BRECLIM

Breast Cancer Liver Metastasis

A multicentre randomized clinical trial investigating local treatment for breast cancer liver metastasis

CRF overview

CRF1	1	Registration. Performance status. Somatic comorbidities. Quality of life.
CRF1	1A.	Characteristics of breast cancer liver metastases. Liver disease and liver function.
	1B.	Breast cancer characteristics. Oncological and surgical breast cancer treatment.
CRF2	2A.	Liver metastases and response.
	2B.	Oncological treatment after inclusion. Toxicity.
	2C.	Result of randomization.
CRF3	Local treatment. Only for those randomized to local treatment.	
CRF4	Complications and PAD, only for those randomized to local treatment.	
CRF5	Follow up 3, 6, 9, 12, 18, 24, 30, 36 months (5a-h) Oncological treatment and complications.	
CRF 6	Relapse. Progression.	
CRF 7	End of study. Vital status.	

Version 2020-09-09

CRF1 Registration

Study participant number___
Date of birth (ddmmyyyy)
Sex
Date of registration
Study Site

Participant fulfill inclusion criterias; § 1-4 liver metastasis amendable to surgery with functional liver remnant volume >30%.
§ Liver metastasis (and skeletal metastasis) stable or responding to preoperative oncological treatment
§ Signed informed consent
§ >18 years old
§ ECOG 0-1
§ Breast cancer history
§ Breast cancer liver metastasis verified by biopsy
§ Patient amendable for liver surgery and pre- and postoperative oncological treatment

Participant do NOT have any exclusion criteria;
§ Previous or present non-skeletal extrahepatic disease
§ Pregnancy
§ > 4 liver metastases on preoperative or previous examination
§ Progression of disease upon oncological treatment

Ca15-3 (kU/L)
Date taken

Performance status ECOG 0/1/2/3/4 or not done

CHARLSTON COMORBIDITY INDEX

(Age <50/50-59/60-69/70-79/>80)	
Diabetes	None/Uncompl/End organ damage
Liver disease	None/Mild/Moderate to severe
(Malignancy all metastatic tumor)	
Leukemia	YES/NO
Lymphoma	YES/NO
AIDS	YES/NO
Moderate to severe Kidney disease	YES/NO
Congestive Heart failure	YES/NO
Myocardial infarction	YES/NO
Chronic obstructive pulmonary disease	YES/NO
Peripheral vascular disease	YES/NO
CVA or TIA	YES/NO
Dementia	YES/NO
Hemiplegia	YES/NO
Connective tissue disease	YES/NO
Peptic ulcer	YES/NO

CRF1a Liver metastases

DIAGNOSIS – HOW WAS THE METASTASES FOUND?
Clinical signs and symptoms
Surveillance or due to risk factor for metastatic disease
”En passant” from other radiology examination

DIAGNOS
Date of first diagnosis by radiology
Date for biopsi
Pathology/cytology lab or clinic
Pathology/cytology number or code
Deciding hospital and department

LIVERMETASTASES
ER____% positive/negative/missing
PgR positive/negative/missing
HER2 IMMUNOHISTOCHEMISTRY 0-1/2/3/missing
HER2 ISH-analys amplified/non_amplified/missing
Ki67___% low/intermediate/high/missing
Received converting therapy to get operable

Date MDT with liver surgeon
MRI liver YES/NO Date
PET-CT YES/NO Date
CT thx abdomen YES/NO Date

STAGING
Size longest axis for the largest metastases (mm): .....
Number of met: 1/2/3/4
Involved segments; 1, 2, 3, 4, 5, 6, 7, 8, unknown
Locally advanced extrahepatic growth No / Yes
Thrombosis in intrahepatic porta or liver vein No / Yes
- If yes, yumourthrombosis No / Yes

Tumour growth extrahepatic No/Yes bone progress no progress

LIVER DISEASE
Cirrosis
Primary biliary cirrosis
Primary sclerosing cholangitis
Porphyria
Hepatit B
Hepatit C
Hemokromatosis
Alcohol associated liver disease
NASH (non-alcoholic steatohepatitis)

LIVER FUNCTION
Bilirubin _____ (µmol/l)
Albumin _____(g/l)

PK _____ (INR)
Creatinin _____(µmol/l)
Ascites None/Mild/Severe
Encephalopaphy None/Mild/Severe

