impossible or unethical
8. Patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections must be excluded.
9. Any other reason why, in the opinion of the investigators, the patient should not participate.

Exclusion Excalibur 1

Any of the following will preclude inclusion into Excalibur 1 (but not into Excalibur 2)

1. BRAF positivity
2. Any sign of extra-hepatic metastatic disease or local recurrence on PET/CT scan, and on CT or MRI thorax/abdomen/pelvis dated within 6 weeks prior to the trial hospital MDT meeting (exception allowed for ≤3 resectable lung lesions all ≤ 15mm).
3. Liver lesion >10cm
4. Patient BMI > 30
5. Any previous non colorectal malignancy within latest five years
6. Age ≥ 70 years

5 TREATMENT

For this study the drugs that are used for HAI are fluorodeoxyuridine also known as floxuridine (FUDR, Fresenius Kabi, LLC, USA) and dexamethasone. These drugs are defined as Investigational Medicinal Product (IMP). The patients will receive 20 mg proton pump inhibitor.

All patients will receive second line standard systemic chemotherapy at the discretion of the treating medical oncologist. Resection in the HAI and standard care groups will be undertaken only provided sufficient response on 2nd line chemotherapy (with or without HAI/FUDR) has been achieved (defined as ≥ 10 % response on median diameter of two target lesions, i.e. measured as with RECIST 1.1. but with a trial-specific cut-off). The study is a three- armed study, where the control arm receives systemic 2nd line chemotherapy only, one arm receive systemic chemotherapy and HAI and the third arm 2nd line systemic chemotherapy and liver transplantation.

5.1 Technical procedures

5.1.1 Second line systemic chemotherapy

The medical oncologist at the local hospital who knows the patient's response and side-effects of first line chemotherapy will decide on second line chemotherapy and schedule the treatment. If the patient is randomized to HAI, the systemic chemotherapy will have to be given according to the planned HAI schedule. Study nurse at OUS will be responsible for coordinating HAI treatment and systemic treatment

Patients randomized to liver transplantation or systemic chemotherapy (and resection if possible) will have transplantation/resection when the MDT-meeting considers surgical treatment possible. All patients will receive chemotherapy at their local oncological departments. Dose reduction/dose delay will be administered according to standard procedure at the different treating oncological departments. Depending on logistics, some patients in the HAI group will have commenced 2nd line chemotherapy prior to insertion of the pump.

5.1.2 Liver transplantation

Patients randomized to liver transplantation will be listed on the extended donor criteria (EDC) waiting-list when the MDT meeting consider the patients a candidate for liver transplantation. The

oncologist and transplant surgeon will decide if the patient should continue on chemotherapy after being listed for transplantation. Patients treated with bevacizumab will stop bevacizumab at time of being listed for transplantation.

5.1.3 Hepatic Artery infusion (HAI)

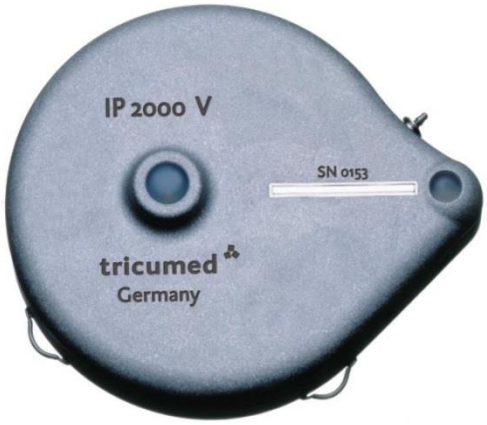
Hepatic artery infusion will be administered via a pump (Tricumed IP2000V (tricumed Medizintechnik GmbH, Röntgenstraße 7a, 24143 Kiel) titan infusion pump with a 35 ml reservoir (product no. 200 V 025 035 0WA) connected to a Brown silicone intraarterial catheter. The catheter is inserted into the gastroduodenal artery during a formal laparotomy. The treatment will be administered as established as standard operating procedure at Memorial Sloan Kettering Cancer Centre as previously described [14-16]. Patients in the HAI group will also receive systemic chemotherapy.

5.1.4 Surgical procedure

5.1.4.1 Placement of the pump.

The pump (Tricumed IP2000V Infusion Pump, 35ml, CE number: I7120728744042) for HAIP chemotherapy is compatible with the use of intravascular infusion of floxuridine. The Pump Catheter 1000 of Tricumed (CE number: I7120728744042) will be connected to the intra-arterial catheter of B.Braun, (CE: 04430042), which has beads that allow for securing the catheter with non-absorbable ties in the gastroduodenal artery (GDA). The two catheters are linked with the Catheter Connector 2000 of Tricumed (CE number: I7120728744042).

Figure A. The Tricumed IP2000V pump



5.1.4.2 HAIP catheter placement

The catheter is positioned in the GDA allowing perfusion of the entire liver without obstructing the flow in the hepatic artery. In patients with abnormal hepatic arterial anatomy, the GDA is still the preferred site, as long as it connects with a proper hepatic artery perfusing of the liver. Perfusion of the entire liver can be achieved in these patients by ligating all accessories and replaced hepatic arteries. Intrahepatic shunts will typically reassure that the catheter perfuses all liver segments, which can be confirmed intraoperatively with a bolus injection of methylene blue in the pump after clamping accessory and replaced hepatic arteries.
If the GDA is not suitable for catheter placement because of small calibre (rare) or absence of the GDA, the bifurcation of the proper hepatic artery into a left and right hepatic artery can be used. After an (extended) hemihepatectomy, the stump of the artery of the resected liver can be used as a conduit for the catheter. In minor liver resections, the left hepatic artery can be sacrificed for retrograde placement of the catheter with perfusion of the right hepatic artery, resulting in cross-perfusion of the entire liver through intrahepatic shunts. Cross- perfusion can sometimes not be confirmed intraoperatively. However, most patients will eventually develop cross-perfusion after four weeks, as will be ascertained with a postoperative nuclear scan.

5.1.4.3 Technique HAIP catheter and pump placement

The common hepatic artery (CHA) and the GDA are both palpable superior to the body of the pancreas and the first portion of the duodenum. The GDA runs parallel to and lies immediately to the left of the common bile duct, and it is advisable to start by dissecting the CHA to minimize the risk of injuring the bile duct. The right gastric artery is ligated and divided. The distal CHA, the entire GDA, and the proximal proper hepatic artery are dissected circumferentially from their attachments. The full length of the extra-pancreatic GDA is mobilized over 2-3 cm to facilitate insertion of the catheter. Suprapyloric side-branches of the GDA are often encountered and must be ligated. Frequently, branches to the pancreas and duodenum arise from many of these dissected vessels, and it is essential to identify and ligate these branches to avoid inadvertent perfusion of the pancreas, stomach, or duodenum. The common hepatic artery is mobilized 1 cm proximally, and the proper hepatic artery is mobilized about 2 cm distally from the origin of the GDA. Branches to the retroperitoneum from the right or left hepatic artery are common and should be ligated. Review of preoperative CT angiography to look specifically for these branches is important, because they are often found in retrospect. At this point, a complete circumferential dissection of the common hepatic artery, GDA, and proper hepatic artery should be ensured such that no vessels to the pancreas, stomach, or duodenum remain. The GDA should be temporarily occluded with palpation of the proper hepatic artery to rule out retrograde flow to the liver through the GDA secondary to celiac artery stenosis. The intraoperative methylene blue infusion ensures that the blockage og the retroperitoneal perfusion from the GDA is complete.

The pump pocket will be created in the left lower abdomen so that the pump lies below the ribs to avoid contact with the iliac spine and the edge of the ribs. (Figure B) In extremelyobese patients, placing the pump over the ribs should be considered, because this may help in locating and accessing the pump. The pump and catheter will be handled carefully, avoiding contact with the patient's skin. The catheter is tunneled through the abdominal wall into the abdominal cavity. The pump is secured to the abdominal fascia with nonabsorbable sutures; the catheter should be positioned behind the pump to prevent injury by a needle. The catheter that comes attached to the pump is then connected with the intra-arterial catheter that has rings close to the tip to facilitate fixating the catheter to the artery with ties.

The GDA is then ligated with a nonabsorbable tie as far away from the CHA as possible and vascular control of the common and proper hepatic arteries is achieved with vascular clamps or vessel loops. Isolated vascular control of the GDA at its orifice also can be used to avoid occlusion of the hepatic artery. An arteriotomy is made in the distal GDA, and the catheter is inserted up to, but not beyond, the junction with the hepatic artery. If the catheter protrudes into the common hepatic artery, turbulence of blood flow can lead to thrombosis of the vessel. Failure to pass the catheter to the junction leaves a short segment of the GDA exposed to full concentrations of floxuridine without the diluting effect of blood flow, potentially resulting in sclerosis, thrombosis, or late dislodgment. When positioned, the catheter should be secured with three nonabsorbable ties proximal to the tying rings on the catheter. Perfusion of both lobes of the liver and lack of extrahepatic perfusion is confirmed by a bolus injection of 2 to 3 mL of methylene blue. After the perfusion test, the catheter is flushed with heparinized saline, and the wounds are closed.

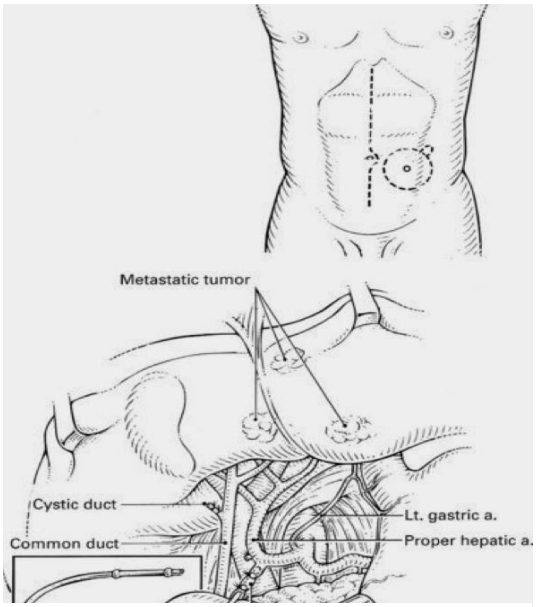


Figure B. Placement of the catheter in the gastroduodenal artery (GDA), Right gastric artery is shown adjacent to the GDA and is ligated

5.1.4.4 Postoperative procedures

Prior to the first administration of intra-arterial chemotherapy, bilobar hepatic perfusion and lack of extrahepatic perfusion are confirmed by post-operative technetium-99-labeled

macroaggregated albumin (MAA) nuclear medicine scanning. MAA is administered through the IP2000V bolus port. Within 1 hour after MAA injection, a SPECT/CT scan is performed.

In addition, a CT with contrast injection through the bolus port of the pump is performed. The contrast agent is administered through the bolus port of the IP2000V pump while acquiring images using dual source perfusion CT at a temporal resolution of 1.5 second.

Both scans are obtained after recovery from surgery, just prior to hospital discharge. Patients with extrahepatic perfusion are evaluated angiographically and aberrant branches embolized with re-testing prior to treatment. All other postoperative procedures are done according to local hospital procedures.