CRF1b Breast cancer

Date of breast cancer diagnosis
Premenopausal/Postmenopausal/Unknown

OPERATION OF PRIMARY BREAST CANCER
Surgery first/Surgery after preoperative oncological treatment
Operation Partial mastectomy
Mastectomi
No breast operation
Subcutanous mastectomi with conserved areola
Axilliary operation Yes/No
If yes Only SN (PJA10)
SN and axillary lymph node dissection (PJA10 + PJD42)
Only axillary lymph node dissection (PJD42)
Secondary breast surgery due to tumour data (PAD) Yes/No
Secondary axillary surgery due to tumour data (PAD) Yes/No

PATHOLOGY REPORT BREAST CANCER SURGERY
Only ductal cancer
Ony lobular cancer
Both ductal and lobular cancer
Ductal and other than lobular cancer
DCIS
LCIS
DCIS and LCIS

Number of invasive tumours 0/1/2/3/4/missing
Size of largest tumour (mm)
ER.....%
ER-status Positive yes/no/Missing
PgR.....%
PgR-status Positive yes/no/Missing
HER2 immunhistokemi 0–1+ /2+ /3+/Missing
HER2 ISH-analys Amplified/Non amplified/Missing
Histology grade 1/ 2/ 3 /Missing
Ki67 .....%
Ki67-status Mild/moderate/severe
S-CA 15-3 (kU/L) date
Total number of examined lymph nodes from all examinations
Total number of nodes with metastases (> 0,2 mm)
TNM8 pT 1/2/3/4
pN 0/micro/1/2/3
M 0/1 (at breast cancer diagnosis)

PREOPERATIVE NEOADJUVANT TREATMENT PRIOR TO BREAST SURGERY

Chemotherapy		yes/no
	If yes	EC yes/no
		Taxan yes/no
		Carboplatin yes/no
		Other……..
		Number of courses
Endocrine treatment		yes/no
	If yes	Tamoxifen
		Aromatase inhibitor
		Other……..
Her2		yes/no
	If yes	Pertuzumab yes/no
		Trastuzumab yes/no
		Other……..

Any other neoadjuvant treatment……

POSTOPERATIV ADJUVANT TREATMENT AFTER BREAST SURGERY

Chemotherapy		yes/no
	If yes	EC yes/no
		Taxan yes/no
		Carboplatin yes/no
		Other……..
		Number of courses
Endocrine treatment		yes/no
	If yes	Tamoxifen
		Aromatase inhibitor
		CDK4/6
		Fulvestrant
		Other……..
Her2		yes/no
	If yes	Pertuzumab yes/no
		Trastuzumab yes/no
		Antibody conjugated drug yes/no
		Other……..
Radiotherapy		yes/no
	If yes	local/locoregional
		Dose per fraction…….
		Total dose…….
Bone modifying agent		yes/no
	If yes	Bisphosphonate
		Denosumab YES/NO
		Other ……..

Any other adjuvant treatment……

CRF2

Study participant number___
Date of birth
Name
Date
Clinic

CRF2a Liver metastases

Date MDT with liver surgeon
MRI liver YES/NO Date
PET-CT YES/NO Date note mandatory if done on CRF1
CT thx abdomen YES/NO Date

STAGING
Size longest axis for the largest metastases (mm): .....
Number of met: 1/2/3/4
Involved segments; 1, 2, 3, 4, 5, 6, 7, 8, unknown
Locally advanced extrahepatic growth yes/no
Thrombosis in portal or hepatic vein yes/no
if yes, tumour thrombosis yes/no
Response RECIST 1.1 Mixed response
Regression
Stable
Progression

Extrahepatic disease
No Yes, Skeletal without progress
Yes, Skeletal with progress - exclusion
Yes, other - exclusion

CRF2b Oncological treatment

TREATMENT BEFORE RANDOMIZATION

Chemotherapy		yes/no
	If yes	EC yes/no
		Taxan yes/no
		Carboplatin yes/no
		Other……..
		Number of courses
Endocrine treatment		yes/no
	If yes	Tamoxifen
		Aromatase inhibitor
		Other……..
Her2 treatment		yes/no
	If yes	Pertuzumab yes/no
		Trastuzumab yes/no
		Other……..
Radiotherapy		yes/no
	If yes	local/locoregional
		Dose per fraction…….
		Total dose…….
Bone modifying agent		yes/no
	If yes	Bisphosphonate
		Denosumab YES/NO
		Other ……..