5.1.4.5 Pump removal

In the case of progressive disease or any other reason where use of pump/catheter in HAI group becomes obsolete and is not acceptable to the patient, the pump may be removed (at OUH, dept of GI surgery, HPB-section) through a local insicion. The catheter will be ligated and left in situ. In the case of liver resection the catheter may be removed (with the pump) or left in situ, at the surgeon's discretion. During longer drug-free periods, a glycerol solution will be added in the pump chamber to prevent trobosis of the catheter until the next treatment cycle. Post-resectional use of HAI will be off protocol.

5.1.4.6 Dosage of FUDR, Dexamethasone (Dex), proton pump inhibitors and pump administration.

All patients start HAIP chemotherapy 4 to 8 weeks after surgery, after confirmation of bilobar hepatic perfusion and lack of extrahepatic perfusion.

The pump reservoir is filled percutaneously with 0.12 mg/kg floxuridine together with 35,000U of heparin, 25 mg of dexamethasone and enough normal saline for a total volume of 35cc. Both are to be delivered as a 14-day continuous infusion through the pump. For patients who are more than 25% above ideal body weight, the actual dose of floxuridine is calculated by using a weight that averages the patient's actual weight and their ideal weight.

Patients will commence treatment at a minimum 2 weeks after pump placement. Therapy will be administered in a 4-week cycle. HAI therapy starts on day 1 of each cycle, and the pump will be emptied and filled with heparin (35,000 units) and normal saline on day 15. Systemic chemotherapy will be administered on day 2 and day 16 of each cycle.

Until completion of HAI chemotherapy, patients will receive prophylactic proton pump inhibitor 20mg once daily.

To assess early side effects and toxic reactions, patients will be hospitalized at the Gastrointestinal ward at Rikshospitalet for 24 hours following start of first FUDR administration. At later occations, the treatment will be offered as an outpatient procedure.

5.1.4.7 Drug Information floxuridine.

The drug that is used for HAIP is fluorodeoxyuridine or floxuridine (FUDR, Fresenius Kabi, LLC, USA). Floxuridine has been administered using HAI pumps since the early 80s for patients with CLM in the adjuvant, neo-adjuvant, and induction chemotherapy setting. Floxuridine has a half-life of 10 minutes and the liver extracts 95% of floxuridine during the first pass. Toxic effects have been well characterized and are described in detail below. The most important serious adverse drug reaction is biliary toxicity.

5.1.4.8 Dose adjustments

Patients' complete blood counts and liver function tests are monitored every 2 weeks during HAIP chemotherapy. In the case of abnormal blood tests, dose reduction or postponement of HAIP chemotherapy is done according to the protocol (Table 2) that has been used at MSKCC for many years.

Table 2 complete blood counts and liver function tests:

	Reference Value (RV)*	% Floxuridine dose
Aspartate aminotransferase	2-3 * RV	80%
	3-4 * RV	50%
	>4 * RV	Hold
Alkaline phosphatase	1.2-1.5 * RV	50%
	>1.5 * RV	Hold
Total bilirubin	1.2-1.5 * RV	50%
	>1.5 * RV	Hold

**Reference value is defined as the patient's value on the first day of the most recent floxuridine dose.*

If treatment is held for any of the above situations, treatment will not be reinstituted until values come down below 3* RV for aspartate aminotransferase or below 1.2*RV for alkaline phosphatase or total bilirubin, at which time treatment will resume at 25% of the last dose received.
If the patient develops a total bilirubin level above 51mmol/L (i.e. 3.0 mg/dL), the pump should be emptied and dexamethasone 25mg plus 35,000 U of heparin and enough normal saline to fill the pump reservoir should be placed in the pump for 14 days. Once there is no longer evidence of toxicity, the dexamethasone dose should be tapered in increments of 5mg every 14 days. Tapering will continue unless enzymes increase. Floxuridine should be permanently discontinued. Epigastric pain unresponsive to H2 blocker use should prompt a diagnostic workup including a technetium scan to rule out extrahepatic perfusion and an upper endoscopy to assess ulcer disease.

5.1.4.9 Duration of Therapy

Patients will receive HAI chemotherapy with floxuridine until progressive disease, until resection or until discontinuation due to toxicity or withdrawel of informed consent. After the end of adjuvant treatment the removal of the subcutaneous pump will be discussed with both the patient and the local expert panel. If the pump is removed, the catheter is tied off and will be left in place at the fascial level.

5.1.4.10 Expected toxicities

Systemic side effects with HAIP of floxuridine almost never occur; in particular, myelosuppression, nausea, and vomiting do not occur.(27) Diarrhoea is rare and should raise the suspicion of shunting of floxuridine to the bowel. Ulcer disease and biliary sclerosis are the most common toxicities. Ulcer disease results from inadvertent floxuridine perfusion of the stomach and duodenum that can be avoided by ligating all branches from the hepatic artery to the stomach and duodenum. Ulcer disease should be suspected when a patient develops severe epigastric pain after administration of the first dose. Diagnosis is confirmed with upper endoscopy and treated with embolization of the hepatic artery branch responsible for extrahepatic perfusion. If an ulcer or gastroduodenitis will be identified, therapy will be withheld for one month to allow healing. Pain treatment and proton-pump inhibitors will be started therapeutically. Severe abdominal pain or diarrhoea during hepatic arterial infusion will

require immediate emptying of the drugs from the pump and the instillation of heparin- treated saline until the result of the workup will be available.

The bile ducts are particularly sensitive to HAIP chemotherapy because they derive most of their blood supply from the hepatic artery. Close monitoring of liver enzymes and dose adjustment (as described in section 5.1.3) are necessary to avoid biliary sclerosis. Patients with severe biliary sclerosis may sometimes require percutaneous or endoscopic drainage and stent placement. A CT scan should be performed prior to biliary drainage to rule out intrahepatic recurrence causing biliary obstruction.