Any other neoadjuvant treatment……

TOXICITY AND SIDE EFFECTS (CTC4.03)

Infection	Grade 1/2/3/4/5
Abdominal pain	Grade 1/2/3/4/5
Nausea	Grade 1/2/3/4/5
Vomiting	Grade 1/2/3/4/5
Anorexia	Grade 1/2/3/4/5
Fatigue	Grade 1/2/3/4/5
Thromboembolic event	Grade 1/2/3/4/5
Procedural complication	Grade 1/2/3/4/5
Hepatobiliary disorder	Grade 1/2/3/4/5
Neutropeni	Grade 1/2/3/4/5
Other	Grade 1/2/3/4/5

CRF2c Randomization

Participant still fulfill inclusion criteria and have no exclution criterias YES/NO
Randomization date……
ALEA Randomization; Site study id number
Participant study id number
Randomize to LIVER SURGERY/ONCOLOGY

CRF3 Local treatment

Only for those randomized to local treatment

Study participant number___
Date of birth
Name
Date
Clinic

Preoperative Ca-15-3 date…….. value……. (recommended)
Ablation, SBRT or resection done? YES/NO
Date

CLINICAL OPERATIVE ASSESSMENT OF THE LIVER
- Steatosis
- Cirrosis
- Chemotherapy associated liver injury
- Normal
- Missing

Previous surgery for tumour in the liver YES/NO
Portal vein emolization or ligation prior to surgery YES/NO
Preoperative drainage of bile ducts YES/NO

CLINICAL OPERATIVE ASSESSMENT OF BREAST CANCER LIVER METASTASES
Number of metastases 1/2/3/4/5/6-9/>10
Local Extrahepatic tumour yes/no
Synchronous intervention outside liver or gall bladder YES/NO

LOCAL TREATMENT (MULTIPLE OPTIONS POSSIBLE)
- Resection of one segment
- Resection of two segments
- Right-sided hemihepatectomy
- Left-sided hemihepatectomy
- Atypical or wedge resection
- Microwave ablation
- Radiofrequency ablation
- SBRT

Acces
- Percutanous (ablation or SBRT)
- Laparoscopic
- Laparoscopic converted
- Open midline incision
- Open transverse incision

SBRT Total dose…

CLINICAL ASSESSMENT OF INTERVENTION
Peroperative comlication YES/NO
Radical intervention, all macroscopic tumor treated Yes/no

Bleeding…..ml
Operation time….min

CRF4 After local treatment

Only for those randomized to local treatment.

Study participant number___
Date of birth
Name
Date
Clinic

Date of discharge to home from hospital
Date of revisit
Readmission for treatment in hospital within 30 days yes/no

Postoperative complications within 30 days yes/no
If yes specify yes/no for

Bile leakage
Bile duct injury
Postoperative liver failure (PK INR >1.3 or bilirubin >50 postoperative day 5)
Gastrointestinal perforation
Other intestinal complication
Wound or abdominal wall complication >Clavien 1
Bacterial infection demanding antibiotics more than 24h
Bleeding (loss of Hb>30g/l compared to preoperative value)
Vascular complication in the hepatobiliary tract including thrombosis
Thrombosis or embolus (pulmonary or deep veins)
Renal failure demanding dialysis
Ascites demanding treatment
Pleural fluid demanding treatment
Other pulmonary complication
Other_____
Cardiovascular complication (arrythmia demanding treatment, myocardial infarction, heart failure or stroke)

Grading of the most severe complication according to Clavien Dindo; I/II/IIIa/IIIb/IVa/IVb/V

Grade I	*Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.*
Grade II	*Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition also included.*
Grade III	*Requiring surgical, endoscopic or radiological intervention*
- IIIa	*Intervention not under general anesthesia*
- IIIb	*Intervention under general anesthesia*
Grade IV	*Life-threatening complication (including CNS complications) requiring IC/ICU-management*
- IVa	*single organ dysfunction (including dialysis)*
- IVb	*multiorgan dysfunction*
Grade V	*Death of a patient*

Grading of most severe complication according to CTC4.03; I/II/III/IV/V

Procedural complication

Grade I	*Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated*
Grade II	*Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL*
Grade III	*Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL*
Grade IV	*Life-threatening consequences; urgent intervention indicated*
Grade V	*Death*