5.1.4.11 Expected complications related to the HAI pump

Surgical complications related to HAI pump placement may occur. A retrospective review of 544 HAI pump placements was performed at MSKCC.(19) Pump placement was typically combined with a partial liver resection. A simultaneous partial colectomy was performed in 136 patients (25%). No mortality attributed to the pump was reported. The most common complications were unrelated to the pump: wound infection of the laparotomy wound, atelectasis, prolonged ileus, and intra-abdominal abscess. Pump related morbidity (including dysfunction) occurred in 120 patients (22%). HAIP chemotherapy with floxuridine was impossible or discontinued in only 9% of patients. In 9 patients (2%) extrahepatic perfusion was found postoperatively, which could be resolved in 7 patients. In 9 patients (2%) postoperative technetium scan showed incomplete liver perfusion. Most common explanation was a non-ligated accessory or replaced hepatic artery, which was resolved with embolization or surgical ligation. Cross-over flow developed instantly or could be confirmed after four weeks. Hepatic arterial thrombosis can occur immediately after surgery (13 patients, 2%), of which a third could be salvaged with anti-coagulation. Thrombosis also occurred in 11 patients (2%) as a late complication resulting from HAIP chemotherapy. However, in the second half of the study only one patient developed a hepatic arterial thrombosis. The higher incidence in the first half was attributed to the intra-arterial administration of mitomycin C. Pump pocket infection was found in 24 patients (4%) and could be salvaged with parenteral antibiotics in half of these patients. In some patients with pump site infection, replacement and reposistioning of the pump may be necessary. Simultaneous partial colectomy did not increase the rate of pump pocket infection. Arterial haemorrhage occurred in only 1 patient. The incidence of biliary sclerosis due to HAIP chemotherapy in a retrospective analysis of 293 patients was 5.5%. Risk factors most significantly associated with biliary sclerosis were dose, number of cycles, abnormal nuclear medicine scan, and postoperative infections. All patients were managed successfully with biliary stenting and/or dilatation.(28)

5.1.4.12 Expected toxicities related to the postoperative perfusion CT

Only a low dosage of radiation (15mSv) and a low dosage of contrast agent (5 - 10 ml) dosage are sufficient. These low numbers result in a negligible effect on renal function. The radiation dose is comparable to a diagnostic scan of the abdomen.

5.2 Drug Accountability - IMP

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug will be performed and documented according to the sponsor's standard operating procedures and according to agreement with the Department of Pharmacy.

5.3 Drug Labeling

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children.
The pharmacy will prepare and label the IMP in accordance with Norwegian requirements.

Labels will also include blank lines (in Norwegian) for:

- For Clinical trials administration
- Patient's initials
- Patient's enrolment code
- Protocol code
- Date dispensed
- Name of prescribing doctor
- Name of Principal Investigator

5.4 Subject Numbering, different arms of the study

Each subject is identified in the study by a unique subject number that is assigned when subject signs the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject. STUDY procedures

5.5 Schedule of events

- Identification
    - Patients are identified from referrals or during MDT-meetings by surgeon or oncologist.
    - A trial specific MDT evaluation of liver metastases and resectability is performed.
    - Following this MDT-meeting, the patient is invited for out-patient visit within 10 days.
    - If no updated high-quality thoracic/abdominal CT and MR scan is available (No older than 4 weeks by date of out-patient visit), these are booked.
- At out patient clinic:
    - Eligibility for *Excalibur* 1 or 2 is assessed.
    - In house review of new images if applicable.
    - Eligible patients receive written and oral information about the trial and risks pertaining to HAI-catheter insertion/transplant/systemic chemotherapy
    - Measurement of CEA and standard blood chemistry
    - If patient consents:
        - Baseline QoL survey (C30) and EQ5D questionnaire is completed
        - Patient's latest CT or MRI scans are referred to next MDT meeting for designation of three target lesions for RECIST evaluation
        - Availability of mutation status is confirmed. If mutation status is not already perfomed, this is ordered from pathology lab.
        - Decision of eligibility for *Excalibur* 1 or 2 is decided by two trial investigators. If a patient is found to be eligibility for *Excalibur* 1 a member of transplant team will concur and provide specific information about transplants.
        - If a patient has begun or is planned for 2^{nd} line chemotherapy, the randomization MUST take place before any evaluation of 2^{nd} line treatment effect, i.e imaging (CT/MR). (PET for evaluation of extra hepatic disease is allowed). The choice of drugs for 2^{nd} line chemotherapy must be decided on <u>prior</u> to randomization.

    - Inclusion is confirmed
    - Patient card
    - The following appointments are booked within two weeks:
        - A PET scan following 4 week chemo abstention. If the patient has recently received systemic chemotherapy, a 4 week chemo abstention must be ensured and randomization may need to be somewhat delayed.
        - Patients eligible for Excalibur 1 for individual assessment by transplant team
        - An operation theatre for insertion of HAI-pump catheter at four weeks from inclusion

- PI meeting two weeks following inclusion:
    - Documents, inclusion details, transplant assessment and PET results are reviewed

- If satisfactory, a web-based randomization is performed.

- All patients:
  - Monthly pregnancy testing should be performed in women of childbearing potential (WOCBP) as long as they recive chemotherapy according to study protocol. This can be done with a urine test at home combined with contact with the study team by phone
  - A calendar for oncologist visits and provision of systemic chemotherapy is created by coordinating nurse.Control scans are ordered for each 2nd month for the first year following randomization and as long as the patients receive chemotherapy, each 3rd month for the second year and each 6th month for the third year. MDT meetings are scheduled for one week following each new scanning to assess response and possible resectability
  - Out-patient control appointments are scheduled for outcome assessment including QoL-scoring (3, 6, 9, 15, 18, 21 and 24 months)
- Patients in HAI group (group 2 a and 2b)
  - A calendar of reservoir refills is created and harmonized with provision of systemic treatment.
  - A laparotomy is performed within 2 weeks from randomization with insertion of catheter and reservoir for HAI-pump.
- Patients in transplant group
  - Oncologists are instructed to avoid Avastin in systemic chemotherapy while the patient is listed.

Table 3: Overview of screening procedures, End of study/Withdrawal

Overview of screening procedures, End of study Withdrawal												
Item	ICF	Inc/ Ex	Med Hist	Prior Trea	Phys Exam	Vit Sign	ECOG	CT/ MR	QoL	Blood Sample	Adverse Event	Survival Assess-ment
Screening	x	x	x	x	x	x	x	x	x	x	x	
EOS/ Withdrawal											x	x

Table 4: Calendar of cycles and events for patients in HAI group

Calendar of cycles and events for patients in HAI group							
Day cycle 1 + 2	1	2	15	16	29	30	44
Day cycle 3 + 4	61	62	75	76	89	90	104
Pump refill FUDR at OUS	x				x		
Pump refill HepNaCl at OUS			x				x
Systemic chemo local hospital		x		x		x	

Table 5: Calendar of cycles and events for patients in control group and on waiting list for LTx-group

Calendar of cycles and events for patients in control group and on waiting list for LTx- group							
Day cycle 1 + 2	1		15		29		44
Day cycle 3 + 4	61		75		89		104
Systemic chemo local hospital	x		x		x		x

5.6 By Visit

Informed consent

Informed consent will be obtained voluntarily by each subject before any study specific procedures are initiated. Patients will be given information about inclusion in the study at the out-patient clinic at Rikshospitalet, Oslo University Hospital.

The following tests will be done at screening:

Clinical status

A medical history will be recorded, including disease history and corresponding treatment details, physical examination e.g. cor/pulm/abdomen and peripheral lymph node status), vital signs (weight, blood pressure, temperature and pulse) and ECOG performance status.

Tumor evaluation: CT thorax/abdomen (pelvis) and MRI-liver within 4 weeks of MDT-meeting at Rikshospitalet. All patients included in the study will receive systemic chemotherapy as standard of care. This treatment will be given at local hospitals and as standard of care blood chemistry will be performed before administration of chemotherapy. Patients randomized to HAI will in addition have blood chemistry the day the pump is filled for a new 14-day treatment. The safety measures for the systemic chemotherapy will be standard of care and documented in the patient records according to standard procedures at the different hospitals. CT (MRI)-scans will be performed at local hospital and the CT (MRI) scans showing stable disease or response will be submitted to the HPB-meeting at Rikshospitalet for evaluation of resectability. Resectable patients (from both the control and HAI groups) will have liver resection at Rikshospitalet.

Laboratory analysis

Blood samples will be taken to determine CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin, bilirubin CEA and CA 19-9. Pregnancy test will be secured within the last 14 days in fertile women.

5.6.1 Before Treatment Starts

Eligible and consenting patients will be randomized. Patients randomized to systemic chemotherapy will receive chemotherapy at their local hospital. Patients randomized to HIA and systemic chemotherapy will have the pump placement and HAI administration at the department of gastrointestinal surgery/HPB section at OUH/Rikshospitalet. The systemic chemotherapy will be administered at local hospitals. The patients in these two groups will repeatedly be evaluated for liver resection at the MDT-meeting at Rikshospitalet and patients who become resectable will have liver resection/local ablation at Rikshospitalet. Patients randomized to liver transplantation will be evaluated for liver transplantation and receive liver transplantation according to standard procedure at the department of Transplantation Medicine, Rikshospitalet. These patients will receive chemotherapy at their local hospital until time of receiving a liver transplant.

5.6.2 During Treatment

The patients will receive systemic chemotherapy/HAI treatment and regular aout-patient visites as described in flowchart. All patients will have their first visit at 8 weeks post randomization.

5.6.3 Progressive disease or toxicity

In the case of progressive disease (PD) in the systemic chemotherapy arm, this treatment will be halted and shifted to 3rd chemotherapy as appropriate or to best supportive care (BSC). In the case of PD in the HAI-group, systemic chemotherapy will be changed to 3rd line as appropriate and the use of pump is discontinued. In the case of PD in the transplant group, listing is upheld but chemotherapy is changed to 3rd line as appropriate until available organ is available. In the case of toxicity a change in systemic chemotherapy to 3rd line is attempted and if unaltered toxicity, halted.

5.6.4 End of Treatment

The patients will receive systemic chemotherapy/HAI treatment until progressive disease, until resection or until discontinuation due to toxicity or withdrawel of informed consent. Patients receiving liver resection or liver transplantation will have a follow-up for up to 10 years after surgery or until they start palliative chemotherapy. Information on treatment given after liver resection or liver transplantation will be collected. Treatment after relapse of liver resection or liver transplantation will be at the discretion of the treating physision. Patients receiving HAI treatment and having liver resection may have the pump removed at time of liver resection. Patients receiving HAI treatment and not obtaining sufficient response for liver resection will only have the pump removed if the pump is causing symptoms.

5.6.5 After End of Treatment (Follow-up)

Patients having a liver resection or liver transplantation will have follow-up according to Table 6-7. These patients will have follow-up uptil 10 years after surgery or until they start palliative treatment.