Most severe complication _____
Need for treatment in intensive care unit yes/no

DIAGNOSIS
Pathological Anatomical Diagnosis in text……
Breast cancer liver metastases yes/no
PAD no……
Name of pathology clinic……
Number of breast cancer liver metastases in PAD 0 1 2 3 4 >4
Size of biggest metastasis (mm)
Vascular inqrowth yes/no
Locally advanced disease involving adjacent organs yes/no
Lymph nodes in specimen yes/no
Lymph node metastases yes/no
Radical resection R0/R1/R2
Shortest distance to resection margain (mm)_____
Radical ablation on CT if ablation or SBRT yes/no

LIVER METASTASIS

Estrogen receptor status	____% POSITIVE /unknown
	Positive/negative/unknown
Progesterone receptor status	Positive/negative/unknown
HER-2 immunohistochemistry	0-1/2/3/unknown
HER-2 in situ hybridisation	amplified/non-amplified/unknown
Ki-67	___% or unknown
	Low/intermediate/high/unknown

CRF5 follow-up 3, 6, 9, 12, 18, 24, 30, 36 months

Study participant number___
Date of birth
Name
Date
Clinic

Patient status this visit alive/alive with signs of disease/dead/lost to follow up
if dead go to CRF7 end of study visit

Breast cancer recurrence or progression since last visit yes/no
if yes go to CRF6 recurrence progression visit

Ca-15-3 date…….. value…… (recommended at 12 and 24 months)
CT thx abdomen Yes/no date

Secondary local intervention against metastases yes/no
if yes date
localization liver/lung/bone/brain/other
Procedure_____

TREATMENT AFTER RANDOMIZATION OR LATEST CRF5

Chemotherapy		yes/no
	If yes	EC yes/no
		Taxan yes/no
		Carboplatin yes/no
		Other……..
		Number of courses
Endocrine treatment		yes/no
	If yes	Tamoxifen
		Aromatase inhibitor
		CDK 4/6 therapy
		Fulvestrant
		Other……..
Her2		yes/no
	If yes	Pertuzumab yes/no
		Trastuzumab yes/no
		Antibody conjugated drug
		Other……..
Radiotherapy		yes/no
	If yes	local/locoregional
		Dose per fraction…….
		Total dose…….
Bone modifying agent		yes/no
	If yes	Bisphosphonate
		Denosumab YES/NO

Other ……..

Any other oncological or surgical treatment……

TOXICITY AND SIDE EFFECTS (CTC4.03)

Infection	Grade 1/2/3/4/5
Abdominal pain	Grade 1/2/3/4/5
Nausea	Grade 1/2/3/4/5
Vomiting	Grade 1/2/3/4/5
Anorexia	Grade 1/2/3/4/5
Fatigue	Grade 1/2/3/4/5
Thromboembolic event	Grade 1/2/3/4/5
Procedural complication	Grade 1/2/3/4/5
Hepatobiliary disorder	Grade 1/2/3/4/5
Neutropeni	Grade 1/2/3/4/5
Other	Grade 1/2/3/4/5

PERFORMANCE SCORE ECOG (recommended at 12, 24 and 36 months) 0/1/2/3/4

0	*Fully active; no performance restrictions.*
1	*Strenuous physical activity restricted; fully ambulatory and able to carry out light work.*
2	*Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.*
3	*Capable of only limited self-care; confined to bed or chair >50% of waking hours.*
4	*Completely disabled; cannot carry out a*

Quality of life EORTC QLQc30 (recommended at 3, 12, 24 months)

CRF6 Recurrence Progression during follow-up

Study participant number___
Date of birth
Name
Date
Clinic

Breast cancer recurrence or progression since last visit yes/no

Recurrence

Site	*yes/no*	*date*
Liver		
Lung		
Bone		
Brain		
Other		

Progression

Site	*yes/no*	*date*
Liver		
Lung		
Bone		
Brain		
Other		

CRF7 End of study

Study participant number___
Date of birth
Name
Date
Clinic

Date of visit

Reason the patient ended study	Completion of protocol treatment and follow up Disease progression Toxicity Death Investigator decision Patient wish Protocol violation Lost to follow up Study closure Other Not known

Specify if toxicity, protocol violation or other_____

If dead, primary cause of death	Diagnosis (breast cancer) Study treatment toxicity Intercurrent disease New primary cancer Other Not known

Date of death