Table 6. Follow-up of resected Excalibur study patients

Follow up Ltx patients	Visits 1st year (every month)	Visits 2nd year (every 3 month)	Visits 3rd-10th years (every 6 month)
Hb CRP, Hv, Trc, Na, K, Crea	X	X	X
Bilirubin, ASAT, ALAT, ALP, Alb	X	X	X
INR, Cholesterol, glucose, HbA1c	X	X	X
CEA, CA 19-9,	Every 3 months	X	X
TIMP-1, TPA (stop at relapse)	Every 3 months	X	X
5 ml EDTA plasma for later analyses (until relapse)	Every 3 months	X	X
5 ml serum for later analyses (until relapse)	Every 3 months	X	X
Weight	X	X	X

BP	X	X	X
CT thorax/abdomen/pelvis (only in Ltx patients without relapse)	Every 2 months	Every 3 months	Every 6 months
US Liver w/Doppler (only Ltx patients)	Every 3 months		
Coloscopy (only in Ltx patients without relapse)	At 12 months	At 36 months	At 60 months
PET scan (only in patients without lesions on CT)	At 12 months	At 24 months	
EORTC QLQ-C30 and EQ5D	3, 6, 12, months	2 times/year	2 times 3.year

Table 7 Follow-up of Control group, HAI-group and patients not receiving LTx

arm		Outcome	Palliative treatment	Follow Up
3 and 2	Chemo therapy FUDR/HAI	Surgery	No	10 Years
		PD/Toxicity	yes	Will do “End of treatment visit”. OS will be collected.
1	Liver Tx	Transplant	No	10 Years.
		Extra-hepatic disease	yes	Will do “End of treatment visit”. OS will be collected.
		Metastasis to lymfnodes	yes	Will do “End of treatment visit”. OS will be collected.

5.7 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrolment ie, the patient does not meet the required inclusion/exclusion criteria for the study

- Patient lost to follow-up
- Patient's non-compliance to study treatment and/or procedures

5.8 Procedures for Discontinuation

5.8.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment according to protocol.

Patients who are withdrawn from study treatment will be followed up at local hospitals according to standard procedure.

If possible, a final assessment shall be made (end of study visit). The reason for discontinuation shall be recorded. The patients will have follow-up for any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown.

All patients randomized will be included in the study population.

Patients who withdraw or are withdrawn from the study after randomisation cannot be replaced.

5.8.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

5.9 Laboratory Tests

Blood samples will be taken to determine CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin, bilirubin CEA and CA 19-9. The samples will be collection and handeled in accordance with hospital/laboratory standard procedures.

5.10 Assessment of Efficacy

Overall survival, liver resection rates and surgical complications will be recorded from patient medical records.

Assessment of tumor response (prior to resection or transplant): tumor response will be assessed according to RECIST version 1.1, based on CT scans of thorax, abdomen and pelvis. This procedure cannot be blinded as the HAI catheter will show on all CT series.

Chemotherapy related toxicity will be evaluated using NCI-CTC v. 5.0, grade 3-5 related to systemic chemotherapy will be assessed.

Surgical complication will be assessed by Accordion grading system, only grade 3-6 will be recorded.

Quality of life will be assessed by EORTC QLQC30 and EQ5D.

Biomedical marker related to clinical outcome will be developed based on blood samples and liver biopsies collected

5.11 Safety and Tolerability Assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the CRF. For details on AE collection and reporting, refer to Section 6.

For the assessment schedule refer to Flow chart in Section 5.6.

5.12 End of study (EOS)

Last Patient Last Visit is defined as End of Study.

6 SAFETY MONITORING AND REPORTING

The investigators are responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigators immediately should they manifest any signs or symptoms they perceive as serious.

The methods for collection of safety data are described below.

6.1 Definitions

6.1.1 Woman of childbearing potential (WOCBP)

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

6.1.2 Birth Control Methods

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as one month after the end of study treatment.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:

- oral

- intravaginal
- transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation 1:

- oral
- injectable
- implantable 2

Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

6.1.3 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

6.1.4 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

A pre-planned hospitalization admission (ie, elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

6.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any serious adverse reaction where the nature or severity is not consistent with the product information mentioned in the Reference Safety Information in the SPC and for HAI in the publication by Pak and colleagues

6.1.6 Serious Adverse Reaction

A Serious adverse reaction (SAR) is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject, and meets the criterias for SAE above.

6.2 Recording procedure

6.2.1 Adverse Events

All adverse events related to standard systemic chemotherapy and all adverse events related to FUDR pump administration will be recorded in the Case Report Form (CRF).

6.2.2 Disease Progression/Recurrence

Death due to progressive disease is to be recorded as an SAE.

Only (unexpected) SARs related to IMPs need to be reported to the Competent Authorities, by using a CIOMS reporting form.

6.2.3 Duration Period for Reporting AE and SAE

Any new primary cancer (non-related to the cancer under study) should be recorded in the CRF.

For each patient the standard time period for collecting and recording of AE and SAEs in the CRF (reporting of SAE to sponsor) will begin at start of study treatment and will continue for at least 30 days following the last dose of study treatment for each patient in patients receiving FUDR.
.

6.2.4 Recording of Adverse Events

All adverse event(s) independent of treatment arms will be recorded by study personell in the CRF as required below:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event:NCI-CTC 5.0
- The Causal relationship of the event to the study medication will be assessed as one of the following

  Unrelated:

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

Unlikely:

There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

Possible:

There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

Probable:

There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Definite:

There is a reasonable causal relationship between the investigational product and the AE.

- Action taken
- The outcome of the adverse event – whether the event is resolved or still ongoing.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

6.3 Reporting Procedure

6.3.1 AEs and SAEs

All adverse events and serious adverse events will be recorded in the patient's CRF. A SAE in a patient without HAI must also be reported from the investigator to the Sponsor, within the proper timelines.

SAEs must be reported to sponsor within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the investigator on the SAE pages to be found in as part of the CRF. The Serious Adverse Event Report Form must be completed, signed. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to causality and expectedness. Based on, among other, SAE reports the sponsor will evaluate whether the risk/benefit ratio associated with study is changed.

6.3.2 SUSARs

SUSARs will be reported to the Competent Authority according to national regulation.
If both the investigator and the Sponsor find the event to be related to a non-IMP, this SAR does not need to be reported as a SUSAR. However, new side-effects of approved drugs should be reported to National Competent Authorities in accordance with normal clinical practice.

The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

6.3.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

6.3.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

6.4 Procedures in Case of Emergency

Administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Medical emergencies during the study will be handeled according to standard operating procedure at Department of Transplantation Medicine/ Department of HBP surgery at Rikshospitalet

All adverse events and serious adverse events will be recorded during the trial until resolved.

6.5 Data Monitoring Committee (DMC)

In case of death occurs in the HIA/FUDR arm, the independent Data Monitoring Committee (DMC) will recommend whether to continue, modify or terminate the trial.
The DMC will consist of two independent liver surgions, Dr. Kim Mortensen and Dr. Erling Bringeland who both are employed at hospitals outside of Oslo University Hospital.

7 DATA MANAGEMENT AND MONITORING

7.1 Case Report Forms

The Clinical Data Management System (CDMS) used for the eCRF in this study is EpiData.The setup of the study specific eCRF in the CDMS will be performed by Clinical Project assistant, OUS.

The designated investigator staff will enter the data required by the protocol into the eCase report forms (eCRF). The Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

7.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- WHO performance status assessments conducted as part of the study, if applicable;
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice.

A source data list will be agreed upon for each site specifying the source at a module or a variable level.

7.3 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of adverse events in the HAI-treatment arm and all other safety data

- Adherence to protocol
- Maintenance of required regulatory documents
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness in accordance with monitoring plan and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

7.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

8 STATISTICAL METHODS AND DATA ANALYSIS

8.1 Determination of Sample Size

We estimate an overall survival at two years in the standard care group (group 3) to be 30 %. We aim to decide whether the use of HAI (group 2) can increase this to 75 % and if liver-TX (group 3) can increase this to 90 %. For a two-sided parallel-group test of proportions to answer both questions with a power of 0.80 and an alpha of 0.05, this will require 16 completed patients per group 3 and 2 to show superiority for HAI over standard care (systemic chemotherapy). An additional 7 patients is needed in the transplant group (1) to show superiority over standard care group (3), bringing the total to 39 patients. This is based on a three-year accrual time, and a total of five-year follow-up from the first patient, ensuring at least two years follow-up for all patients. The trial is not powered to show a difference between group 2 and 1. Adding 15 % to allow for drop-outs, we aim to randomise a total of 18 + 18 + 9 = 45 patients in a 2:2:1 ratio.

8.2 Randomization

8.2.1 Allocation-sequence generation

Randomized lists are generated for three groups in *Excalibur* 1 in a 1:1:1 distribution and with a variable but unknown block-size of 3 or 6. Further, lists are generated for two groups in *Excalibur* 2 in a 1:1 distribution. These will be generated and stored by personell not participating in the trial, and in offices physically removed from the clinical facilities.

8.2.2 Randomization and allocation procedures

A computer generated random sequence is generated with three groups for Excalibur 1 and two groups for Excalibur 2. Randomization is blocked with a variable and unknown block-size of 2-6. Allocation is by phone to a centralized office physically removed from the clinical premises, or by web and performed after inclusion is judged appropriate and the patient has consented. For patients who are switched to 2nd line chemotherapy, randomization can only be allowed prior to first evaluation on 2nd line chemotherapy regimen.

Patients will be approached, informed and consented by study group members (surgeons or oncologists).

8.3 Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomized participants, regardless of protocol adherence. The primary endpoint analysis will be performed on all subjects on an intention-to-treat basis.

- Per-protocol population (PP): Includes all subjects who have undergone the treatment for which they were allocated.

- Patients randomized to HAI-treatment or liver transplantation accually receiving these treatments'

- Safety population: Includes all subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.

- Subgroups defined by: Left versus right sided primary tumour, degree of PET uptake in liver, FONG/Oslo-score

8.4 Planned analyses

The main statistical analysis is planned when

- The planned number of patients have reached two years follow-up from date of randomization, and

- All data have been entered, verified and validated according to the data management plan

Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A separate statistical analysis plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to database lock.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report.

8.5 Statistical Analysis

8.5.1 Primary analysis

- Primary variable: Overall survival at 2 years from randomization

- Assessment: From the electronic medical records (EPJ)

- Metric: Hazard ratio

- When the last recruited patient has reached two years follow-up or censor.

The primary analysis will be done by Cox regression with treatment group as covariate, adjusted for stratification factors in the randomization.

Primary population: By intention-to-treat (ITT), i.e. all randomized patients regardless of protocol adherence.

The treatment effect will be presented as hazard ratios between the two treatment groups and the standard of care group, in addition to 95% confidence intervals.

The null hypothesis to be tested is that there is no difference between the treatment groups on overall survival after 2 year. If the null hypothesis is rejected on a 5% significance level, the pairwise treatment group's differences will be tested on the 5% level with the family-wise error rate sustained by the closed test principle.

There will be no handling of missing values. All patients will be followed-up until 2 years or death of any reason. Patients lost to follow-up will be censored at time of last observation, and handled accordingly.

8.5.2 Secondary analyses

- Per-protocol comparison of overall survival at 2 years
- ITT liver-progression-free survival,
- Rates of liver resection in HAI group compared with control group and with transplantation rate for TX group. Standard approximation to binary outcomes with Fisher exact test or chi-square.
- Quality-of-life as measured by EORTC-30

8.5.3 Safety analyses

The adverse events will be presented descriptively by means of frequency and percentages to evaluate both the rate of incidence and event occurrence among the different treatment groups. The descriptive tables will be presented with respect to intensity, seriousness and relationship to the treatment.

8.5.4 Other analyses (eg health economics, patient reported outcomes etc)

Patient reported outcomes are recorded by the use of EORTC-C30 and the EQ5D questionnaires.

8.5.5 Descriptive statistics

All categorical (including binary and ordinal) data will be summarized using frequency counts and percentages of patient incidence. Percentages will be calculated using the appropriate study population; any exceptions to this will be highlighted in the table footnote. Continuous variables will be summarized using number of patients (N), mean, standard deviation (SD), median, 25/75 percentile and range (minimum/maximum)

9 STUDY MANAGEMENT

9.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training

relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

9.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

9.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

9.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

10 RISK VERSUS BENEFIT ASSESSMENT

It is the firm view of the investigators that the potential side-effects of the two interventions in question are more than outweighed by their potential benefit and by the reduced side effects from a sparing effect on standard systemic chemotherapy.

This is a randomized trial where the control arm receives standard systemic chemotherapy.The overall prognosis for this selected group of patients is very poor and 2nd line chemotherapy comes with a range of side effects that are (to a variable extent) tolerated as (today) no other treatment alternative exist. Irinotecan and Oxaliplatin may induce liver toxicity to en extent completely precluding liver surgery.

From the available literature, patients receiving additional intra-arterial chemotherapy (HAI) may expect a better response and greater possibility of reaching surgery (liver resection) and improved overall survival. Patients receiving liver transplant can expect a significantly improved survival compared to standard chemotherapy alone. The hypothesis is that the experimental treatments are better than today's standard treatment and thus more patients will reach resectional surgery in the trial and henceforth in non-trial settings in the future.

The insertion of HAI pump is an operative intervention with marginal operational risk. Apart from a 1-2 % risk of wound dehiscence, there are no significant risks from the surgery as such. General anaesthesia risk is considered negligible. HAI (FUDR) may cause biliary toxicity. These findings have previously been published and are well known as the drugs have been in clinical use for more than 10-years in the US.The well-documented risk of bile duct inflammation resulting from HAI has been significantly reduced with the use of steroids and dose reduction in the event of increasing LFTs. As HAI is assumed to reduce the dosage and cycles necessary of systemic chemotherapy, we believe that the side effects/complications of the two regimens may well be balanced even with a laparotomy only in the intervention groups.

Liver transplant is an established treatment today. It is a major surgical intervention with accompanying risk: those pertaining to major surgery in general and those resulting from prolonged systemic immunosuppression following reception of an allograft.It is nevertheless associated with vastly increased survival for eligible patients with cirrhosis, HCC and even colorectal liver metastases. Again, a successful liver transplant wills largely obliviate the need for systemic chemotherapy.

For society, such a study with a positive outcome (experimental treatment better than current treatment) would be of immediate value. A positive study result will mean that patients in the future can be offered better treatment than today's standard treatment – a standard treatment with very poor outcome.

A positive study will form the basis for more use of the experimental treatments; while a negative study will clarify that there is no intention of offering future patients such treatment. For the community it is also important to clarify whether or not the experimental treatment options are effective. A treatment that is not effective should not be offered to future patients.

11 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

11.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

11.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth.

12 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by OUS. Applications for external funding of the study will be made.

13 TRIAL INSURANCE

The Principal investigator has insurance coverage for this study through membership of the Drug Liability Association (see http://www.laf.no for more details).

14 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will be submitted for publication in medical journal /at scientific meetings and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

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16 LIST OF APPENDICES

A. EORTC QLQ C-30

B. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

C. ECOG Performance Status

APPENDIX A – EORTC QOL C30

~~EORTC QLQ-C30~~ (version 3.0)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss ☒ i den boksen som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar. Alle opplysningene vil bli behandlet konfidensielt.

Ditt navns forbokstaver: ☐☐☐☐

Født (dag, mnd, år): ☐☐ - ☐☐ - ☐☐☐☐

Dato for utfylling: ☐☐ - ☐☐ - ☐☐☐☐

		Ikke i det hele tatt	Litt	Endel	Svært mye
1.	Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2.	Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3.	Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4.	Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5.	Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:

		Ikke i det hele tatt	Litt	Endel	Svært mye
6.	Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7.	Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8.	Har du vært tung i pusten?	☐	☐	☐	☐
9.	Har du hatt smerter?	☐	☐	☐	☐
10.	Har du hatt behov for å hvile?	☐	☐	☐	☐
11.	Har du hatt søvnproblemer?	☐	☐	☐	☐
12.	Har du følt deg slapp?	☐	☐	☐	☐
13.	Har du hatt dårlig matlyst?	☐	☐	☐	☐
14.	Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

I løpet av den siste uka:

		Ikke i det hele tatt	Litt	Endel	Svært mye
15.	Har du kastet opp?	☐	☐	☐	☐
16.	Har du hatt treg mage?	☐	☐	☐	☐
17.	Har du hatt løs mage?	☐	☐	☐	☐
18.	Har du følt deg trett?	☐	☐	☐	☐
19.	Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20.	Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21.	Har du følt deg anspent?	☐	☐	☐	☐
22.	Har du vært engstelig?	☐	☐	☐	☐
23.	Har du følt deg irritabel?	☐	☐	☐	☐
24.	Har du følt deg deprimert?	☐	☐	☐	☐
25.	Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26.	Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27.	Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28.	Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den ruten som best beskriver din tilstand.

29. Hvordan har din helse vært iløpet av den siste uka?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
Svært dårlig						Helt utmerket

30. Hvordan har livskvaliteten din vært iløpet av den siste uka?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
Svært dårlig						Helt utmerket

APPENDIX B – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE), VERSION 5.0

The CTCAE grading criteria are available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX C – ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead