Study Name: SIRCCA

Study Number: STX 0115

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Study Title A prospective, multicentre, randomised, controlled study evaluating SIR-Spheres Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy versus CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma (SIRCCA)

Clinical Investigation Plan

Version 5

Document Date: 12 April 2019

The SIRCCA Study

A prospective, multicentre, randomised, controlled study evaluating SIR-Spheres® Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy versus CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic CholangioCArcinoma (SIRCCA)

Study Sponsor:

Sirtex Technology Pty Ltd
Level 33, 101 Miller Street
North Sydney
NSW 2060 Australia
Tel: +61 2 9964 8400
Fax: +61 2 9964 8410

Co-Principal Investigator:

[redacted]

Signature

APRIL 16, 2019
Date

Co-Principal Investigator:

[redacted]

ammersmith Hospital

12th April 2019
Date

Approved by:

[redacted]

Date: Apr 16 2019

Date: 16 APR 2019

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CHANGE HISTORY

CR #	Reason for change
1927	New Document March 2016
2009	Section 7.3, Page 23 – change “gemcitabine” to “radiation” and “be cleared from the body” to “have decayed”
2072	See Changes Document Rev 1 to Rev 2 Sept 06 2016
2074	See Changes Document Rev 2 to Rev 3 Sept 20 2016
2074	See Changes Document Rev 3, 28 Sep 2016 to Rev 4, 20 Jun 2018
2519	See Summary of changes Rev 4 - Rev 5

TABLE OF CONTENTS

1 CLINICAL INVESTIGATION PLAN (CIP) APPROVAL & AGREEMENT

I have read and understand the requirements of this study plan (protocol), entitled **'A prospective, multicentre, randomised, controlled study evaluating SIR-Spheres Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy versus CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma (SIRCCA)'**.

I agree to treat all patients entered into the study in accordance with the study plan and to keep the appropriate records and documentation required. I will ensure that all staff participating in this study are appropriately trained and informed about the study and I will document such training appropriately.

_____ _____

Investigator Signature Date (dd / mm / yyyy)

_____

Investigator Name

_____

Institution

2 STUDY SYNOPSIS

This clinical study is a prospective, multicentre, randomised, controlled study evaluating SIR-Spheres Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy vs. CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma.

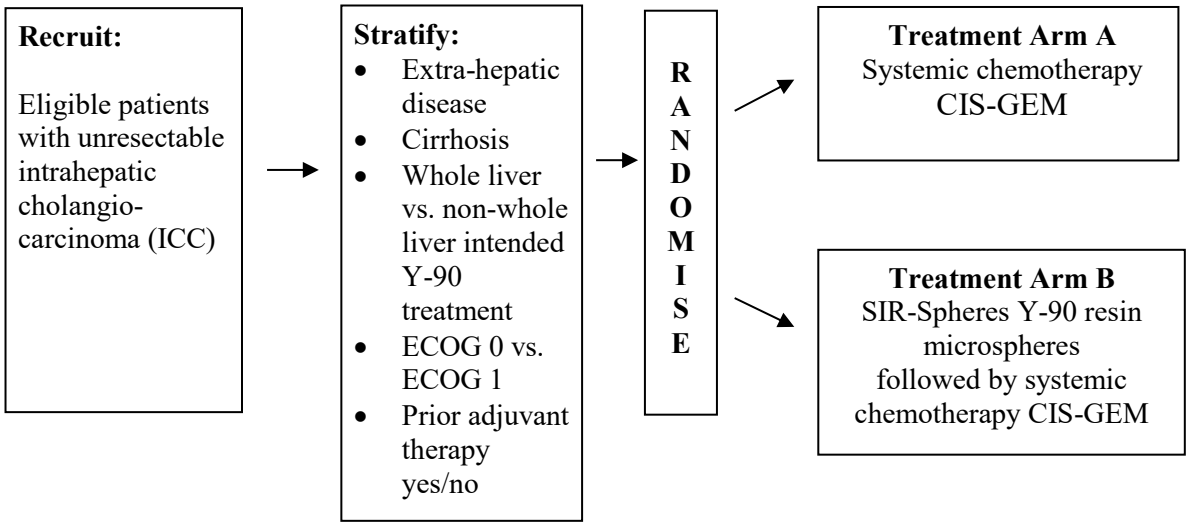
The target recruitment is about 180 randomised patients who started treatment. However, it is expected that about 160 of the patients in both arms will satisfy the compliance criteria i.e. (Arm A: completed at least one cycle; Arm B completed SIRT treatment and complete at least one cycle).

Patients will be randomised 1:1 (about 90 patients in each arm) to receive either:

1. Treatment Arm A: Standard of care systemic chemotherapy with an intention to treat with 8 cycles of cisplatin + gemcitabine, or until progression, toxicity or patient choice. Treatment may be continued beyond 8 cycles in the absence of significant disease progression, at the treating clinicians' discretion.

2. Treatment Arm B: A single treatment of hepatic arterial injection of SIR-Spheres Y-90 resin microspheres followed 14-16 days later by standard of care systemic chemotherapy (ABC-02 CIS-GEM protocol) with an intention to treat with 8 cycles of cisplatin + gemcitabine, or until progression, toxicity or patient choice. Treatment may be continued beyond 8 cycles in the absence of significant disease progression, at the treating clinicians' discretion.

Patients will be stratified by: presence of extra-hepatic disease, presence of cirrhosis, intention for whole liver versus non-whole liver Y-90 treatment, ECOG status (0 versus 1) and prior adjuvant therapy vs no prior adjuvant therapy.



Cirrhosis:
Absence of cirrhosis should be registered when
- The non-tumoural part of the liver is regular and without nodularity on imaging *and*
- There is no evidence of portal hypertension with no clinically significant ascites, oesophageal varices or splenomegaly with dilated portal vein in the absence of portal vein thrombosis.

Detection of any of the above findings, and/or a positive biopsy diagnosis (F4=cirrhosis according to the METAVIR scoring system) and/or an increased elastography value, establishes the existence of cirrhosis.

Randomised patients will be followed until death, withdrawal of consent, or until end of study. Non-randomised patients are addressed in Section 10.1.

The enrolment period for the study is estimated to be 40 months. The study will be conducted in approximately 45 selected investigational sites worldwide. The sponsor will maintain a list of principal investigators, investigational sites, and institutions. The definitive list will be provided with the final clinical study report.

A comparison between treatment arms will be made by assessment of the following criteria:

Primary endpoint:

Survival at 18 months

Secondary endpoints:

Liver-specific PFS
PFS at any site
Objective response rate by RECIST 1.1 and refined RECIST* - liver
Objective response rate by RECIST 1.1 and refined RECIST* - at any site
Overall Survival
Liver surgical resection
Liver ablation rate
Safety (CTCAE v4.03) and tolerability
Quality of Life

*Refer to APPENDIX 7 for RECIST1.1 and refined RECIST assessments

Inclusion Criteria

a) Willing, able and mentally competent to provide written informed consent
b) Aged 18 years or older
c) Histologically or cytologically confirmed unresectable and non ablatable intrahepatic cholangiocarcinoma
d) Liver-only or liver predominant intrahepatic cholangiocarcinoma. Patients are permitted to have loco-regional lymph node involvement defined as: portal LN ≤ 2 cm and/or para aortic LN ≤ 1.5 cm in longest diameter, and/or up to 2 indeterminate lung lesions < 1 cm if these lung lesions are PET negative.
e) Chemotherapy for advanced disease naïve. Capecitabine only based adjuvant chemotherapy is permitted (last administered dose of capecitabine ≥ 6 months prior randomization in the study).
f) ECOG performance status 0 or 1
g) Adequate haematological function defined as:
   Haemoglobin ≥ 10g/dL
   WBC ≥ 3.0 x 10^9/L
   Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   Platelet count ≥ 100,000/mm^3,
h) Adequate liver function defined as:

Total bilirubin ≤ 30 μmol/L (1.75 mg/dL)
Albumin ≥ 30 g/L

i) Adequate renal function defined as:
Serum urea and serum creatinine < 1.5 times upper limit of normal (ULN)
Creatinine clearance ≥ 45 ml/min (calculated with Cockcroft-Gault Equation)

All blood test results must be within 14 days prior to randomisation.

j) Life expectancy of at least 3 months without any active treatment
k) Female patients must either be postmenopausal, sterile (surgically or radiation- or chemically-induced), or if sexually active use an acceptable method of contraception during the study.
l) Male patients must be surgically sterile or if sexually active must use an acceptable method of contraception during the study.
m) Considered suitable to receive either treatment regimen in the clinical judgement of the treating investigator.

Exclusion Criteria

a) Patients with only non-measurable lesions in the liver according to RECIST criteria
b) Incomplete recovery from previous liver surgery, e.g. unresolved biliary tree obstruction or biliary sepsis or inadequate liver function
c) Biliary stent in situ
d) Main trunk Portal Vein Thrombosis (PVT)
e) Ascites, even if controlled with diuretics (a minor peri-hepatic rim of ascites detected at imaging is acceptable).
f) Mixed HCC-ICC disease.
g) History of prior malignancy. Exceptions include in-situ carcinoma of the cervix treated by cone-biopsy/resection, non-metastatic basal and/or squamous cell carcinomas of the skin, recurrent intra-hepatic cholangiocarcinoma post local treatment or any early stage (stage I) malignancy adequately resected with curative intent at least 5 years prior to study entry
h) Suspicion of any bone metastasis/metastases or central nervous system metastasis/metastases on clinical or imaging examination.
i) Prior internal or external radiation delivered to the liver.
j) Pregnancy; breast feeding,
k) Participation within 28 days prior to randomisation, in an active part of another clinical study that would compromise any of the endpoints of this study.
l) Evidence of ongoing active infection that may affect treatment feasibility or outcome.
m) Prior Whipple's procedure

The study will be performed in accordance ISO 14155 **Clinical investigation of medical devices for human subjects – Good clinical practice** (current version), ICH-GCP (current version) and World Medical Association Declaration of Helsinki (APPENDIX 9). All participating institutions must obtain approval from their Institution's Ethics Committee (EC) or Institutional Review Board (IRB) and forward a copy of this to Sirtex Technology Pty Ltd prior to enrolling patients.

3 STUDY ENDPOINTS

The study will evaluate the benefit of applying Selective Internal Radiation Therapy (SIRT) using SIR-Spheres Y-90 resin microspheres prior to receiving a standard of care (See APPENDIX 5) systemic chemotherapy treatment regimen (CIS-GEM) in the experimental arm (Arm B) against the standard of care systemic chemotherapy treatment regimen (CIS-GEM) alone in the control arm (Arm A) in patients with unresectable intrahepatic cholangiocarcinoma.

Randomised patients will be followed until death, withdrawal of consent, or until end of study.

A comparison between treatment arms will be made by assessment of the following criteria:

3.1 Primary endpoint

Survival at 18 months

3.2 Secondary endpoints

Liver-specific PFS
PFS at any site
Objective response rate by RECIST 1.1 and refined RECIST* - liver
Objective response rate by RECIST 1.1 and refined RECIST* - at any site
Overall Survival
Liver surgical resection rate
Liver ablation rate
Safety (CTCAE v4.03) and tolerability
Quality of Life

Toxicity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

*: refer to APPENDIX 7 for RECIST 1.1 and refined RECIST assessments

4 SIR-SPHERES Y-90 RESIN MICROSPHERES

4.1 Product Description

SIR-Spheres Y-90 resin microspheres consist of biocompatible resin microspheres containing yttrium-90, with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27MeV, with a mean of 0.93MeV. The maximum range of emissions in tissue is 11mm, with a mean of 2.5mm. The half-life of yttrium-90 is 64.1 hours and it decays to stable zirconium-90. In clinical use requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days, leaving only background radiation with no therapeutic value. SIR-Spheres Y-90 resin microspheres themselves are a permanent implant and each device is for single patient use.

Each device consists of sufficient microspheres to provide 3.0GBq (±10%) at a predetermined time on the day of calibration (as shown on the product label). The SIR-Spheres Y-90 resin microspheres are suspended in sterile water for injection. Each vial of 3.0GBq is dispatched in a volume of ~5ml (microspheres and water together).

4.1.1 Mode of Action

Intrinsic to the concept of selective internal radiation therapy is the preferential placement of the radioactive microspheres selectively into the distal microvascular supply of tumours (Mackie 2011 (44)), Kennedy 2004 (36)); Campbell 2000 (11)).

A study in a porcine kidney model established unequivocally that the direct irradiation of tissue and microvascular bed destruction, rather than embolization, is responsible for the tissue destructive effects of SIRT (Mackie 2011 (44)).

SIRT, which may also be known as radioembolisation (RE) involves two procedural components:

1. **Embolisation:** injection into the distal arterial tumour feeding vessels of permanently embolic microspheres (SIR-Spheres Y-90 resin microspheres) which act as the delivery vehicle for the therapeutic moiety yttrium-90, and

2. **Irradiation:** once located in the distal microvasculature of the tumour, SIR-Spheres Y-90 resin microspheres deliver high dose beta irradiation to the tumour microvascular plexus and to tumour cells directly.

4.1.2 Form and Stability

SIR-Spheres Y-90 resin microspheres do not exhibit pharmacodynamics in the classic sense, but induce cell damage by emitting beta radiation. Once implanted, the microspheres remain within the vasculature of hepatic tumours, with small amounts within the vasculature of normal parenchyma. The device is not phagocytised nor does it dissolve or degrade after implantation. High dose radiation emitted from the device is cytocidal within the range of the beta radiation. After the yttrium-90 has decayed, the non-radioactive microspheres remain intact and are not removed from the body.

SIR-Spheres Y-90 resin microspheres have the potential to interact with other cytotoxic agents and are typically administered concomitantly with systemic chemotherapeutic agents. This interaction may be exploited to the benefit of the patient, as there may be an additive toxicity on tumour cells, which can enhance the cell kill rate. This interaction may also lead to additive toxicity on non-tumorous cells.

4.2 Regulatory Status

SIR-Spheres Y-90 resin microspheres are regulated as a medical device product based on international definitions of devices, as they have no primary therapeutic pharmaceutical, chemical or metabolic activity. SIR-Spheres Y-90 resin microspheres are classified as a sealed source brachytherapy device and have the following regulatory approval status in major markets:

European Union
SIR-Spheres Y-90 resin microspheres were approved in October 2002 as an active implantable medical device under the Active Implantable Medical Device (AIMD) Directive (90/385/EEC), indicated for:

'the treatment of primary and secondary (metastatic) liver cancer'.

USA
SIR-Spheres Y-90 resin microspheres were approved as a Class III medical device product via PMA P990065 in March 2002 in the United States for:

'the treatment of unresectable metastatic liver tumours from primary colorectal cancer together with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine)'.

Australia
SIR-Spheres Y-90 resin microspheres were listed on the TGA Australian Register of Therapeutic Goods (ARTG) in February 1998 as a medical device in accordance with the Therapeutic Goods Act 1989, under AUSTL No. 63369 and subsequently as an included active implantable medical device (AIMD) in January 2008 under ARTG 149332 with the following purpose:

'for the treatment of inoperable liver cancer'.

4.3 Manufacture

The SIR-Spheres Y-90 resin microspheres being supplied for this clinical study will be from batches of product approved for supply commercially for the treatment of hepatic tumours, manufactured under the approved Sirtex Quality Management System processes and at the approved locations. The SIR-Spheres Y-90 resin microspheres will be manufactured by Sirtex from a production facility located in Boston (USA), Singapore, or Frankfurt (Germany).

4.4 Radiation Safety

The following information on radiation exposure to the treating clinicians and to nursing staff or visitors following the implantation of SIR-Spheres Y-90 resin microspheres is presented here in a summary form. These data are presented in detail in the Sirtex Training Manual, which is provided by Sirtex to all institutions that use SIR-Spheres Y-90 resin microspheres. By way of comparison with the figures listed herein, the radiation dose from normal background radiation

is approximately 2mSv per year.

4.4.1 Radiation Dose Levels for Staff involved in SIRT

The following exposure levels are representative for the nuclear medicine technician preparing a typical patient dose of SIR-Spheres Y-90 resin microspheres and for the interventional radiologist implanting that dose.

			Trunk (mSv)	Lens of Eye (mSv)	Hands (mSv)
Nuclear Medicine Technician	Shallow dose Deep dose	(0.07 mm) (10 mm)	0.027 0.003	0.026 0.004	0.35
Interventional Radiologist	Shallow dose Deep dose	(0.07 mm) (10 mm)	0.038 0.004	0.12 0.054	0.32
Radiation Safety Officer	Shallow dose Deep dose	(0.07 mm) (10 mm)	< 0.02 0.01	0.04 0.017	0.2

The International Commission on Radiological Protection (IRCP) Occupational Radiation Dose Limits are as follows:

Whole body effective dose limit:	20mSv per year (averaged over 5 years) and no more than 50mSv in any 1 year
Lens equivalent dose limit:	150mSv per year
Extremity (e.g. finger) equivalent dose limit:	500 mSv per year over any 1cm^2

These representative exposure levels are additive to other sources of exposure for workers.

4.4.2 Radiation Dose Levels for Nursing Staff or Visitors

The following dose rates may be expected at various distances from a patient with an implanted activity of approximately 2.0GBq when taken approximately 5 – 6 hours after implantation.

Distance from Patient (m)	Radiation Dose (µSv/hr)
0.25	18.8
0.5	9.2
1	1.5
2	0.4
4	< 0.1

In the adjoining room at the wall immediately behind a patient's bed head, the measurement was < 0.1µSv/hr. Typical measurements within limits are 20µSv in any hour and 250µSv in any seven days.

While the median implanted activity of SIR-Spheres Y-90 resin microspheres for this current study is presently unknown – as this will be determined by: 1) the volume of the tumour in

patients recruited to the study; and 2) the dose cohort that the patient is recruited to – the median implanted activity for hepatic tumours is 1.8GBq (range, 0.75GBq to 2.44 GBq) (van Hazel 2009 (66)).

5 CLINICAL EXPERIENCE WITH SIR-SPHERES Y-90 RESIN MICROSPHERES

SIR-Spheres Y-90 resin microspheres have been in use since the late 1990s and approved for the treatment of inoperable hepatic tumours since 2002 in the EU (see Section 4.2 for US and Australian approvals).

Over the past two decades, many theoretical and clinical aspects of the use of SIR-Spheres Y-90 resin microspheres for the treatment of primary and metastatic liver cancer have been published, including:

- microsphere characteristics (Meade 1987 (47)),
- the relationship between the amount of yttrium-90 administered and radiation dose received by the tumour and normal liver compartments (Burton 1990 (8); Burton 1989 (9); Gray 1989 (22); Klemp 1989 (41)),
- the tolerance of the liver to yttrium-90 radiation (Gray 1990 (21)),
- enhancement with vasoactive drugs (Burton 1985 (10)),
- dosimetry (Fox 1991 (16); Klemp 1989 (41)),
- and clinical responses to treatment in both metastatic colorectal cancer (Seidensticker 2012 (60); Cosimelli 2010 (14); Hendlisz 2010 (25); van Hazel 2009 (67); Sharma 2007 (61); van Hazel 2004 (66); Gray 2001 (20); Gibbs 2015 (18));
- metastatic neuroendocrine cancer (Cao 2010 (12); Kalinowski 2009 (30); Kennedy 2006 (33); Kennedy 2008 (32); King 2008 (40); Meranze 2007(48); Murthy 2008(49);
- hepatocellular carcinoma (Gulec 2007 (23); Jakobs 2007 (28); Sangro 2011 (57)),
- and intrahepatic cholangiocarcinoma (Coldwell 2006 (13)); Hoffman 2011 (27); Saxena 2010 (58)); Khanna 2009 (38); Rafi 2011 (0); Gaba 2009 (17).

6 STUDY JUSTIFICATION

The following discusses the justification for this clinical study in intrahepatic cholangiocarcinoma:

6.1 Biliary Tract Cancer

Malignant tumours of the biliary tract and gallbladder (biliary tract system) are rare diseases with an incidence of estimated 5 new cases per 100,000. Biliary tract cancer (BTC) is a rare cancer with a large worldwide variation. According to Randi (Randi 2009 (52)) and collaborators the incidence is relatively low in several European countries and in the United States, while it is relatively high in selected central and eastern European countries, and very high in some countries of Latin America and Asia. However the incidence is rapidly rising even in western countries. While biliary tract cancer is diagnosed more often in male patients the incidence of malignant tumours in the gallbladder is found more often in females: the male/female ratio is 2:1. Intrahepatic cholangiocarcinoma is the second most prevalent intrahepatic primary cancer. It occurs in the middle-aged and elderly with no obvious sex differences.

6.2 Current Treatment Options for Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is defined as a cholangiocarcinoma originating within the liver and located proximally to the second degree bile ducts.

6.2.1 Surgery

Although surgery of the tumour represents the only curative treatment modality the 5-years survival rates for cholangiocarcinoma are low (< 30%) and the patients are often diagnosed too late for surgical treatment.

6.2.2 Transplantation

Liver transplantation is reported as a potentially curative option for selected patients with perihilar but not with intrahepatic or distal cholangiocarcinoma (Razumilava 2014 (53)). This option is not available in most countries and often requires neo-adjuvant multi-modal treatment.

6.2.3 External Beam Radiation Therapy

Radiation therapy (RT) may be employed as a local modality as the technologies are improving both for efficacy and safety. There is no current standard of care of radiotherapy as a routine modality. The optimal radiation dose in the definitive treatment of biliary malignancies is unknown, however higher dose radiotherapy (RT) approaches that use either a combination of transcatheter brachytherapy plus external beam radiation therapy (EBRT), three-dimensional conformal radiation therapy (3D-CRT), or intensity modulated radiation therapy (IMRT) with or without chemotherapy may be associated with better local control (LC) and possibly prolonged survival. Advances in imaging and radiation technology delivery such as image guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT) ((Maithel 2013 (45), Kim, 2013 (39), Aitken 2014 (3) now permit tumouricidal doses of radiation to be delivered safely.

The evidence regarding the use of radiotherapy in cholangiocarcinoma is scarce. Systematic Reviews and Meta-Analyses (PRISMA) review of the role of radiotherapy in primary liver malignancies. (Aitken 2014(3))

6.2.4 Chemotherapy

After the publication of ABC-01 (Valle 2009 (63)) and ABC-02 (Valle 2010 (64)) studies, the combination of gemcitabine plus cisplatin as per the ABC-02 protocol, became the standard of care or reference treatment in most countries. Between 2005 and 2009, the National Cancer Research Institute (NCRI) Upper Gastrointestinal Clinical Studies Group (CSG) conducted the ABC-02 trial, a randomised phase III design evaluating the benefit of gemcitabine with or without cisplatin in advanced or metastatic BTC. The ABC-02 (Valle 2010 (64)) data was combined with data from a previous randomised phase II study with an identical design [ABC-01 (Valle 2009 (63)]. This pre-planned analysis of the combined data demonstrated an improvement in overall survival (OS; from 8.3 to 11.7 months hazard ratio 0.64 [95% CI 0.52 – 0.80, p<0.001]), progression-free survival (PFS; from 5.0 to 8.0 months, p<0.001) and tumour control rate (radiological stable disease, partial or complete response, 71.8% to 81.4%, p=0.049). This improvement was achieved with no significant increase in toxicity and improved quality of life.

The ABC-02 (Valle 2010 (64)) study has established cisplatin and gemcitabine (CIS-GEM) as the standard of care for advanced BTC as well as providing a backbone for subsequent studies. A meta-analysis (Valle 2014 (65)) including data from the BT22 Japanese study (Okusaka 2010 (50)) using the same treatment arms as the ABC-02 study (Valle 2010 (64)) has confirmed that CIS-GEM combination is the 1st line standard of care in good performance status (PS) patients regardless of ethnicity, in both intra and extrahepatic tumour locations.

The CIS-GEM regimen as developed in the ABC studies is confirmed as reference treatment in the current ESMO and EASL guidelines.
According to the ESMO guideline (Valle JW et al. Ann Oncol. (2016)), "*Cisplatin/gemcitabine is the reference chemotherapy regimen for good PS (0-1) patients*".
According to the EASL guideline (Bridgewater J et al, J Hepatol. 2014 Jun (7)), "*Cisplatin and Gemcitabine is a systemic therapy practice standard for iCCA in patients with ECOG performance status 0 or 1, but the data are too limited to make this an established standard of care"*

Because the curative options are still limited and the outcome is poor, enrolment in clinical trials is recommended when possible.

6.3 Justification for this Clinical Study

Despite the advances in different modalities for cholangiocarcinoma the 3 and 5 year survival in non-surgically resected selected patients remains below 50% and 10% respectively.

This approach to integrating potentially curative tumouricidal therapies (ablation, locoregional SIRT and external beam radiotherapy) in patients with unresectable intrahepatic cholangiocarcinoma has to be compared to the current standard of care therapy – cisplatin and gemcitabine (CIS-GEM) systemic chemotherapy (Valle 2009 (63), Valle 2010 (64)) – in order to judge potential benefits.
SIR-Spheres Y-90 resin microspheres have been studied for the treatment of patients with inoperable intrahepatic cholangiocarcinoma. Although no randomised controlled study has been performed to date, the results of SIRT in patients with ICC, in either prospective or retrospective cohort studies, look very promising and provide preliminary evidence that SIRT is a safe and effective treatment option for unresectable ICC. The studies are summarised in table 1 below.

Table1. Summary of prospective and retrospective Clinical Study Results of SIR-Spheres Y-90 resin microspheres in unresectable intrahepatic cholangiocarcinoma

Study Author & Design	n	Treatment	ORR (%)	SD	Median Survival Post SIRT	Median Survival Post Diagnosis
Saxena 2010 (59)	25	SIRT alone	24%	48%	9.3 months	20.4 months
Coldwell 2006 (13)	23‡	SIRT alone	45%	NR	74% alive at 14 months	NR
Khanna 2009 (38)	9‡	SIRT	66%		13.5 months	20.0 months
Rafi 2011 (0)	19‡	SIRT	79%		11.3 months	24.7 months
Hoffmann 2011 (27)	33‡	SIRT alone	36.4%	51.5%	22 months	43.7 months
Gaba 2009 (17) **(Single arm)**	1‡	SIRT alone	1 CR	Na	Alive at 17 months	NR

NR: not reported
ORR: objective response rate (complete response + partial response) by RECIST
SD: stable disease
na not applicable
‡ Retrospective study

Accordingly, this study will assess the benefit of applying SIRT prior to the initiation of the standard regimen of cisplatin and gemcitabine (CIS-GEM) systemic chemotherapy in unresectable liver-only or liver predominant intrahepatic cholangiocarcinoma.

Patients will be offered the accepted treatment in conventional practice and in the active arm of the trial, the standard of care will be preceded with radioembolisation. Such a trial design guarantees that patients do not lose the benefits of conventional therapy and allows the determination of survival benefits of the SIRT treatment. As a consequence, the trial design does not pose any ethical concern that would exist if standard of care would not be incorporated. The investigator must at the outset, before consent, have the intention to provide the standard of care chemotherapy regimen irrespective of which treatment arm the patient is randomised.

7 CLINICAL RISK SUMMARY

7.1 Complications of SIR-Spheres Y-90 Resin Microspheres

As at July 2015, approximately 50,000 doses of SIR-Spheres microspheres have been supplied globally for the management of patients with inoperable liver cancers at more than 800 medical centres in over 40 countries. Overall, the incidence of complications after SIR-Spheres Y-90 resin microspheres therapy in broader clinical use is low. This is enhanced if patients are selected appropriately and target delivery (i.e. liver) is performed meticulously.

7.1.1 Post Embolisation Syndrome

Mild symptoms attributable to the radiotherapeutic and embolic effect of microsphere deposition into the hepatic vasculature have been reported (Sirtex Package Insert and Ahmadzadehfar 2010 (2)). These may include fever, mild to moderate abnormality of liver function tests, nausea, vomiting, constipation, dehydration and associated symptoms/sequelae including acute renal failure, confusion, fatigue, and weakness. Symptoms are typically mild to moderate, transitory and manageable with the administration of oral corticosteroids, IV steroids and analgesics, as necessary.

7.1.2 Gastrointestinal Complications

Gastrointestinal complications occur in less than 10% of those treated (Kennedy 2006 (33); Stubbs 2004 (62) and are largely preventable. In the SIRFLOX study (Gibbs 2015 (18)), the gastric and duodenal ulceration rate have been reported after SIRT in 3.7% (per ITT), they are related to the inadvertent intestinal deposition of microspheres via extra-hepatic visceral arterial branches. Even in the absence of extra-hepatic activity on ^{99m}Tc labelled MAA and bremsstrahlung emission images, gastrointestinal symptoms have been reported to develop. The risk of gastrointestinal ulceration can be minimised via the routine coil embolisation of the extra-hepatic visceral arteries (e.g. gastroduodenal, right gastric, supraduodenal arteries) before infusion of SIR-Spheres Y-90 resin microspheres (Liu 2005(43)).

The gallbladder may also receive SIR-Spheres Y-90 resin microspheres through a patent cystic artery, leading to radiation cholecystitis. In order to avoid this potential complication, infusion of the SIR-Spheres Y-90 resin microspheres distal to the origin of the cystic artery may be possible. However, even with infusion of SIR-Spheres Y-90 resin microspheres proximal to the cystic artery, the risk of radiation cholecystitis requiring cholecystectomy is low (Liu 2005(43)). This issue is addressed at the time of administration by the treating interventional radiologist via catheter placement and/or selective embolisation/optimization of the hepatic arterial vasculature.

7.1.3 Hepatic Complications

Radioembolisation induced liver disease (REILD) is a rare complication following SIRT (Sangro 2008 (56)) and is characterized by a well-defined constellation of temporal, clinical, biochemical and histopathologic findings. REILD typically manifests approximately 4 – 8 weeks post-SIRT and is characterized clinically by jaundice and ascites in the absence of tumour progression or bile duct obstruction. The typical biochemical picture of REILD is an elevated bilirubin (>3mg/dL) in almost all cases, elevated alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) in most cases, accompanied by virtually no change in the transaminases (AST and ALT). In the event that a liver biopsy is performed, the typical histological appearance is of sinusoidal obstruction.

REILD may occur in both non-cirrhotic and cirrhotic patients. In non-cirrhotic patients, the main risk factors for the development of REILD include prior exposure to systemic chemotherapy and whole-liver SIRT. In cirrhotic patients, the main risk factors are small liver volume (< 1.5L) and elevated bilirubin (> 1.2mg/dL) at baseline. The treatment of REILD is absolutely empiric and may comprise a tapering schedule of initially high dose corticosteroids, and standard dose ursodeoxycholic acid. If liver decompensation develops, imaging, diuretics, defibrotide or early TIPS placement should be considered on an individual basis. Low molecular weight heparin may also be considered but both corticosteroids and heparin may only be useful if commenced very early in the course of the disease.

7.1.4 Pulmonary Complications

Progressive pulmonary insufficiency secondary to radiation pneumonitis and radiation-induced lung fibrosis can be avoided by excluding from SIRT any patient with significant liver-to-lung shunting (Leung 1995 (42)). The shunting of microspheres through the liver and thence into the lungs occurs via abnormal arterio-venous malformations (AVMs), which are characteristic within primary hepatocellular carcinomas but are rare in metastatic liver tumours. It is relevant to note that there have not been any cases of radiation induced lung disease reported in HCC patients undergoing SIRT since routine pre-treatment liver-to-lung shunt quantification has been standard practice.

7.1.5 Haematological Complications

Pancytopenia as a result of bone marrow suppression from the leaching of yttrium-90 was reported after the use of the earliest microsphere device (Mantravadi 1982 (46)). The development of SIR-Spheres Y-90 resin microspheres – which are classified as a sealed-source device – solved the problem of leaching of yttrium-90 from the microsphere carrier. Consequently, this complication has very rarely been reported since that time. Transient and reversible lymphopenia or neutropenia (including febrile neutropenia) are possible, particularly if concomitant immunosuppressive agents are used with SIR-Spheres Y-90 resin microspheres. In the SIRFLOX study which compared the addition of SIR-Spheres Y-90 resin microspheres with oxaliplatin based chemotherapy vs oxaliplatin based chemotherapy, (N = 530 patients) grade 3/4 neutropenia was reported in 40.7% of the patients in the SIRT arm compared to 28.5% in the control group, thrombocytopenia in 9.8% versus 2.6%. The toxicities were as expected and manageable (Gibbs 2015 (18)).

7.2 Known Contraindications to SIR-Spheres Y-90 resin microspheres

In the treatment of liver cancer, it is established that SIR-Spheres Y-90 resin microspheres are contraindicated (Sirtex Package Insert) in patients who have:

- Received previous external beam radiation therapy to the liver
- Ascites or other clinical signs of liver failure
- Abnormal synthetic and excretory liver function tests as determined by serum albumin (must be > 3.0 g/dL) and total bilirubin (must be < 2.0 mg/dL), respectively
- Disseminated extra-hepatic disease
- Tumours amenable to surgical resection or ablation with intent to cure
- Greater than 20% liver-to-lung shunting, as determined by pre-treatment nuclear medicine shunt quantification study
- Pre-assessment angiogram and MAA nuclear medicine scan demonstrating significant and

uncorrectable activity in the stomach, duodenum or pancreas
- Been treated with capecitabine within the previous 8 weeks, or who will be treated with capecitabine within 8 weeks of treatment with SIR-Spheres Y-90 resin microspheres

7.3 Identifying risks of combining SIR-Spheres Y-90 resin microspheres with chemotherapy

Previous studies documenting the combined use of SIR-Spheres Y-90 resin microspheres and contemporary systemic chemotherapy have indicated that when used in combination with either 5-FU/LV, or with irinotecan that there has been no detectable increase in adverse events in comparison with SIR-Spheres microspheres alone (van Hazel 2004 (67), van Hazel 2009 (66)).

Concomitant use of SIR-Spheres Y-90 resin microspheres and oxaliplatin (as part of a FOLFOX regimen), as demonstrated in a 20 patient dose-escalation study, has resulted in a slight increase in neutropenia in the immediate cycles following treatment. This decrease was transient, being resolved by a 1-week delay in the administration of chemotherapy. Besides the early neutropenia the rate of adverse events reported in this study was similar to those normally reported for FOLFOX chemotherapy alone (Sharma 2007 (61)).

More recently, the SIRFLOX randomised controlled study reported on the efficacy and safety of SIR-Spheres Y-90 resin microspheres when administered concurrently with mFOLFOX6 chemotherapy (Gibbs 2015 (18)). Recently reported early safety data from this study showed a statistically significant increase in the rate of grade 3 or higher neutropenia, febrile neutropenia and thrombocytopenia in patients receiving mFOLFOX6 chemotherapy + SIR-Spheres Y-90 resin microspheres compared to patients receiving mFOLFOX6 chemotherapy alone. The study also reported a statistically significant increase in the rate of grade 3 or higher gastric or duodenal ulcers and ascites in patients receiving the combination therapy. However, the addition of SIR-Spheres Y-90 resin microspheres to mFOLFOX6 chemotherapy was shown to have no negative impact on the duration of systemic chemotherapy and the study investigators concluded that these toxicities were acceptable and as predicted.

To date, there are no formal prospectively collected clinical data reporting the efficacy, tolerability or safety of SIR-Spheres Y-90 resin microspheres given concurrently with either cisplatin, gemcitabine, or a combination of these two agents. In the present study however, the systemic agents, cisplatin and gemcitabine, will not be administered concurrently with SIR-Spheres Y-90 resin microspheres but instead will be withheld until 14-16 days following the administration of SIR-Spheres Y-90 resin microspheres.

The half-life of yttrium-90 is approximately 64.1 hours so that in therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. Given these decay characteristics for the yttrium-90 isotope approximately 3% of the radiation will be expected to be remaining at the time of initiation of cisplatin-gemcitabine chemotherapy 14 -16 days post-SIRT. In addition, gemcitabine is a potent radiosensitizer, and has a half-life of up to 94 minutes when administered in a short infusion over < 70 minutes. Given the time between administration of SIR-Spheres Y-90 resin microspheres and commencement of gemcitabine, the vast majority of the radiation will have decayed, thereby minimising any additive toxicities between the radiation emitted from SIR-Spheres Y-90 resin microspheres and gemcitabine. Given this therapeutic sequencing, the risk of toxicity due to an unknown or unforeseen interaction between the therapeutic agents is considered acceptable, within this study setting.

8 DEVICE RISK ANALYSIS

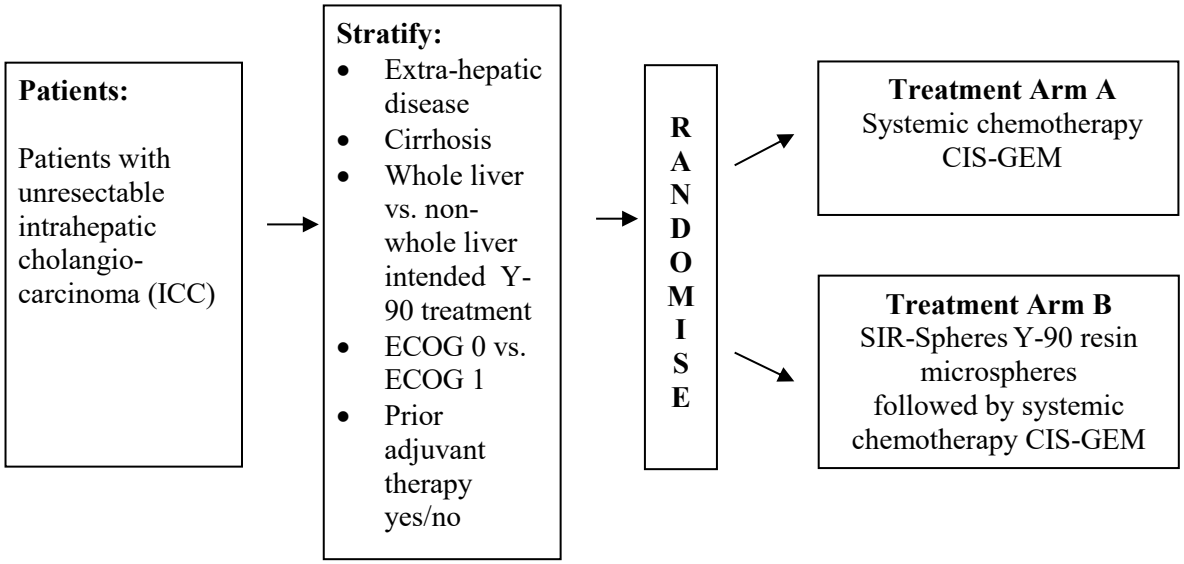
As CIS-GEM is the reference chemotherapy regimen for cholangiocarcinoma, a risk analysis performed in accordance with ISO 14971 addressing the use of SIR-Spheres Y-90 resin microspheres followed by cisplatin-gemcitabine chemotherapy is maintained on file at Sirtex as part of the Design File for this study. This is a Quality Record and is recorded and maintained under the Sirtex Quality Management System, which includes additional Risk Management relating to production processes. All risk analysis documents are updated as required or reviewed at least every two years.

For the use outlined in this Clinical Investigational Plan (CIP), all identified unacceptable hazards have been addressed and control strategies are in place to render the hazards acceptable. It is concluded that there are no unacceptable hazards remaining and based on supporting published literature the potential patient benefits of SIRT (using SIR-Spheres Y-90 resin microspheres plus Delivery Set and V-Vial) outweigh the risks with an anticipated 15% improvement in survival at 18 months.

9 STUDY DESIGN

The study is a prospective, multicentre, randomised, controlled study evaluating SIR-Spheres Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy vs. CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma.

Patients will be randomised 1:1 (about 90 patients in each arm) and will be stratified by: presence of extra-hepatic disease, presence of cirrhosis, intention for whole liver versus non-whole liver Y-90 treatment, ECOG (0 versus 1) and prior adjuvant therapy vs no prior adjuvant therapy.



Cirrhosis:
Absence of cirrhosis should be registered when

- The non-tumoural part of the liver is regular and without nodularity on imaging *and*
- There is no evidence of portal hypertension with no clinically significant ascites, oesophageal varices or splenomegaly with dilated portal vein in the absence of portal vein thrombosis.

Detection of any of the above findings, and/or a positive biopsy diagnosis (F4=cirrhosis according to the METAVIR scoring system) and/or an increased elastography value, establishes the existence of cirrhosis.

Randomised patients will be followed until death, withdrawal of consent, or until end of study. A comparison between treatment arms will be made.

The enrolment period for the study is estimated to be 40 months. The study will be conducted in approximately 45 selected investigational sites worldwide. The sponsor will maintain a list of principal investigators, investigational sites, and institutions. The definitive list will be provided with the final clinical study report.

9.1 Patient Eligibility

Patients must have histologically or cytologically confirmed intrahepatic cholangiocarcinoma.

In order to be considered eligible for this study, patients must fulfil the inclusion and exclusion

criteria specified in 9.2 below.

9.2 Inclusion/Exclusion Criteria

9.2.1 Inclusion Criteria

a) Willing, able and mentally competent to provide written informed consent
b) Aged 18 years or older
c) Histologically or cytologically confirmed unresectable and non ablatable intrahepatic cholangiocarcinoma
d) Liver-only or liver predominant intrahepatic cholangiocarcinoma. Patients are permitted to have loco-regional lymph node involvement defined as: portal LN ≤ 2 cm and/or para aortic LN ≤ 1.5 cm in longest diameter, and/or up to 2 indeterminate lung lesions < 1 cm if these lung lesions are PET negative.
e) Chemotherapy for advanced disease naïve. Capecitabine only based adjuvant chemotherapy is permitted (last administered dose of capecitabine ≥ 6 months prior randomization in the study).
f) ECOG performance status 0 or 1
g) Adequate haematological function defined as:
   Haemoglobin ≥ 10g/dL
   WBC ≥ 3.0 x 10^9/L
   Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   Platelet count ≥ 100,000/mm^3,
h) Adequate liver function defined as:
   Total bilirubin ≤ 30 µmol/L (1.75 mg/dL)
   Albumin ≥ 30 g/L
i) Adequate renal function defined as:
   Serum urea and serum creatinine < 1.5 times upper limit of normal (ULN)
   Creatinine clearance ≥ 45 ml/min (calculated with Cockcroft-Gault Equation)

All blood test results must be within 14 days prior to randomisation.

j) Life expectancy of at least 3 months without any active treatment
k) Female patients must either be postmenopausal, sterile (surgically or radiation- or chemically-induced), or if sexually active use an acceptable method of contraception during the study.
l) Male patients must be surgically sterile or if sexually active must use an acceptable method of contraception during the study.
m) Considered suitable to receive either treatment regimen in the clinical judgement of the treating investigator.

9.2.2 Exclusion Criteria

a) Patients with only non-measurable lesions in the liver according to RECIST criteria
b) Incomplete recovery from previous liver surgery, e.g. unresolved biliary tree obstruction or biliary sepsis or inadequate liver function
c) Biliary stent in situ
d) Main trunk Portal Vein Thrombosis (PVT)
e) Ascites, even if controlled with diuretics (a minor peri-hepatic rim of ascites detected at imaging is acceptable).
f) Mixed HCC-ICC disease.

g) History of prior malignancy. Exceptions include in-situ carcinoma of the cervix treated by cone-biopsy/resection, non-metastatic basal and/or squamous cell carcinomas of the skin, recurrent intra-hepatic cholangiocarcinoma post local treatment or any early stage (stage I) malignancy adequately resected with curative intent at least 5 years prior to study entry
h) Suspicion of any bone metastasis/metastases or central nervous system metastasis/metastases on clinical or imaging examination.
i) Prior internal or external radiation delivered to the liver.
j) Pregnancy; breast feeding,
k) Participation within 28 days prior to randomisation, in an active part of another clinical study that would compromise any of the endpoints of this study.
l) Evidence of ongoing active infection that may affect treatment feasibility or outcome.
m) Prior Whipple's procedure

10 SCREENING AND STUDY ENTRY

No patient may undergo any screening procedures that are not considered standard of care to assess his/her eligibility to receive protocol treatment, or commence protocol treatment, prior to signing the informed consent form.

The study Sponsor should be contacted in the event of any query or uncertainty relating to a patient's eligibility:

Sirtex Technology Pty Ltd
Clinical Operations

Europe	Tel: +49 228 18407 30 Fax: +49 228 18407 35
United States	Tel: +1 781 721 3840 Fax: +1 877 221 0256
Australia	Tel: +61 2 9964 8400 Fax: +61 2 9964 8410

10.1 Patient Screening

All patients referred for possible participation in this study must be assessed at screening to confirm the patient's eligibility to be randomised into the study. Screening assessments must be performed within 28 days prior to randomisation, in the exception of haematology/biochemistry assessments, which must be performed within 14 days prior to randomisation.

All documentation in support of the inclusion and exclusion criteria and screening investigation results are to be retained by the Investigator and made available for monitoring by the study Sponsor.

Study entry is defined as the date that the Informed Consent has been signed by the patient. After signing the informed consent, the patient will be allocated with a screening number.

All patients assessed as ineligible after study entry (date of informed consent) are considered screening failures. The reasons for screen failures will be collected and capture in the eCRF as well as on the screening log. The Patient Screening Log will include the reason(s) for the patient not meeting the eligibility criteria and will be maintained by the site and copies retained by the study Sponsor. These patients will be treated with best available care at the discretion of the treating physician and local guidelines. No further information will be captured.

10.2 Histological / Cytological Investigation

Histological or cytological evidence of intrahepatic cholangiocarcinoma must be available prior to randomisation and is commonly available as routine clinical practice.

10.3 Clinical Assessments

All patients must be assessed clinically by the Investigator to determine the patient's eligibility to receive protocol treatment prior to the study entry. Clinical assessment includes a

comprehensive medical history with concurrent illnesses and concomitant medication.

10.4 Physical Examination and Performance Status

Physical examination and patient's height, weight, blood pressure and temperature must be performed within 28 days prior to randomisation.

All patients must have an ECOG performance status 0 or 1.

10.5 Haematological and Biochemical Investigations

All patients are required to undergo the following haematological and biochemical assessments in order to confirm their eligibility to be randomised into the study.
All blood test results must be within 14 days prior to randomisation

Haematological	Haemoglobin
	WBC
	Absolute neutrophils
	Platelets
Liver	Total bilirubin
	Albumin
Renal	Serum urea
	Serum creatinine
	Creatinine Clearance
Pregnancy test	Serum or urine pregnancy test in premenopausal female patients

Local practice guidelines such as NICE guidance, EASL guidelines or AASLD-IDSA Recommendations should be followed for Testing, Managing, and Treating Adults Infected with HCV or HBV which may interfere with systemic treatment of the protocol.

10.6 Radiological Investigation: CT Scan of the Abdomen, Chest, Pelvis

All patients are required to have the following radiological investigation in order to confirm their eligibility to be randomised in the study, and to demonstrate the extent of the disease, and the intention for whole liver or non-whole liver treatment. This scan must be performed within 28 days prior to randomisation.

A contrast enhanced CT scan of the chest, abdomen and pelvis must be available for assessment of local-regional, or distant spread, staging, and resectability.

Refer to APPENDIX 6 for recommended acquisition guidelines for CT scanning

If the CT scan which was performed prior to study entry was also obtained within 28 days prior to commencement of protocol treatment, it can be used for baseline RECIST assessment too. The same acquisition parameters should be maintained and also need to be consistent with the follow up scans.

If the CT scan performed prior to study entry was obtained > 28 days before start of protocol treatment or the acquisition parameters will not be consistent with the follow up parameters, then the baseline CT scan must be repeated.

10.7 Quality of Life

Quality of life (QoL) will be measured by using the EQ-5D questionnaire. The EQ-5D will be completed at screening.

10.8 Randomisation

Upon documentation of confirmed eligibility, the patient will be randomised and allocated with a patient enrolment number. The patient enrolment number will be multi-digit, to represent the investigational site and will be unique to each subject. This will be the patient's ID number to be used throughout the entire study.

The subject's ID number will be used in the electronic CRF. A total of about 180 patients will be randomised 1:1 between the two treatment groups (about 90 patients in each group).

Any patients who are not able to receive the treatment according to the assigned study arm, irrespective of the reason, will continue to be followed and assessed according to the CIP and their data will be captured in the eCRF. They will be analysed per the assigned study arm according to the intention to treat principle (see 15.3)

11 BASELINE ASSESSMENTS

The following baseline assessments are required within **7 days** prior to start of protocol treatment:

11.1 Physical Examination and ECOG performance status

All patients are required to undergo a full physical examination including weight, blood pressure and body temperature. Also, the ECOG performance status has to be assessed by the Investigators.

Full Physical examination includes assessment of the following body systems:

Dermatological
HEENT / Neck
Respiratory
Cardiovascular
Gastrointestinal / Digestive
Genitourinary
Neurological
Musculoskeletal
Endocrine
Hematologic / Lymphatic
Metabolic / Nutritional
General Appearance

11.2 Haematological and Biochemical Investigations

All patients are required to undergo the following haematological and biochemical assessments within 7 days of treatment commencement in order to confirm their eligibility to receive protocol treatment.

Haematological	Haemoglobin
	WBC
	absolute neutrophils
	platelets
Liver	Total bilirubin
	Albumin
	ALT, AST, AP, GGT
Renal	Serum urea
	serum creatinine
	sodium, potassium, calcium, phosphate, glucose
	creatinine clearance
Tumour markers	CEA
	CA 19-9
	CA125
	AFP

Additionally, for patients randomised to Arm B, tumour markers are also to be done within 7 days prior to SIRT eligibility workup, and do not need to be repeated prior to SIRT treatment.

11.3 Radiological Investigation: CT Scan of the Abdomen, Chest, Pelvis

A contrast enhanced CT scan of the chest, abdomen and pelvis must be available for assessment of local-regional, or distant spread, staging, and resectability.
Refer to APPENDIX 6 for acquisition guidelines for CT scanning

Imaging must be performed within 28 days prior to the start of protocol treatment. In case a CT scan of chest, abdomen, pelvis was obtained for eligibility confirmation more than 28 days prior to commencement of protocol treatment, a new baseline CT scan must be obtained during the Baseline period, i.e. within 28 days prior to start of protocol treatment.

11.4 Baseline Measurement of Lesions

The extent of disease will be recorded and measured according to the RECIST 1.1 Guidelines (RECIST: Response Evaluation Response Criteria In Solid Tumours) and refined RECIST (Reig 2014 (54)) (See APPENDIX 7).

11.5 Selective internal radiation therapy (SIRT)

The SIRT procedure comprises of a baseline mapping angiogram to determine the vascular anatomy of the liver and potential coil embolisation of afferent vessels that may arise from the hepatic arteries and supply other organs, followed by the actual implantation of the SIR-Spheres Y-90 resin microspheres which occurs 3 – 8 days after the baseline mapping angiogram. The full process is described in detail in the Sirtex Training Manual, which is provided by Sirtex to all users.

11.6 Commencement of Protocol Treatment

Protocol treatment may commence once patients have been randomised into the study. Suitability to receive SIRT (patients in Arm B) must be reconfirmed prior to the implantation of SIR-Spheres Y-90 resin microspheres. The study Sponsor should be contacted in the event of any query or uncertainty relating to patient's suitability to receive SIRT.

12 TREATMENT

Consenting patients satisfying the study eligibility criteria, will be randomised to receive either

a) Treatment Arm A:

Standard of care systemic chemotherapy (as per ESMO guidelines) consisting of 8 cycles of cisplatin + gemcitabine (CIS-GEM) or until progression

or

b) Treatment Arm B:

A single treatment of hepatic arterial injection of SIR-Spheres Y-90 resin microspheres followed by standard of care systemic chemotherapy (as per ESMO guidelines) consisting of 8 cycles of cisplatin + gemcitabine or until progression.

Treatment may be continued beyond 8 cycles, in the absence of disease progression, at the treating clinicians' discretion.

12.1 Treatment Arm A: Chemotherapy Arm – CIS-GEM (as per ESMO guidelines)

Systemic chemotherapy (CIS-GEM) to start within 14 days (+ 2 days) of randomisation:

The reference regimen as per ESMO guidelines and ABC 02 protocol consists of:

Cisplatin 25 mg/m^2 in 1000ml 0.9% saline given over 1 hour followed by 500 ml 0.9% saline over 30 minutes followed by

Gemcitabine 1000 mg/m^2 in 250 - 500ml 0.9% saline over 30 minutes by intravenous infusions on days 1, and 8 of a 21-day cycle.

8 treatment cycles will be given; in the absence of progression treatment may be continued at discretion of the clinician.

	Cycle 1			Cycle 2			Cycle 3			Cycle 4 onwards		
Week	1	2	3	4	5	6	7	8	9	10	11	12
Day	1	8		1	8		1	8		1	8	
Cisplatin	x	x		x	x		x	x		x	x	
Gemcitabine	x	x		x	x		x	x		x	x	

See APPENDIX 5 for recommended guidelines for CIS-GEM chemotherapy administration as per the ABC-02 regimen.

12.2 Treatment Arm B: Sequential Therapy Arm – SIRT followed by CIS-GEM

SIR-Spheres Y-90 resin microspheres to be administered at the calculated dose within 14 days of randomisation followed by standard of care systemic chemotherapy (CIS-GEM), to start 14-16 days after SIRT treatment (or at the earliest point thereafter on recovery of any haematological, bilirubin or albumin derangements if they occur).

12.2.1 Assessing patient suitability for SIRT (Work-Up)

Patients randomised to receive the SIR-Spheres Y-90 resin microspheres plus systemic chemotherapy (Arm B) need to be assessed in order to determine their suitability for SIRT.

12.2.1.1 Hepatic angiogram

Patients must undergo a preliminary mapping angiogram of the liver, between 3 and 8 days prior to the implantation of SIR-Spheres Y-90 resin microspheres to determine the vascular anatomy of the liver and to perform a nuclear medicine 'break-through' scan performed with ^{99m}Tc-MAA. The hepatic angiogram will provide a road map of the arterial supply of the liver in order to plan delivery of the SIR-Spheres microspheres. (See the Training Manual provided by Sirtex). It is important to note that the MAA have to be delivered at the same anatomical place where the SIR-Spheres Y-90 resin microspheres are intended to be administered. The hepatic angiogram should be performed together with the nuclear medicine 'break-through' scan and results must be available prior to the implantation of SIR-Spheres Y-90 resin microspheres. Anonymised copies of the ^{99m}Tc-MAA imaging, i.e. planar images, SPECT/CT, and/or SPECT/MRI, will be collected for potential central review.

Patients showing abnormal vascular anatomy on the angiogram which would result in a significant reflux of blood from the hepatic artery to the stomach, the pancreas or the intestines that cannot be prevented by coil embolisation of the appropriate arteries are not suitable for SIRT treatment.

Liver-to-lung nuclear medicine break-through scan

In some patients there will be significant arterio-venous shunts in the liver which will allow more than 10% of the SIR-Spheres Y-90 resin microspheres injected into the liver to pass through the liver and lodge in the lungs. As excessive liver-to-lung shunting may cause radiation damage to the lungs, a nuclear medicine 'break-through' scan must be performed in all patients to exclude this level of arterio-venous flow.

The percentage of technetium-99m labelled macro-aggregated albumin (MAA) that has escaped through the liver and lodged in the lungs can then be expressed as a 'per cent lung shunting'. Normally this is less than 10% in patients with liver metastases from colorectal cancer. The total lung radiation dose delivered by SIR-Spheres Y-90 resin microspheres must be kept at 25 Gy or lower. It is assumed that the mass of both lungs plus blood is 1000gm and allows estimation of lung parenchymal radiation doses for any given amount of shunting. The administered dose of SIR-Spheres Y-90 resin microspheres must be reduced to ensure that the lung dose does not exceed 25 Gray.

Patients unable to receive SIRT will receive treatment as in the control arm but will be followed – and their safety and efficacy data recorded – and analysed as in the SIRT arm (intention to treat analysis). See APPENDIX 2

12.2.2 Calculation of SIR-Spheres Y-90 resin microspheres activity

The activity of SIR-Spheres Y-90 resin microspheres to be administered is detailed in APPENDIX 3. The method of calculation will depend on the presentation of disease in the liver [e.g. bi-lobar vs. lobar, focal vs. diffuse, cirrhotic vs. non-cirrhotic, extent of tumour involvement, extent of radiation exposure to normal parenchyma] (Gil-Alzugaray, 2013 (19)). In the case of bi-lobar disease, whole liver targeted or selective administrations are possible at the discretion of the investigator to be determined on a case by case basis. SIR-Spheres Y-90 resin microsphere administration is to be conducted in one session even when a whole-liver approach is used.

SIRT cannot be performed in patients with only non-measurable liver disease according to RECIST criteria, since activity calculation requires the tumour volume to be measured.

If the whole liver will receive SIR-Spheres Y-90 resin microspheres, the BSA method will be used for activity calculation. The % tumour volume involvement, targeted and total liver volumes are calculated from the baseline CT scan of the liver (Kennedy 2007(35), Kennedy 2012 (34)). The following formula will be applied:

$$\text{Dose activity[GBq]} = (\text{BSA} - 0.2) + \frac{V_{tumour}}{V_{TotalLiver}}$$

V_{tumour} = volume of tumour
$V_{TotaLiver}$ = volume of total liver, including tumour

If at least 2 adjacent segments of the liver are spared from SIRT, the partition model may be used to define the activity to be injected. On the basis of tumour and liver volumes measured on CT or MRI images and MAA imaging, representative regions of interest of tumour and non-tumour liver are drawn. MAA imaging such as SPECT CT/MRI or MAA planar images may be used and MAA SPECT CT/MRI are preferred (Hamami 2009 (24); Kao 2012(30); Roshan 2015 (54)). The Partition Model estimates the dose of radiation that will be absorbed by tumour and non-tumoural liver compartments.

When the spared liver volume is equal to or less than 40% of the total liver volume and the patient is cirrhotic, the Model is used to determine the activity that would result in the non-tumoural liver absorbing not more than 40 Gy. Conversely, when the spared liver volume is more than 40% of the total liver volume or the patient is not cirrhotic, the Model is used to calculate an activity that would result in the tumour absorbing 120 Gy.

Spared Volume	Cirrhosis	No Cirrhosis
≤ 40%	≤ 40 Gy (Non Tumour)	120 Gy (Tumour)
> 40%	120 Gy (Tumour)	120 Gy (Tumour)

If there is a contraindication to the use of the Partition Model (tumours cannot be delineated on MAA SPECT CT/MRI or planar MAA to calculate the T: N ratio), then the activity will be calculated using the BSA method.

12.2.3 Administration of SIR-Spheres Y-90 resin microspheres

Sequential treatment is not permitted in this study.
For patients randomised to Arm B, in case of progression in the liver after more than 6 months from start of protocol treatment (i.e. start date is SIR-Spheres Y-90 resin microspheres implant date), retreatment with SIRT is allowed if the patients remain within the safety criteria for SIRT treatment.

However, the whole liver, selective or super-selective administration of the SIRT is left to the discretion of the physicians.

The technique for delivering SIR-Spheres Y-90 resin microspheres is provided in the SIR-Spheres Y-90 resin microspheres Training Manual and in APPENDIX 1.
The administration of the SIR-Spheres Y-90 resin microspheres should be delivered exactly in the same vascular anatomical place where ^{99m}Tc-MAA was administered.

Patients will receive the calculated dose of SIR-Spheres Y-90 resin microspheres as described in APPENDIX 3.

The batch number of the used vials of SIR-Spheres Y-90 resin microspheres will be captured for accountability purposes.

12.2.4 Ancillary protocol treatment

A prophylactic H2 blocking agent or proton pump inhibitor (e.g. ranitidine, omeprazole) is to be administered to patients receiving SIRT for a minimum period of four weeks, commencing either just prior to or at the time of administration of SIR-Spheres Y-90 resin microspheres and must be recorded as concomitant medication.

Prophylactic narcotic analgesia is to be administered in conjunction with SIRT as per standard hospital policy. Although minor opiates analgesia (e.g. codeine, dihydrocodeine) is usually sufficient, major opiates (e.g. pethidine) may be required within the first 24 hours after SIRT.

All supportive treatment should be recorded, including any supportive treatment provided for the implantation of SIR-Spheres Y-90 resin microspheres.

12.2.5 Treatment Arm B: Post-SIRT Bremsstrahlung scan

Following the administration of SIR-Spheres Y-90 resin microspheres, Bremsstrahlung scan (SPECT/CT), Y-90 PET/CT or Y-90 PET/MRI must be performed on the same day or day 1 post-SIRT. These studies detect the Bremsstrahlung radiation or positron emission from the yttrium-90 and are performed in order to confirm the placement of SIR-Spheres Y-90 resin microspheres in the targeted lesions and to exclude non-targeted delivery of SIR-Spheres Y-90 resin microspheres. Anonymised copies of the Bremsstrahlung scan (SPECT/CT) or a Y-90 PET/CT or Y-90 PET/MRI will be collected for potential central review.

12.2.6 Treatment Arm B: Administration of CIS-GEM

Patients randomised to receive the SIR-Spheres Y-90 resin microspheres followed by systemic chemotherapy will commence administration of CIS-GEM (European guidelines on biliary tract cancer; Valle et al. *New England Journal of Medicine* 2010), 14 -16 days after SIRT treatment, (or at the earliest point thereafter on recovery of any haematological, bilirubin or albumin derangements if they occur).

The reference regimen as per ESMO guidelines and ABC 02 protocol consists of:

Cisplatin 25 mg/m^2 in 1000ml 0.9% saline given over 1 hour followed by 500 ml 0.9% saline over 30 minutes followed by

Gemcitabine 1000 mg/m^2 in 250 - 500ml 0.9% saline over 30 minutes by intravenous infusions on days 1, and 8 of a 21-day cycle.

14-16 days after SIRT	Cycle 1			Cycle 2			Cycle 3			Cycle 4 onwards		
Week	1	2	3	4	5	6	7	8	9	10	11	12
Day	1	8		1	8		1	8		1	8	
Cisplatin	x	x		X	x		x	x		x	x	
Gemcitabine	x	x		X	x		x	x		x	x	

See APPENDIX 5 for recommended guidelines for CIS-GEM chemotherapy administration as per the ABC-02 regimen.

In the absence of disease progression or unacceptable toxicity 8 treatment cycles will be given. Beyond 8 cycles, treatment may be continued in the absence of disease progression at the treating clinicians' discretion.

Note: Patients randomised to receive SIRT (Arm B) but for whom SIRT implantation is not safely feasible (e.g. following initial angiographic work-up) will be treated according to arm A (but retained in Arm B for intention-to-treat analysis within the study).

12.3 Supportive Treatment

Supportive treatment should be administered when required according to the patient's condition. Such supportive treatment may include, but is not limited to antiemetics, analgesia, corticosteroids, antibiotics etc. All supportive treatment should be recorded on the eCRF, including any supportive treatment provided for the implantation of SIR-Spheres Y-90 resin microspheres.

Ursodeoxycholic acid (300 mg bid for the first 3 cycles) may provide benefit in terms of adequate bile flow and is routinely recommended for SIRT treated patients.

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures will be undertaken to diagnose (e.g. by ultrasound and/or CT scan) and relieve the obstruction (e.g. by ERCP/PTC +/- stent insertion/drainage). Chemotherapy will be deferred until the Liver Function Tests have improved to adequate levels (i.e. total bilirubin ≤ 1.5 X ULN; ALT, AST & alkaline phosphatase ≤ 5 x ULN. Chemotherapy may then resume at the start of the next treatment cycle.

12.3.1 Recommendation for antibiotic prophylaxis and treatment of patients with intrahepatic cholangiocarcinoma (ICC) undergoing radioembolisation followed by chemotherapy

Recommend diligent antibiotic prophylaxis in the following situations:

a) Treatment naïve patients with a history of suspected cholangitis (even mild events)
b) Treatment naïve patients with a history of ERC (endoscopic retrograde cholangiography) or PTCD (Percutaneous Transhepatic Cholangio-Drainage) with or without papillotomy. This is even more important in patients who present with segmental dilation of bile ducts, e.g. through tumour compression, since there may exist cholangitis without any clinical evidence (e.g. normal CRP value and normal leucocyte count).
c) Treatment naïve patients with biliodigestive surgical anastomosis
d) Patients who have undergone radioembolisation and chemotherapy who undergo endoscopy or any other biliary intervention during follow up. In ICC, abscess formation in irradiated ICC may occur even months or more than a year after irradiation when the biliary tree is exposed to bacteria colonization.

12.3.2 For patients undergoing a biliary intervention during follow up (after RE and chemo) the recommended treatment is:

Endoscopy/any other biliary intervention under antibiotic prophylaxis
Antibiotics that cover biliary flora, such as enteric gram-negative organisms and enterococci, should be used, e.g. ciprofloxacin 2 x 400 mg, metronidazole 3 x 500 mg i.v.

- first Infusion terminated ½ hour before the intervention.
- i.v. Antibiotics during the hospital stay
- after discharge: ciprofloxacin monotherapy 2 x 500 mg for 10 days p. o.
- followed by: once a month ciprofloxacin 2 x 500 mg for 1 week for a duration of at least 6 months

12.3.3 For patients with risk profile (see above, e.g. history of ERC) undergoing radioembolisation the recommended treatment is:

Radioembolisation under antibiotic prophylaxis, e.g. ciprofloxacin 2 x 400 mg, metronidazole 3 x 500 mg i.v.

- first Infusion terminated ½ hour before the intervention.
- i.v. Antibiotics during the hospital stay
- after discharge: ciprofloxacin mono 2 x 500 mg for 10 days p. o.
- followed by : once a month ciprofloxacin 2 x 500 mg for 1 week for a duration of at least 6 months

12.4 Concomitant Medications

All medications taken by the patient including medications that are unrelated to their cancer management should be recorded in the eCRF. These include long-term as well as short-term or acute medications ongoing at the time of signing of the informed consent form or started any time after signature of the informed consent form, until 28 days after the last dose of study protocol chemotherapy was administered.

Any concomitant medications administered at the time of any study treatment related SAEs or any SADE which occurred after 28 days post last dose of protocol chemotherapy, will be reported on the SAE Report Form to the study sponsor.

Routine medications should be listed in the appropriate section and need only be recorded in the eCRF for cycle one unless they are changed. Additional routine medications should be recorded on the CRF for the cycle of chemotherapy closest to the commencement of the new medication. Commencement and cessation dates, dosage and route of administration are required.

12.5 Non-Study Treatments

Patients may receive all concomitant therapy deemed to provide adequate supportive care at the investigator's discretion. All such medications or other treatments taken by the patient during the study (including those initiated prior to the start of the study) will be recorded in the patient's clinical notes. However, the use of experimental drugs is not permitted within 28 days of completion of the active part of the study.

12.6 Additional non study anti-cancer treatment

Details of any additional non study anti-cancer treatment from end of study treatment until the

end of study will be collected, i.e. regimen and modality of treatment, including start and stop date.

12.7 Use of contraceptives during study treatment

Female patients with childbearing potential and sexually active men with a premenopausal partner should use an adequate method of contraception during the study treatment and for at least 6 months after stopping study treatment.

13 FOLLOW-UP STUDY ASSESSMENTS

All consenting patients will be assessed at screening, baseline and at appropriate intervals after the commencement of protocol treatment in order to assess their disease status according to the following schedule:

13.1 Study Calendar

Scheduled event	**Screening Assessments**	**Baseline Assessments**	**SIRT treatment**	**Chemo treatment**	**Follow-up Assessments**	
	≤ 28 days prior to randomisation	within 7 days prior to start of chemo in arm A and work up in Arm B	SIRT (Arm B only)	Arm A and Arm B	Every 12 weeks (+/- 2 weeks) from start of treatment until progression in the liver – regardless patient is on chemo	FU visit after progression in the liver every 12 weeks (+/- 2 weeks)
Informed Consent	X					
Demographics	X					
Medical history and concurrent illness	X					
Concomitant medication [a]	From informed consent until 28 days post last dose of protocol chemotherapy at each patient visit					
Physical examination, height, weight, blood pressure, temperature [b]	X	X	X[f]	X[m]		
ECOG performance status	X	X	X[f]	X[m]	X	
Haematology, biochemistry, creatinine clearance	X[i]	X	X[f, j]	X[g, j]	X[j,n]	
Tumour markers CEA, CA 19-9, CA125, and AFP		X		X[h]	X[n]	X
EQ-5D Quality of Life Questionnaire	X				X[k]	X[l]
Pregnancy test for females	X					
CT-scan chest, abdomen, pelvis (until progression) and RECIST 1.1 & refined RECIST assessments [c]	X	repeated if > 28 days prior start of chemo or SIRT implantation			X	
Adverse events [d]	From informed consent until 28 days post last dose of protocol chemotherapy at each patient visit (Unless new study treatment related AEs/SAEs or new ADE/SADE)					
Randomisation (IWRS)		X				
Work up-Hepatic angiogram/ ^{99m}Tc-MAA (must be 3-8 days prior to SIRT) (arm B only)			X			
SIRT (Arm B only) [e]			X			
Post SIRT Bremsstrahlung scan (SPECT/CT), Y-90 PET/CT or y 90 PET/MRI (Arm B only)			X			
CIS-GEM treatment				X		
Assessment for resection/ablation					X	X
Additional non-study anti-cancer treatment					X	X
Ongoing review of survival						X

a. Concomitant medications administered at the time of onset of any new treatment related SAE or any SADE which occurred after 28 days post last protocol chemotherapy, must be reported on the SAE Report Form to the study sponsor.
b. At baseline a full physical examination is required. The post-baseline physical examinations may include only the body systems clinically indicated by symptom or anticipated treatment side effect. Height is only required to be collected during Screening Assessments.
c. In case MRI is the standard radiological assessment for ICC, MRI is permitted on the condition that the same method of assessment and the same technique is used for the entire course of the study for a particular patient. However, CT scans (chest-abdomen-pelvis) are mandatory in any case for extra-hepatic assessments. 12 weekly CT scans must be performed until progression in liver detected by both RECIST 1.1 and refined RECIST.
d. All treatment related AEs and all SAEs should be followed until resolution or death or end of study. Any new SAE/AEs related to treatment or any new ADE/SADE occurring after 28 days post last dose of study chemotherapy will be recorded as well until resolution or death, or the end of study.
e. Suitability to receive SIRT to be re-confirmed prior to implantation
f. To be performed within 3 days before SIRT implantation
g. Within 3 days prior to chemotherapy treatment. In the event of an extended delay due to total bilirubin > 30 µmol/L (1.75 mg/dL) greater than 3 weeks, total bilirubin should be assessed at least once every TWO weeks until recovery, or disease progression, patient choice or intolerance or permanent discontinuation at investigator's discretion. Prophylactic treatment with steroids, ursodeoxycholic acid and ciprofloxacin should be considered if there is 2 weeks or greater delay due to total bilirubin > 30 µmol/L (1.75 mg/dL). Refer to Section 7.1.3 Hepatic Complications for further consideration
h. Before every chemotherapy cycle (+/- 1 week); if chemo cycle is delayed due to abnormal lab tests, tumour markers do not need to be repeated.
i. Screening haematology/biochemistry assessments to be performed within 14 days prior to randomisation.
j. Same assessments to be performed as baseline.
k. To be performed every 12 weeks after start of treatment (+/- 2 weeks) until progression in the liver.
l. To be performed once, 12 weeks (+/- 2 weeks window) after the first CT scan with detection of liver progression.
m. Within 3 days prior to chemotherapy treatment.
n. Laboratory assessments that are required to be performed during the pre-progression 12 weekly follow up visit do not need to be repeated if already performed while the patient is on chemotherapy. The pre-progression 12 weekly laboratory assessment must be within +/- 2 weeks from the date of follow up.

14 RESPONSE ASSESSMENT

The following criteria will be used to assess response to treatment and for the evaluation of study end points.

14.1 Survival at 18 months (Primary Endpoint)

Survival at 18 months is defined as the proportion of patients alive 18 months from the date of randomisation.

14.2 Liver resection / ablation rate (Secondary Endpoint)

A proportion of patients radiologically down-staged by protocol therapy (Arm A or B) will proceed to partial hepatic resection, ablation or other forms of surgical management during or after protocol therapy. The date and type and details of such procedures will be recorded, as well as the duration of in-patient admission, surgical complications, drug therapy required during and after in-patient admission, surgical notes from the procedure (Brisbane Terminology (4)), post-operative imaging and the histopathological results (presence of viable tumour/fibrosis, nearest resection margin, classification of resection as R0, R1 or R2).

14.3 Safety and tolerability (Secondary Endpoint)

Safety and tolerability will be assessed using the NCI Common Terminology Criteria for Adverse Events version 4.0 (see APPENDIX 4). Patients are to be followed for safety and tolerability from the time of providing informed consent until 28 days after last dose of protocol chemotherapy or until resolution of treatments related adverse events. Definitions and the requirements for reporting adverse events (AE) and serious adverse events (SAE) are detailed in Section 17 Adverse Events.

14.3.1 Independent Data Safety Monitoring Committee (IDSMC)

The safety profile of Treatment Arm B will be assessed by the IDSMC after 10, 20 and 30 patients have been treated with SIRT and have had a minimum of 8 weeks safety evaluation post SIRT treatment. The results will be compared to patients treated in the control group for increased risk related to either the SIRT therapy or the time interval between SIRT and standard of care chemotherapy. The IDSMC will notify the Sponsor of recommendations to revise the treatment regimen or discontinue enrolment after which, the Investigators will be notified.

After the review of 30 SIRT patients is complete, the IDSMC will determine the subsequent IDSMC meeting intervals based on the SIRT patient safety profile established; additionally, the IDSMC will receive SAE listings during the scheduled meeting interims and may convene ad hoc meetings for safety review if a single event or aggregate events raise concern by any of the IDSMC members.

14.4 Tumour Response Rate (Secondary Endpoint)

Response will be calculated using response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) (Eisenhauer 2009 (15)). There will also be a lesion based assessment if at all applicable and refined RECIST (Reig (54)) (See APPENDIX 7).

14.4.1 RECIST 1.1 Guidelines

All baseline evaluations should be performed as closely as possible to the beginning of treatment start and never more than 28 days before beginning of the treatment.

All measurable lesions (lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional techniques and ≥ 10 mm with spiral CT scan) up to a maximum of 2 lesions per organ with a maximum of 5 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis.

A sum of the diameter (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameter which will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to < 15 mm short axis), should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.4.1.1 RECIST: Response Criteria

Complete Response (CR): Disappearance of all target lesions associated with the disappearance of all non-target lesions and normalisation of tumour marker levels. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Partial Response (PR): At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum of diameters of target lesions, or a CR associated with persistence of non-target lesion(s) and/or maintenance of tumour marker levels above normal limits.

Progressive Disease (PD): At least 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum recorded since on study (this may include baseline sum) or the appearance of new lesions. The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD with or without persistence of non-target lesion(s) and or maintenance of tumour marker levels above normal limits.

Note: Elevated serum tumour markers on their own are not sufficient evidence of progression and only imaging examinations can assess and confirm disease progression.

14.4.1.2 Refined RECIST: Response Criteria

The conventional RECIST was amended for the SHARP trial in order to prevent over-staging and non-accurate assessment of progression in the following instances:

- Detection of lymph nodes in the hepatic hilum, as this may be seen in cirrhotic patients and does not reflect cancer involvement.
- Detection of ascites or pleural fluid at baseline or during follow-up, as this may reflect hydrosaline retention because of impaired liver function and not malignant spread.

- Detection of macro regenerative nodules. This may be observed in cirrhotic livers and does not reflect progression, even if the nodules are larger than 1 cm.

To prevent the above, the amendments state:

- Lymph nodes are classified as malignant if their size exceeds 20 mm or if arterial vascularization is present.
- For ascites or pleural effusion, in order to declare malignant, it should be proven by positive cytology.
- New lesions outside the liver follow the same definitions as for RECIST1.1. New intrahepatic lesions have specific consideration:
- ≤ 10 mm should be considered as equivocal and not progression.
- > 10 mm should be considered malignant if arterial hypervascularisation is present.

Note: As patients in both treatment arms may be considered 'resectable' after treatment, it is possible that undiagnosed disease may be found at the time of attempted resection of the liver disease. For the purpose of defining Progressive Disease, any disease that is found solely as a result of the patient undergoing laparotomy for resection will not be considered as Progressive Disease. i.e. Only radiological assessments can define and confirm progression

14.5 Progression-Free Survival (PFS) and Liver-specific PFS

Progression-free survival (PFS) is defined as the time interval between randomisation and the date of tumour progression.

Liver-specific PFS (LPFS) is defined as the time interval between randomisation and the date of tumour progression in the liver.

Tumour progression is determined from serial CT scans.

Recommended acquisition guidelines for CT scanning are provided in APPENDIX 6.

Diagnosis of tumour progression should be made by using RECIST Criteria (version 1.1) and refined RECIST (see APPENDIX 7).

The documented date of progression will be the date of confirmation of the progression strictly by RECIST 1.1 only. At the time of progression, the investigator should clearly indicate the site of tumour progression (intra-hepatic or extra-hepatic or indicate both simultaneously).

14.6 Quality of Life

Quality of life (QoL) will be measured by using the EQ-5D questionnaire. The EQ-5D will be completed at screening, then at follow up assessments every 12 weeks after start of treatment until progression in the liver (according to both RECIST 1.1 and refined RECIST), and then completed once more 12 weeks after the first CT scan with detection of liver progression according to both RECIST 1.1 and refined RECIST.

15 STATISTICAL CONSIDERATIONS & METHODOLOGY

15.1 Study Hypothesis

18-month survival proportion in SIRT arm (Arm B) is no better than in the chemo only arm (Arm A) by at most 15% versus 18-month survival proportion in SIRT arm (Arm B) is better than in the chemo only arm (Arm A) by at least 15%.

15.2 Study Design and Sample Size

This randomised study is a preliminary efficacy and safety assessment of standard regimen of CIS-GEM versus SIRT preceding the standard regimen of CIS-GEM. In this single stage design, the standard 18-month overall survival proportion in the CIS-GEM arm is assumed to be 55% (under the null hypothesis). The SIRT preceding CIS-GEM regimen is considered worthy of further research if the null hypothesis can be rejected in favour of the alternative hypothesis where the proportion surviving at 18 months is assumed to be at least 70%. Therefore, if the proportion surviving after 18 months was less than 55%, the assumption is made that there would be no interest in pursuing the SIRT preceding standard CIS-GEM regimen. The assumption is also made for the probabilities of making the wrong conclusions. First, the probability of concluding that the survival proportion is at least 70% when in fact it is no more than 55% (i.e. false positive) should be low, say 5% or less. Second, the probability of concluding that the true survival proportion is no more than 55% when in fact it is at least 70% (i.e. false negative) should also be low, say 20% or less.

Consequently, based on exact (binomial) statistic with actual error rates (Khan 2012 (37)), the decision rule provides that a sample size of 80 patients and a minimum of 50 patients surviving at 18 months in the SIRT followed by chemotherapy arm are required to warrant further investigation of SIRT preceding CIS-GEM, such that statistical significance is achieved. This sample size corresponds to an 88% power to detect a significant difference of at least 15% in survival proportion at 18 months as per the study assumption. If the number of patients surviving at 18 months is at most 50, then this number is the maximum number of survivors for which statistical significance is not achieved.

In order to study the true effect, the population of interest is defined as those patients having completed at least one cycle of chemotherapy in the control arm and those having completed SIRT followed by at least 1 cycle of chemotherapy in the experimental arm.

The primary analysis will be based on only the SIRT arm. However, in order to have a comparative arm for secondary endpoint analyses, the sample size has been calculated based on a randomization between the SIRT arm and a chemotherapy arm. This resulted in a total sample size of 160 patients in the randomized study as per 1:1 randomisation.

Assuming a noncompliance rate of at most 10% patients who would not complete at least one cycle of chemo in Arm A and those who would not complete SIRT treatment followed by at least one cycle of chemo in Arm B. The number of patients to be recruited will potentially increase from 160 patients to 180 patients.

Stratification and Randomisation:
Randomising patients equally between the two (2) arms, the Fleming's single stage design with exact binomial test (which minimises the total number of patients needed) will be applied to the data from the study.

Prior to randomisation, patients will be stratified according to (a) the presence or absence of extra-hepatic metastases and (b) the presence or absence of cirrhosis, (c) intention to treat by whole liver versus non-whole liver Y-90 treatment; (d) ECOG 0 vs. ECOG 1 and (e) prior adjuvant therapy vs no prior adjuvant therapy. Treatment will be allocated randomly and balanced for the above strata using a computer generated allocation.

Cirrhosis:

Absence of cirrhosis should be registered when

- The non-tumoural part of the liver is regular and without nodularity on imaging *and*
- There is no evidence of portal hypertension with no clinically significant ascites, oesophageal varices or splenomegaly with dilated portal vein in the absence of portal vein thrombosis.

Detection of any of the above findings, and/or a positive biopsy diagnosis (F4=cirrhosis according to The METAVIR scoring system) and/or an increased elastography values, establishes the existence of cirrhosis.

15.3 Statistical Analyses

Efficacy Analyses

The primary endpoint will be analysed in those patients that received at least 1 cycle of chemotherapy (arm A) and in those patients who received SIRT and at least 1 cycle of chemotherapy (Arm B). Secondary endpoints will be analysed according to the intention-to-treat principle with patients being analysed in the treatment group to which they were randomised irrespective of what treatment they end up receiving, as well as per efficacy evaluable population who received at least 1 cycle of chemotherapy or SIRT followed by at least 1 cycle of chemotherapy respectively.

Primary efficacy measure for the study is survival at 18 months from time of randomisation with no formal comparison between treatment arms. Secondary efficacy analyses will compare efficacy between both treatment groups using the log rank test (Mantel-Haenszel version), and time to event secondary endpoints will be compared using the logrank test. The secondary efficacy measure liver specific PFS for all ITT patients will be analysed. In addition, separate analyses will be conducted for difference in 18 month survival by subgroups of stratification factors. Note that, actual proportion in the trial however will be based on the Kaplan-Meier estimate which takes into account both lost to follow-up and censored data (i.e. at the end of the study, not all patients would necessarily be followed up for 18 months). A 55% survival rate at 18 months corresponds to a median survival of 21 months and a 70% 18 month rate corresponds to a 34 month median survival.

For purposes of this study, progression free survival (PFS) is defined as the time, in month, from randomisation in the study until such time as progressive disease at any site (RECIST response criteria) is confirmed or upon patient death if disease progression has not been evident at that time.

Liver-specific time to progression or PFS in the liver is defined, in months, as the time interval from randomisation until progression in the liver (RECIST response criteria).

Exploratory analyses will be performed adjusting for prognostic factors in a multivariate analysis framework. This includes the impact of explanatory variables on various outcomes measures of interest. Proportional hazards regression will be used to model time to event outcomes, and multiple linear regression will be used to model continuous outcomes with appropriate transformations if necessary. Logistic regression will be used to model binary response, and proportional odds models will be used for categorical outcomes (such as toxicity grades).

Pre-planned sub-group and post-hoc analyses
Primary and secondary endpoints will be explored based on subgroup analyses by stratification factors. Where p-values are reported they will be corrected for multiple comparisons using Bonferroni method.

AFP as a biomarker will be analysed by treatment groups and in a responder exploratory analysis. Analysis of responders versus non-responders by complete tumour treatment or partial tumour treatment will be performed.

Lobar versus bi-lobar disease will be analysed by treatment groups.

Handling Missing Data
All analyses and descriptive summaries will be based on the captured data. Unless otherwise specified, missing data will not be imputed or 'carried forward'. Details of data handling assumptions, including missing and censored data, will be described in the statistical analysis plan.

Protocol Deviations and Violations
Patient data will be monitored to identify protocol deviations, and these deviations will be discussed with investigators and preventive actions will be undertaken.

During the study, the patient data will be interrogated to identify protocol deviations, and any inconsistency will be queried to the sites for confirmation or correction.

Prior to study closure, observed protocol deviations will be reviewed by a medical reviewer(s) and statistician to determine whether these deviations are considered as major.

Patients who are ineligible due to factors unrelated to treatment allocation and outcome whose reason for ineligibility were due to pre-randomisation factors may be excluded from the intention to treat population.

16 PROTOCOL ADHERENCE / PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Adherence

Strict adherence to all specifications laid down in this protocol is required for all aspects of the study conduct; the investigator may not modify or alter the procedures described in this protocol. If protocol modifications are necessary, all alterations that are not solely of an administrative nature require a formal protocol amendment (see section 18.3).

If an investigator has deviated from the protocol in order to eliminate an immediate hazard to patients or for other inevitable medical reasons, the investigator shall document all such deviations, including the reasons thereof, and submit the document to the sponsor and the EC as applicable and according to local regulations.

Lack of adherence to the CIP at an investigational site risks compromising the utility of the collected data and power of the study. Ongoing, unauthorised deviation from the Clinical Investigation Plan will be a matter addressed by the study monitor to the Principal Investigator at the site and may result in plans to correct systemic problems leading to lack of compliance or ultimately, closing the site to recruitment or ongoing participation in the study.

16.2 Premature Termination of the Study

Notwithstanding the potential benefit of treatment, if excess toxicity is observed, then this would provide grounds for treatment modification, dose reduction or stopping the study earlier than planned.

At the discretion of the Sponsor and/or the Co-Principal Investigators, the entire study may be discontinued for medical, feasibility or futility reasons. In case of premature termination, the investigators, IRB/IECs and regulatory authorities will be informed by the study Sponsor.

If the study terminates prematurely, the treating physician of the patient's choice will then provide patient with best available treatment options according to standard of care and in consultation with the patient.

17 ADVERSE EVENTS

17.1 Definitions

17.1.1 Adverse Event

An adverse event (AE) is defined by ISO 14155 as any untoward medical occurrence experienced by a patient and which does not necessarily have a causal relationship with any component of the study treatment.

An AE can be any sign, abnormal laboratory value, symptom or diagnosis/disease that is unfavourable or unintended, that is new, or if pre-existing, worsens in a patient, and that may or may not be related to the study treatment.

AEs will be recorded from the date of signature of the informed consent form up to 28 days after the last dose of chemotherapy was given. Any new AE related to treatment (protocol chemotherapy or SIRT) occurring after this time period will be recorded as well. All chemotherapy and/or SIRT -related Adverse Events will be followed up until resolution, death or the end of the study.

For this study, adverse events that are clearly related to progression of intrahepatic cholangiocarcinoma will not be recorded as Adverse Events and will be considered as lack of efficacy.

17.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined by ISO 14155 as an adverse event that:

a) Lead to a death, or
b) Lead to a serious deterioration in the health of the patient that
    1) Resulted in a life-threatening illness or injury,
    2) Resulted in a permanent impairment of a body structure or a body function,
    3) Required in-patient hospitalisation or prolongation of existing hospitalisation,
    4) Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
c) Lead to foetal distress, foetal death or a congenital abnormality or birth defect.

All SAEs will be followed until resolution or the end of the study.

17.1.3 Adverse Device Effect (ADE) and Serious Adverse Device Effect (SADE)

An adverse device effect is an adverse event related to the use of an investigational medical device.
A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

All SADEs will be followed until resolution, death or the end of the study.

17.2 Reporting

In order to adhere to all applicable laws and regulations for safety reporting, the Investigator must formally notify the study Sponsor, using the supplied SAE form, of any SAE or SADE within 24 hours of becoming aware to:

Email: [redacted] or [redacted]

The causality of all (S)AE/(S)ADEs with study treatments must be assessed by the investigator. Safety information shall be reported to IRBs/IECs and/or regulatory authorities and/or Competent Authorities as per local law and requirements.

For specific safety reporting procedures in the Netherlands, please refer to APPENDIX 11.

17.3 Pregnancy during the Study

Protocol therapy must be discontinued immediately in the event of pregnancy in a female patient enrolled in this study. The Investigator must report the pregnancy to the study Sponsor within 24 hours of becoming aware of the pregnancy. The study Sponsor will monitor the outcome of the pregnancy and the health status of the infant until 1 year of age. The same pregnancy outcome and health status monitoring will also be performed in the event that a female partner of a male patient on study becomes pregnant while the male patient is receiving protocol therapy.

18 ETHICAL CONSIDERATIONS

The study will be performed in accordance with ISO 14155 which includes a requirement to operate in accordance with the World Medical Association Declaration of Helsinki (see APPENDIX 9). The study Sponsor and the Investigator must comply with all instructions, regulations and agreements in this study protocol, using applicable GCP guidelines as specified in ISO 14155, and must also conduct the study according to local regulations.

All patients being treated within this study are covered by a clinical study insurance that the sponsor has set out for this research study. The sponsor has insurance to cover research-related injuries.

All participating institutions must obtain approval from their responsible EC/IRB. A copy of this approval must be forwarded to the study Sponsor before the study may open for patient recruitment.

18.1 Informed Consent

Patients will be provided with a full explanation, in lay terms, of the aims of the study and the potential benefits as well as the possible side effects and risks involved. It will be explained that they may refuse to take part in, or withdraw from the study without prejudice to their future care and treatment.

Written informed consent must be obtained from all patients prior to study entry. The informed consent form must be filed in the patient record. Consent to participate in this study will be obtained from the patient both verbally and in writing. In the case where the patient is not fluent in the local national language, the investigator should ensure that the study information is presented to the subject in their own language in accordance with local ethical and regulatory guidelines. Patients will be issued with a copy of the information provided and their consent to participate in the study. All informed consent forms used in this study must be approved by the relevant EC/IRB.

At any point of the study, the patient may decide to withdraw consent from the study without any particular reason. In this case, the patient will be provided by the treating physician with the best standard of care treatment options available. From the time of withdrawal of consent, no further data will be collected from the patient.

18.2 Confidentiality

All patient data collected as a part of this study will be treated according to ISO 14155 and local regulation. All data generated from this study will remain confidential and no published report will contain any reference to patient names. The patient identification required by the study Sponsor is used to ensure accurate storage and follow-up of individual patients. This information will be stored securely by the study Sponsor and will only be available to data management, audit or monitoring personnel directly involved with the study.

18.3 Changes to the Final Study Plan

All study amendments must be submitted to the relevant EC/IRB. Study modifications that impact patient safety, the scope of the study, or affect the scientific quality of the study must be approved by EC/IRB and submitted to the appropriate regulatory authorities and/or Competent Authorities in accordance with local regulations before implementation of such modifications to the conduct

of the study. This applies also to any additional requirements imposed by the EC/IRB or regulatory authority. However, the study Sponsor may, at any time, amend this study plan to eliminate an apparent immediate hazard to a patient. In this case, the necessary regulatory authorities and/or Competent Authorities will be notified. In the event of a study plan modification, the informed consent form may require similar modifications.

19 PUBLICATION POLICY

Sirtex, the study Sponsor is committed to the responsible publishing of data from its clinical research program. Sirtex aims to promote the timely presentation of results at an appropriate academic meeting and/or the publication of results in an appropriate scientific journal.

Sirtex will assess authorship eligibility according to Good Publication Practice for company sponsored research. (GPP3 2015 (5)).

In accordance with these recommendations, authorship credit will be based on: 1) substantial contribution to concept and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the manuscript or revising it critically for important intellectual content; and 3) final approval of the version of the manuscript to be published. All three items above should be met to qualify for authorship.

The lead author for any publication must be the Principal Investigator or a major contributor to the study and must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

These criteria apply both to the Investigators who have participated on the study and any Sirtex employee who has contributed to the study.

20 ADMINISTRATIVE PROCEDURES

20.1 Site Initiation Visit

The Investigator must not enrol any patients prior to completion of a site initiation visit conducted by the study Sponsor or its designee. This initiation visit will include a detailed review of the study protocol and procedures with study-associated site personnel.

20.2 Investigator File

The Investigator will be provided with an Investigator File. This file should be used for filing all study-related documents. The Investigator will be responsible for keeping the Investigator File updated and for ensuring that all required documents are filed during and after the study. The Investigator File will be inspected during monitoring visits and will remain with the Investigator for 15 years after closure of the study.

20.3 Monitoring of the Study

During the conduct of the study, the Sponsor's clinical research associate (CRA) or designee will visit the site at regular intervals by prior arrangement. The monitoring visits must be conducted according to ISO 14155 and GCP guidelines to ensure adherence to the study protocol, quality of data, compliance with regulatory requirements, and continued adequacy of the site and its facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The CRA performs monitoring according to the monitoring plan and will be given direct access to relevant source documents (including medical records) to enable source data verification.

20.4 Quality Assurance

During and/or after completion of the study, quality assurance officers named by the study Sponsor or regulatory authorities may wish to perform on-site audits and inspections respectively. The Investigator and site personnel will be expected to cooperate with any audit/inspection and to provide assistance and documentation (including source data) as requested. The Investigator and site personnel will immediately inform the study Sponsor of any inspection to be performed by a regulatory authority.

20.5 Documentation and Data Management

Data management will be performed by [redacted]. Study data will be captured in an electronic Case Report Form (eCRF) complying with national and international data protection guidelines. The web-based eCRF is a linked to a database system [redacted] all systems are validated.

Data will be accessed and processed by a restricted number of users with role-based access restrictions respecting confidentiality.

20.6 Investigational Device Accountability

Access to the investigational devices is controlled and the investigational devices will be used only for clinical investigation and according to the clinical investigation plan.

The investigator will keep records documenting the receipt, use and disposal of the investigational devices; these records include dose orders and lot number of doses should be recorded and maintained at the site to be verified by the study monitors.

20.7 Study Funding

The study Sponsor (Sirtex) will financially support the work of the Investigator related to the conduct of the study. All financial details are provided in the separate Clinical Study Agreement (contract) between the Investigator and/or the Institution and Sirtex Technology Pty Ltd.

20.8 Completion of the Study

The EC/IRB must be notified of completion or termination of this study in a timely manner. The Investigator must provide a final clinical study report to the EC/IRB and maintain in the Investigator File an accurate and complete record of all submissions made to the EC/IRB.

The Competent Authorities and/or regulatory authorities have to be notified of completion or termination of the study according to local law. A final clinical study report will also be provided to the Competent Authorities and/or regulatory authorities.

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22 STANDARD OF CARE GUIDELINES

COUNTRY/ REGION	REFERENCE
International and EU	International Liver Cancer Association (ILCA) & European Association of the study of the Liver (EASL) guidelines: Bridgewater J, Galle PR, Khan SA et al: Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology* 2014; 60: 1268-1289
Europe	Biliary Cancer: ESMO Clinical Practice Guidelines J. W. Valle, I. Borbath, S. A. Khan, F. Huguet, T. Gruenberger and D. Arnold Biliary Cancer:. Ann Oncol (2016) 27 (suppl 5): v28-v37http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Biliary-Cancer
Netherlands	Oncoline http://www.oncoline.nl/galweg-en-galblaascarcinoom
UK	Khan SA, Davidson BR, Goldin RD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut*. 2012;61:1657-1669
Italy	Associazione Italiana di Oncologia Medica (AIOM). *Linee Guida Tumori Delle Vie Biliari*. 2015. http://www.aiom.it/professionisti/documenti-scientifici/linee-guida/1,413,1
France	Société Nationale Française de Gastroentérologie. *8. Cancer des voies biliaires (Dernière mise à jour le 24/01/2014)*. 2014. http://www.snfge.org/content/8-cancer-des-voies-biliaires.
Australia	eviQ Cancer Treatments online https://www.eviq.org.au/Protocol/tabid/66/categoryid/372/id/1200/Biliary+and+Gallbladder+Metastatic+cISplatin+and+Gemcitabine.aspx
USA	NCCN Guidelines Version 1.2016 Hepatobiliary Cancers

APPENDIX 1 Technique for Administration of SIR-Spheres Y-90 resin microspheres

SIR-Spheres Y-90 resin microspheres are administered by injection through a trans-femoral catheter into the hepatic artery. As there are frequent arterial anomalies in the blood supply to the liver, the radiologist must be familiar with those anomalies. Only radiologists who have received formal training and have been approved by Sirtex may participate in this study and administer SIRT. All areas of tumour within the liver are to be targeted with SIR-Spheres Y-90 resin microspheres and this usually involves treating both lobes of the liver. However, it is essential that the SIR-Spheres Y-90 resin microspheres are not delivered to other organs such as the duodenum, stomach, pancreas etc.

If the tumour is limited to only one lobe, the radiologist can insert the microcatheter selectively into the lobar/segmental artery supplying only that lobe. The SIR-Spheres Y-90 resin microspheres will then be delivered only to the lobe containing the tumour with sparing of the other normal lobe. This is an excellent way of delivering high doses of radiation to the tumour without any chance of damaging the normal liver.

It is most important to inject the SIR-Spheres Y-90 resin microspheres slowly into the hepatic artery. In order to achieve a slow delivery rate to maintain SIR-Spheres microspheres in suspension, the flow from the delivery syringe may be given in pulses of 0.25ml to 0.5ml, separated by a pause. The specialist should periodically stop the delivery of SIR-Spheres microspheres and inject IV contrast through flushing tube ‘B’ and perform fluoroscopy. This ensures that the catheter remains in the correct position at all times and allows the specialist to detect imminent stasis or reflux back down the hepatic artery. The speed of the injection must be adapted to the flow of contrast seen while performing the fluoroscopy. If they are injected too quickly they may reflux back down the hepatic artery and lodge in the pancreas, stomach and other organs.

The following principles dictate where the microcatheter is placed when delivering SIRT:

- treat only those parts of the liver that contain tumour e.g. lobar treatment if tumour present only in one lobe, rather than whole liver SIRT
- if possible then try and not treat some normal liver parenchyma from SIRT. Even a small amount of normal liver that remains untreated provides extra protection against the possibility of liver damage e.g. super-selective SIRT is preferred if possible
- use of automated pump injection to identify not only the right and left hepatic arteries, but also the gastric arteries and any other accessory vessels which may need to be embolised in order to ensure safe administration of SIR-Spheres microspheres
- review with extreme vigilance the pre-treatment angiogram to look for anatomical abnormalities
- never allow SIR-Spheres Y-90 resin microspheres to enter any vessel supplying the gut i.e. embolise non-target arteries supplying the gut which cannot be avoided by distal placement of catheter during administration of SIR-Spheres microspheres
- always inject SIR-Spheres Y-90 resin microspheres at the recommended rates with repeated fluoroscopy to check the position of the catheter and to look for any slowing of blood flow and possible reflux blood back down the hepatic artery.

Dealing with Anatomical Anomalies

Note: Inadvertent injection of SIR-Spheres Y-90 resin microspheres into small arteries passing from major arteries vessels in the hilum of the liver to the stomach and duodenum is the commonest cause of serious adverse events. These small aberrant vessels, not described in the standard anatomy texts may be the cause of these SAEs if the radiologists do not recognise these small vessels and allow SIR-Spheres Y-90 resin microspheres to flow to the gut.

Radiologists are referred to the review article of Liu et al, 2005 (43) for an additional comprehensive description of how to administer SIRT.

If there is a dual blood supply to the liver, then the radiologist will have to catheterise each artery separately to inject the SIR-Spheres Y-90 resin microspheres if there is tumour in both lobes. If there is only tumour in one lobe, then the radiologist only needs to inject the SIR-Spheres Y-90 resin microspheres into that side of the liver.

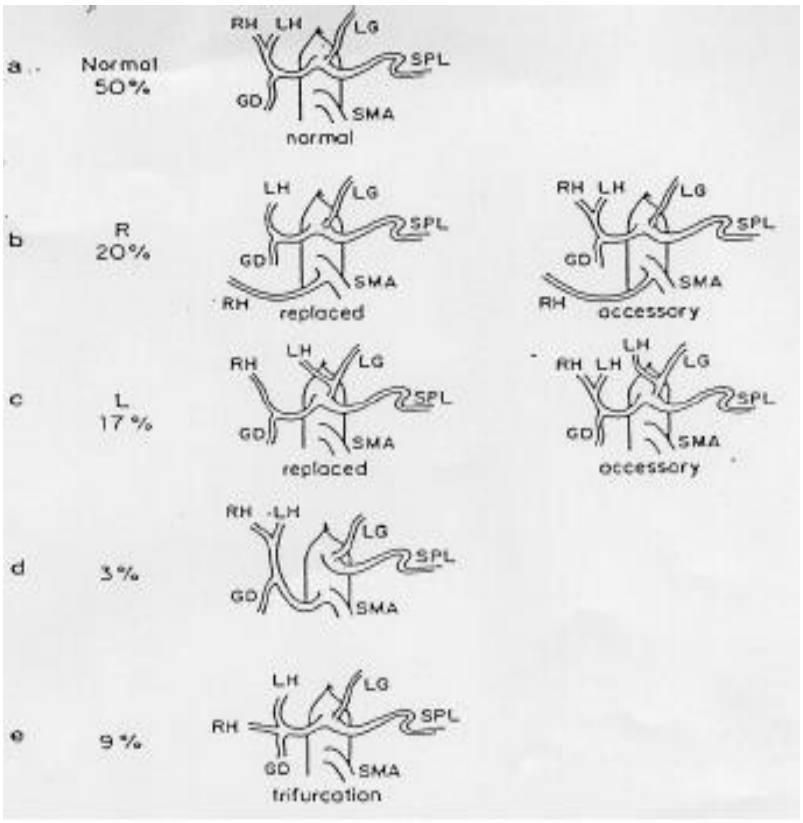
For instance, if all the tumour was in the right lobe of the liver and there was an accessory right hepatic artery arising from the superior mesenteric artery, then injecting all the SIR-Spheres Y-90 resin microspheres into this accessory right hepatic artery would deliver all the radiation to tumour in the right lobe where it is wanted.

If there are separate right and left arteries and there tumour in both right and left lobes, then it is necessary to inject some of the SIR-Spheres Y-90 resin microspheres separately into both arteries in order to deliver radiation to the tumour in both lobes.

The following anomalies in vascular supply must be noted:

1. In 20% of patients there will be a replaced right hepatic artery arising from the superior mesenteric artery (see diagram b below). This replaced right hepatic artery will supply most of the right lobe of liver and is easily demonstrated on an angiogram. If present, it must be accessed to deliver SIR-Spheres Y-90 resin microspheres to the right lobe of the liver as well as the main hepatic artery; otherwise the radiation will not be delivered to the tumour in the right lobe of the liver.
2. In 17% of patients an accessory left hepatic artery will arise from the left gastric artery (see diagram c below). This accessory left artery is usually difficult to demonstrate on an angiogram, and is often not recognised at the time of angiography. It is usually possible to get a co-axial catheter into this artery if it is necessary to deliver SIR-Spheres Y-90 resin microspheres to the left lobe of the liver. If there is no tumour in the left lobe then it can be ignored. An alternative, for some cases, could be to occlude proximally (coiling) any aberrant/accessory vessel by allowing "vascular redistribution" (Bilbao et al (6)) of the arterial intrahepatic flow allowing to perform, both the ^{99m}Tc-MAA evaluation as well as the Y-90 treatment, by the contralateral artery.
3. In a minority of patients the gastro-duodenal artery arises from the main hepatic artery distal to the origin of the left hepatic artery. It is imperative that the SIR-Spheres Y-90 resin microspheres not be delivered into the gastro-duodenal artery, as this will result in the SIR-Spheres Y-90 resin microspheres lodging in the duodenum and pancreas with severe side effects. In this situation the gastro-duodenal artery should be embolised to occlude it before administering the SIR-Spheres Y-90 resin microspheres into the hepatic artery. The systematic occlusion of the gastroduodenal and the right gastric arteries should not be recommended, only when technically needed.

MAJOR VARIATIONS IN ARTERIAL BLOOD SUPPLY TO THE LIVER



1. (50%) In the normal setting the gastro-duodenal (GD) artery comes off the common hepatic artery proximal to the bifurcation into the right hepatic (RH) and left hepatic (LH) arteries. The left gastric (LG) and splenic (SPL) arteries come off the coeliac axis separately.
2. (20%) When the right hepatic artery is replaced the whole blood supply to the right lobe comes off the superior mesenteric artery (SMA). In the case of an accessory right hepatic artery, the vasculature off the coeliac axis is normal but there is an additional right hepatic artery off the superior mesenteric artery.
3. (17%) When the left hepatic (LH) artery is replaced, the whole blood supply to the left lobe comes off the left gastric (LG) artery. In the case of an accessory left hepatic artery the vasculature of the common hepatic artery is normal but there is an additional left hepatic artery off the left gastric artery.
4. (3%) In this situation the entire common hepatic artery arises from the superior mesenteric artery
5. (9%) A trituration occurs when the bifurcation of the left hepatic and right hepatic

APPENDIX 2 **Nuclear Medicine Break-Through Scan**

Purpose:	To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs.
Agent:	Technetium-99 labelled MAA (Macro-aggregated Albumin)
Dose:	150MBq
Equipment:	Any large FOV gamma camera
Administration:	The patient needs to have a trans-femoral catheter placed in the hepatic artery. The Technetium 99 labelled MAA is injected through the catheter into the hepatic artery by a qualified physician.
Imaging:	The patient is positioned supine under the gamma camera and the images recorded.
Analogue:	Anterior and posterior images of planar abdomen and thorax. Measure 700K – 1000K counts for abdomen and equivalent time for thorax. Right lateral abdomen - same time acquisition as for Anterior.
Digital:	4 frames; 300”/ frame. 64 x 64 matrix Word mode. Image anterior and posterior abdomen. Image anterior and posterior thorax.
Analysis:	Draw ROI around whole of liver and whole of lung fields. Calculate G mean for liver region and lung region. Calculate Lung/liver ratio.

APPENDIX 3 **Administered Dose Calculation**

The following document provides patient dosing information and is intended for the use of Interventional Radiologists and Nuclear Medicine specialists performing the Y-90 administration as well as Medical Oncologists, Gastroenterologists or Hepatologists designing the treatment plan.

If the tumour burden involves both lobes of the liver, either whole-liver or more selective administration of SIR-Spheres Y-90 resin microspheres are possible at the discretion of the team; the decision should be made by the multidisciplinary team on a case by case basis. However, a lobar approach is recommended if tumour burden is unequally distributed between both lobes, with the lobe containing most of the tumour load treated first. SIR-Spheres Y-90 resin microspheres should be administered in a single session (with one or more sites of injection) even when a whole-liver approach is used. Consecutive injections into the right and left hepatic artery should be preferred to a single injection from the common hepatic artery.

To determine the amount of SIR-Spheres Y-90 resin microspheres to be implanted the Interventional Radiologist and/or Nuclear Medicine specialist will need to know the following information about the patient to be treated:

1) Lung shunt (%)
2) Body Surface Area (BSA)
3) Tumour Volume (ml), target liver volume (ml), total liver volume (ml)

Tumour and total liver volumes are calculated from the baseline CT scan of the liver.

If the lung shunt is higher than 20% then the patient is ineligible for SIR-SpheresY-90 resin microspheres treatment.

Method of Activity Calculation

The method of activity calculation is based on the presentation of hepatic lesions. If a patient only has non-measurable tumours that will typically present in a too-numerous-to-count (TNC) “salt and pepper” pattern for which tumour volume cannot be measured the patient is not eligible for 90-Y resin microsphere treatment. For patients with measurable disease and additional small satellite tumours, activity calculation should be based on the measurable disease.

<u>Prescribed activity for whole liver treatment using the BSA Method</u>

For whole liver treatment, the BSA method is used to calculate the prescribed activity of SIR-Spheres Y-90 resin microspheres. The BSA method is dependent on the patient’s estimated BSA by Du Bois formula and percentage tumour involvement of the patient’s liver.

$$\text{Dose activity}[\text{GBq}] = (\text{BSA} - 0.2) + \frac{V_{\text{tumour}}}{V_{\text{TotalLiver}}}$$

V_{tumour} = volume of tumour
$V_{\text{TotaLiver}}$ = volume of total liver, including tumour

SIR-Spheres Y-90 resin microspheres are contraindicated in patients with lung shunt of >20%. For patients undergoing SIRT, lung radiation dose should not exceed 25 Gy and appropriate reductions in dose activity should be performed to ensure this safety limit is adhered to.

Selective catheterisation of individual branches is recommended for whole-liver treatment instead of a single injection via the common or proper hepatic artery. In this case, the activity to be injected into each artery should be proportional to the volume of the segments involved. For instance, if the treatment includes one administration each into the right and left hepatic arteries respectively, then the activity injected into each respective hepatic artery will be:

$$\text{Dose activity[GBq]} = \left((BSA - 0.2) + \frac{V_{tumour}}{V_{lobe}} \right) . \frac{V_{lobe}}{V_{TotalLiver}}$$

V_{tumour} = volume of tumour
V_{lobe} = volume of treated lobe, including tumour
$V_{TotaLiver}$ = volume of total liver, including tumour

Where the sum of activity administered in both right and left hepatic arteries will be the same as the BSA formula:

$$\text{Dose activity[GBq]} = (\text{BSA} - 0.2) + \frac{V_{tumour}}{V_{TotalLiver}}$$

V_{tumour} = volume of tumour
$V_{TotaLiver}$ = volume of total liver, including tumour

Prescribed activity for lobar treatment using BSA method

If disease presentation is confined to a single lobe, it is possible to minimise radiation exposure to the contralateral lobe with non-tumourous parenchyma and administer SIR-Spheres Y-90 resin microspheres to a single lobe only. For example, if all liver tumours are confined to the right lobe, then only the right lobe is treated to spare the left lobe from unnecessary radiation exposure. In this instance, an adjustment factor is introduced to the BSA calculation to reduce the activity which accounts for the untreated lobe. The activity to be injected into the treated lobe is given by the following formula:

$$\text{Dose activity[GBq]} = \left((BSA - 0.2) + \frac{V_{tumour}}{V_{lobe}} \right) . \frac{V_{lobe}}{V_{TotalLiver}}$$

V_{tumour} = volume of tumour
V_{lobe} = volume of treated lobe, including tumour
$V_{TotaLiver}$ = volume of total liver, including tumour

Attention should be paid to individual vascular anatomy. When the liver volume infused from the artery where the tip of the catheter is placed is smaller or larger than the corresponding lobe (for instance, in the case of aberrant infusion of the right lobe through an accessory right hepatic artery arising from the superior mesenteric artery, or infusion of segment IV from a branch of the right hepatic artery), the activity to be injected should match the corresponding target volume.

Prescribed activity when at least 2 liver segments are spared from treatment (Partition Model)

Besides the BSA model, the Partition Model may also be used to determine the patient-specific prescribed activities of SIR-Spheres Y-90 resin microspheres when at least 2 liver segments are spared from treatment (typically, in a lobar approach), provided the patient has discrete and measurable tumours that can be delimited on the CT/MRI scan.

The partition model is based on Medical Internal Radiation Dose (MIRD) principles. It relies on the fact that three discrete vascular compartments – the lungs, tumour and uninvolved liver parenchyma – can effectively be partitioned from each other. This model thus only applies to patients with a discrete tumour burden that can be localised from uninvolved parenchyma. Such regions of interest should be defined in MAA SPECT CT/MRI imaging or planar MAA scan (preferably MAA SPECT CT/MRI) in order to calculate the tumour to non-tumour ratio.

For non-cirrhotic patients and provided a significant proportion of the liver volume is spared from radiation – with the likelihood of hypertrophy and functional compensation in the non-targeted volume – the partition model is used to calculate an activity with the highest likelihood of resulting in an objective tumour remission.

For cirrhotic patients or when the amount of volume spared from radiation is low – with the likelihood of increased risk of complications derived from radiation-induced damage in the non-tumoural tissue – the partition model is used to calculate an activity with the highest chance to preserve liver function in the targeted lobe.

On the basis of tumour and liver volumes measured on CT or MRI images and MAA imaging, representative regions of interest of tumour and non-tumour liver are drawn. MAA imaging such as SPECT CT/MRI or MAA planar images may be used and MAA SPECT CT/MRI are preferred. The Partition Model estimates the dose of radiation that will be absorbed by tumour and non-tumoural liver compartments (Kao 2012 (31)).

When the patient is not cirrhotic or the amount targeted volume is less than 60% of the total liver volume, the Model is used to calculate an activity that would result in the tumour absorbing 120 Gy irrespective of the dose delivered to the non-tumoural liver.

$$A\ (GBq) = [120 \times ((M_{liver} / T{:}N) + M_{tumour})] / [49670\ (1\text{-}L/100)]$$

Conversely, when the patient is cirrhotic and the amount of targeted volume (tumour plus non-tumoural liver) is equal to or more than 60% of the total liver volume, the Model is used to determine the activity that would result in the non-tumoural liver absorbing not more than 40 Gy.

$$A\ (GBq) = [40 \times ((T{:}N \times M_{tumour}) + M_{liver})] / [49670\ (1\text{-}L/100)]$$

Spared Volume	Cirrhosis	No Cirrhosis
≤ 40%	≤ 40 Gy (Non Tumour)	120 Gy (Tumour)
> 40%	120 Gy (Tumour)	120 Gy (Tumour)

The prescribed activity should always be lower than the one that would be harmful for the lung tissue as per the following formula:

$$A_{Total} = (30000 \times 100 / \text{Lung Shunt}) / 49670$$

If there is a contraindication to the use of the Partition Model e.g. tumours cannot be delineated on MAA SPECT CT/MRI or planar MAA to calculate the T: N ratio, then the activity will be calculated using the BSA method using the formula below:

$$\text{Dose activity[GBq]} = \left((BSA - 0.2) + \frac{V_{tumour}}{V_{lobe}} \right) . \frac{V_{lobe}}{V_{TotalLiver}}$$

V_{tumour} = volume of tumour
$V_{TotaLiver}$ = volume of total liver, including tumour
V_{lobe} = volume of treated lobe, including tumour"

Note: SIR-Spheres Y-90 resin microspheres are contraindicated in patients with lung shunt of >20%. The same principles of prescribed dose activity reduction should be applied to ensure that lung radiation dose does not exceed 25 Gy.

Calculation of Lung Shunt Activity and Estimated Absorbed Pulmonary Dose When the BSA Method is Employed

For patients exhibiting lung-shunt when the BSA method for calculating activity is employed, estimated activity shunted to the lungs and the associated absorbed dose are to be determined. The calculation of estimated radiation exposure to the lungs is given by the following formulae:

Activity that may potentially reach the lung:

$$A_{lung}\,[GBq] = A_{total} * L/100$$

Where:

A_{lung} = lung activity (GBq)
A_{total} = total prescribed activity (GBq)
L = lung shunt (%)

The resulting lung dose, given that a given amount of activity shunts from the liver to the lung:

$$D_{lung}\,(Gy) = \frac{49670 * A_{lung}}{M_{lung}}$$

Where:

D_{lung} = lung dose (Gy)
A_{lung} = lung activity (GBq)
M_{lung} = mass of the lung (g)

The mass of both lungs plus blood is assumed to be 1000gm and allows estimation of lung

parenchymal radiation doses for any given amount of shunting. The administered dose of SIR-Spheres Y-90 resin microspheres must be reduced to ensure that the lung dose does not exceed 25 Gray.

If, based on: 1) the prescribed activity determined by the BSA method and 2) the lung-shunt percentage as determined by the ^{99m}TC-MAA scan conducted during the baseline angiographic mapping, the lung dose is < 25 Gy, the full prescribed activity will be administered. If it is determined that the estimated lung dose exceeds 25 Gy, the prescribed activity will be reduced (taking into account the lung shunt percentage) to ensure that ≤ 25 Gy is administered to the lungs. In order to provide an additional measure of safety for patients who exhibit lung shunt, any patient whose lung shunt exceeds 20% based on the ^{99m}Tc-MAA scan will be considered ineligible for SIR-Spheres microsphere treatment.

APPENDIX 4 NCI CTCAE v4.03 Recommendation for Grading of Adverse Events

The full **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03** Published 14 June 2010 can be obtained at the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

A brief summary of the key metabolic/laboratory values is listed for easy reference in the table below.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	30 – LLN g/L	20 – 30 g/L	< 20 g/L	-
ALP	> ULN – 2.5 x ULN	2.5 – 5.0 x ULN	5.0 – 20.0 x ULN	> 20 x ULN
ALT	> ULN – 2.5 x ULN	2.5 – 5.0 x ULN	5.0 – 20.0 x ULN	> 20 x ULN
AST	> ULN – 2.5 x ULN	2.5 – 5.0 x ULN	5.0 – 20.0 x ULN	> 20 x ULN
Bilirubin	> ULN – 1.5 x ULN	1.5 – 3.0 x ULN	3.0 – 10.0 x ULN	> 10.0 x ULN
Creatinine	> ULN – 1.5 x ULN	1.5 – 3.0 x ULN	3.0 – 6.0 x ULN	> 6.0 x ULN
Haemoglobin	100 – LLN g/L	80 – 100 g/L	65 – 80 g/L	< 65 g/L
Leucocytes	3.0 – LLN x 10^9/L	2.0 – 3.0 x 10^9/L	1.0 – 2.0 x 10^9/L	< 1.0 x 10^9/L
Neutrophils	1.5 – LLN x 10^9/L	1.0 – 1.5 x 10^9/L	0.5 – 1.0 x 10^9/L	< 0.5 x 10^9/L
Platelets	75 – LLN x 10^9/L	50 – 75 x 10^9/L	25 – 50 x 10^9/L	< 25 x 10^9/L

APPENDIX 5 CIS-GEM Treatment Details according to ABC-02

In Treatment Arm A: Chemotherapy Arm – CIS-GEM

Systemic chemotherapy (CIS-GEM) to start within 14 days (+ 2 days) of randomisation:

Cisplatin 25 mg/m^2 in 1000ml 0.9% saline given over 1 hour followed by 500 ml 0.9% saline over 30 minutes followed by

Gemcitabine 1000 mg/m^2 in 250 - 500ml 0.9% saline over 30 minutes by intravenous infusions on days 1, and 8 of a 21-day cycle.

Variations in fluid administration and cisplatin or gemcitabine dilutions are accepted. Cisplatin has to be administered prior to gemcitabine. Dose banding is allowed.

8 treatment cycles will be given; in the absence of progression treatment may be continued at discretion of the clinician.

	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4 onwards**		
Week	1	2	3	4	5	6	7	8	9	10	11	12
Day	1	8		1	8		1	8		1	8	
Cisplatin	x	x		x	x		x	x		x	x	
Gemcitabine	x	x		x	x		x	x		x	x	

In Treatment Arm B: Sequential Therapy Arm – SIRT followed by CIS-GEM

Patients randomised to receive SIR-Spheres Y-90 resin microspheres followed by systemic chemotherapy, will commence administration of CIS-GEM 14-16 days after SIRT treatment.

Cisplatin 25 mg/m^2 in 1000ml 0.9% saline given over 1 hour followed by 500 ml 0.9% saline over 30 minutes followed by

Gemcitabine 1000 mg/m^2 in 250 - 500ml 0.9% saline over 30 minutes by intravenous infusions on days 1, and 8 of a 21-day cycle.

Variations in fluid administration and cisplatin or gemcitabine dilutions are accepted. Cisplatin has to be administered prior to gemcitabine. Dose banding is allowed.

14-16 days after SIRT	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4 onwards**		
Week	1	2	3	4	5	6	7	8	9	10	11	12
Day	1	8		1	8		1	8		1	8	
Cisplatin	x	x		x	x		x	x		x	x	
Gemcitabine	x	x		x	x		x	x		x	x	

In the absence of disease progression or unacceptable toxicity 8 treatment cycles will be given. Beyond 8 cycles, treatment may be continued in the absence of disease progression at the treating clinicians' discretion.

Note: Patients randomised to receive SIRT (Arm B) but for whom SIRT implantation is not safely feasible (e.g. following initial angiographic work-up) will be treated according to arm A (but retained in Arm B for intention-to-treat (ITT) analysis).

PRE TREATMENT

Hydration schedule for cisplatin

The hydration and electrolyte regimen (KCl +/- MgSO4) for cisplatin administration will be determined by locally agreed pharmacy procedures and guidelines.
The following is recommended:

KCL 20 mmol and $MgSO_4$ 8 mmol during the one hour cisplatin infusion followed by 500 mls 0.9% saline over 30 minutes prior to the gemcitabine
However, alternative local schedules are acceptable.

Anti-emetics

The following schedules are optional; alternatively anti-emetics should be given according to local practice.

Gemcitabine & Cisplatin	
Pre chemo on day 1	8 mg dexamethasone iv **plus** 1 mg Granisetron **or** 4 mg Ondansetron
Day 2	4 mg dexamethasone PO **plus** 1 mg Granisetron PO
Day 3	4 mg dexamethasone PO
Days 1-5	Domperidone 20 mg qid PRN Metoclopramide 10 mg tid PO

RECOMMENDED CRITERIA FOR DOSE ADJUSTMENTS AND DEFERRING SUBSEQUENT TREATMENT COURSES

Dose adjustments and/or deferring chemotherapy treatment administrations will be dependent upon the full blood count taken prior to each treatment day and on the assessment of renal function as well as total bilirubin value.

In order to proceed with administration of full dose of gemcitabine on day 1 and day 8 of each cycle the following are required: WBC $\geq 2x10^9$, ANC $\geq 1x10^9$ and platelets $\geq 100{,}000/mm^3$ and total bilirubin ≤ 30 µmol/L (1.75 mg/dL).

If gemcitabine is deferred, the cisplatin will also be deferred (i.e. cisplatin will not be administered as a single agent).

In the event of a delay due to total bilirubin > 30 µmol/L (1.75 mg/dL) is more than 3 weeks and in the absence of biliary obstruction, treatment may still be resumed when the total bilirubin reduces to ≤ 30 µmol/L (1.75 mg/dL). Treatment will be resumed at Day 1 of the next treatment cycle. After the 3 weeks delay and during the extended delay period, total bilirubin should be assessed at least once every TWO weeks until recovery, or disease progression, patient choice or intolerance or permanent discontinuation at investigators discretion. Prophylactic treatment with steroids, ursodeoxycholic acid and ciprofloxacin should be considered if there is 2 weeks or greater delay due to total bilirubin > 30 µmol/L (1.75 mg/dL). Refer to Section7.1.3 Hepatic Complications for further consideration.

Prior to administration of cisplatin on each treatment day adequate renal function must be demonstrated with a calculated creatinine clearance ≥ 45ml/min.

Treatment on both arms will be deferred for toxicity by one week only (note this does not apply to biliary tract obstruction see section 12.3). If a second deferral is required, the treatment week in question is omitted and the patient will move on to the next treatment point (not necessarily next cycle).

For example: A patient has received cycle 3 day 1 (C3D1) of treatment and is due cycle 3 day 8 (C3D8):

Gemcitabine & Cisplatin

No deferral	C3D1	C3D8	C3D15		i.e. as per protocol
Treatment given	√	√	χ (rest)		
1-week deferral	C3D1	C3D8	C3D8	C3D15	i.e. cycle 3D8 is given 1 week late
Treatment given	√	χ	√	χ (rest)	
2-week deferral	C3D1	C3D8	C3D8	C4D1	i.e. cycle 3D8 is omitted altogether and *next cycle starts (which is C4D1)
Treatment given	√	χ	χ	√*	

RECOMMENDED ADJUSTMENTS

Haematological toxicity

Gemcitabine in both treatment arms will be dose-reduced or delayed if haematological toxicity occurs. The dose to be administered will depend on the FBC result on the day of treatment.

WBC ($x10^9$/L)		ANC ($x10^9$/L)		Platelets ($x1000/mm^3$)	Gemcitabine Dose	Cisplatin Dose
≥ 2	and	≥ 1	and	≥ 100	Full	Full
1-1.9	and/or	0.5-0.9	and/or	50-99	75% dose	Full
< 1	and/or	< 0.5	and/or	< 50	Delay*	Delay

*If delay is > 3 weeks for haematological toxicity, the patient will be withdrawn from treatment and followed according to protocol as shown in section 13.1. Study Calendar.

NB: the dose of gemcitabine will be re-escalated to full dose upon recovery of haematological toxicity despite a previous dose reduction in order to maintain the dose-intensity of therapy.

Renal toxicity

Cisplatin dosage will depend on renal function

	Cisplatin	**Gemcitabine**
Estimated GFR ≥ 45ml/min	full dose	full dose
Estimated GFR < 45ml/min*	omit	full dose

* Repeat the creatinine clearance assessment (consider using the more accurate isotope GFR method, if not available 24 hour urine creatinine clearance could be used) ensuring the patient

is adequately hydrated prior to this test and further cisplatin administration. Proceed with cisplatin if the repeated reading is ≥ 45ml/min, otherwise cisplatin is to be omitted until recovery of renal function. If cisplatin has to be omitted, continue with gemcitabine dosing according to FBC. If a sudden increase in creatinine occurs, haemolytic uraemic syndrome should be ruled out.

Other toxicity

No dose reduction/modification is required for:

Alopecia (any grade)	
Lethargy (grade 1-2)	
Nausea/vomiting (grade 1-2)	May have been reduced from grade 3-4 by appropriate use of anti-emetics
Oedema (grade 1-2)	Give postural advice, consider appropriate diuretics

Recommended dose-modifications* for:

Lethargy (grade 3-4)	Reduce gemcitabine by 25%
Nausea/vomiting (grade 3-4)	Ensure optimal use of antiemetics (according to local policy) Delay until recovery to baseline, then: Omit cisplatin first. If it recurs reduce gemcitabine by 25%.
Peripheral neuropathy (grade 1-2)	Delay cisplatin until recovery to baseline, then continue at full dose. If it recurs, treat as for grade 3-4. Continue with gemcitabine (full dose).
Peripheral neuropathy (grade 3-4)	Omit cisplatin from further treatment. Continue with gemcitabine (full dose).
Oedema (grade 3-4)	Dipstick urine test for protein followed by full 24-hour urinary protein estimation if result ≥ + Delay until recovery to baseline (with use of appropriate diuretics). Then reduce gemcitabine by 25%.
Tinnitus	No dose modification required if full recovery between cycles. Omit cisplatin if no recovery between cycles Continue gemcitabine (full dose)

For increases in bilirubin and other liver function tests, refer to Section 7.1.3

Stop allocated treatment for:

Lethargy (grade 3-4)**	Which has not responded to dose modification
Nausea/vomiting (grade 3-4)**	Which has not responded to optimal anti-emetics or dose reduction
Oedema (grade 3-4)	Which has not responded to dose modification and use of appropriate diuretics
Pulmonary toxicity (grade 2-4)	Supportive therapy (high dose steroids) should be initiated immediately

*Investigator discretion as to whether a particular non-haematological toxicity requires a dose reduction or treatment delay

**If delay is > 3 weeks for non-haematological toxicity (excluding biliary tract obstruction, see section 12.3 Supportive Treatment

In the event of a delay or interruption to trial treatment for reasons other than toxicity or disease related problems, treatment should continue. Resume treatment at Day 1 of the next treatment cycle. Patients who discontinue allocated treatment will still be included in evaluation of toxicity, response to treatment and survival.

APPENDIX 6 Recommended acquisition guidelines for CT scanning

CT Acquisition Guidelines

For the purpose of baseline screening and response assessment the following tables describe the preferred parameters to be used for computed tomography (CT) imaging of the chest, abdomen and pelvis.

CT images are to be acquired from the lung apices to the symphysis pubis. 1) Prior to patients entering this study; and 2) for the follow-up imaging performed on this study.
See Section 13 Follow Up Study Assessments.

Area covered:	Lung apices to pubic symphysis
Scan type:	Spiral
Scan direction:	Cranial-caudal
Injection rate:	2cc/kg @ 4cc/second up to 150cc contrast maximum
Saline chaser:	30cc @ 4cc/second

Phases:	Non-contrast (lung, abdomen and pelvis)
	Arterial @ 35 seconds post injection (abdomen)
	Portal venous @ 70 seconds post injection (lung, abdomen, pelvis)
	Late phases /delayed @ 6-15 mins* post injection (abdomen) **The recommended time for the late phase is at least 10 mins (Adam, Parthasarathy & Miller 2015.) The duration of the late phase should be consistent throughout the study for each patient.*

Parameter	**Phase**					
	Non-Contrast	Arterial (35 sec post injection)			Portal Venous (70 sec post injection)	Late phases / delayed (6-15 mins post injection)
	Recon 1	Recon 1	Recon 2	Recon 3	Recon 1	Recon 1
View	Axial	Axial	Coronal	Sagittal	Axial	Axial
Slice Thickness	5.0mm	1.0mm	1.0mm	1.0mm	3.0mm	3.0mm
Increment/Spacing	2.5mm	1.0mm	1.0mm	1.0mm	2.0mm	2.0mm
Kernel	B25f	B25f	B25f	B25f	B25f	B25f
Window	Abdomen	Abdomen	Abdomen	Abdomen	Abdomen	Abdomen

In case MRI is the standard radiological assessment for ICC patients, it is permitted if, for an individual patient, during the entire course of the study, the same method of assessment and the same technique is used to characterize each identified and reported lesion at baseline and during follow-up.

CT scan (chest-abdomen-pelvis) remains mandatory for assessments outside the liver.

APPENDIX 7 RECIST Assessments

- **RECIST 1.1 Guidelines**

All measurements should be recorded in metric notation, using callipers if clinically assessed.

All baseline evaluations should be performed as closely as possible to the beginning of treatment start and never more than 28 days before beginning of the treatment.

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

I. Measurable Lesions:

- Tumour > 10 mm in longest diameter (LD) on an axial image on CT or MRI with ≤ 5 mm reconstruction interval (> 20 mm with conventional techniques)
- Lymph nodes ≥ 15 mm in short axis on CT (CT slice thickness ≤ 5 mm)

1) Target Lesions:
   - Choose up to 5 lesions and up to 2 per organ
   - Add up longest diameters (LD) of non-nodal lesions (axial plane)
   - Add short axis diameters of nodes
   - This is the sum of longest diameter (SLD)
   - If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be.

The baseline sum diameter will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

2) Non-Target Lesions

- All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to < 15 mm short axis).

They should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

II. Evaluating Response at each Time point:

- Measure previously chosen target lesions (even if they are no longer the largest)
- Evaluate all previously identified non-target lesions
- Look for new definite cancer lesions

Target Lesion Evaluation

- Measure LD (axial plane) for each target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the SLD
- If too small to measure, a default value of 5 mm is assigned (if the lesion disappears completely, the measurement is recorded as 0 mm).

- Splitting or coalescent lesions:
  - If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
  - If target lesions coalesce, the LD of the resulting coalescent lesion is added to the sum

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis.
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum of diameters
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Non-Target Lesion Evaluation

Response	Definition
Complete Response (CR)	• Disappearance of all extranodal non-target lesions • All lymph nodes must be non-pathological in size (< 10 mm short axis) • Normalization of tumour marker level
Non CR/Non PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Subjective judgement by experienced reader)

Note: Elevated serum tumour markers on their own are not sufficient evidence of progression and only imaging examinations can assess and confirm disease progression.

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumour
- If a new lesion is equivocal, continue to the next time point. If confirmed then, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new.

RECIST: Response Criteria

Time Point Response: Patients with Target (+/- non target) disease:

Target Lesions	**Non-Target lesions**	**New Lesions**	***Overall Response***
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD **or** not all evaluated	No	PR
SD	Non-PD **or** not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

- **Refined RECIST: Response Criteria**

The conventional RECIST was amended for the SHARP trial in order to prevent over-staging and non-accurate assessment of progression in the following instances:

- Detection of lymph nodes in the hepatic hilum, as this may be seen in cirrhotic patients and does not reflect cancer involvement.
- Detection of ascites or pleural fluid at baseline or during follow-up, as this may reflect hydrosaline retention because of impaired liver function and not malignant spread.
- Detection of macro regenerative nodules. This may be observed in cirrhotic livers and does not reflect progression, even if the nodules are larger than 1 cm.

To prevent the above, the amendments state:

- Lymph nodes are classified as malignant if their size exceeds 20 mm or if arterial vascularization is present.
- For ascites or pleural effusion, in order to declare malignant, it should be proven by positive cytology.
- New lesions outside the liver follow the same definitions as for RECIST1.1. New intrahepatic lesions have specific consideration:
- <10 mm should be considered as equivocal and not progression.
- ≥10 mm should be considered malignant if arterial hypervascularisation is present.

Table: BCLC- refined RECIST

Baseline lesion categorisation	
Measurable	≥ 20 mm for conventional techniques
	≥ 10 mm with spiral (helical) CT scan or MRI
Minimum lesion size	20 mm or double the slice thickness (and gap if noncontiguous) on conventional technique
	10 mm or double the reconstruction thickness (and gap if noncontiguous) on spiral/helical CT or MRI
Nonmeasurable	All other lesions
	Smaller lesion (< 20 mm for conventional techniques or < 10 mm for spiral (helical) CT scan or MRI)
	Truly nonmeasurable lesions
	Lesion on chest X-rays
Pleural effusion evidenced radiographically	Will be classified as malignant only if pathology (cytology) proven
Ascites	Progressive disease may only be declared on the basis of a new or enlarging ascites if there is cytological confirmation of its malignant nature. New or enlarging ascites detected on imaging but without cytological proof of malignancy should not be assigned as progression.
Portal vein thrombosis	Malignant portal vein thrombosis should be considered nonmeasurable lesion.
Malignant lymph nodes	Lymph nodes detected at the portal hepatis should be considered as malignant if the lymph node longest diameter is at least 20 mm or show arterial enhancement.
Lesion with prior local treatment	Not valid as a target lesion
Target lesion (TL)	
Selection rules	Will not select TL if evidence of prior irradiation is apparent radiographically. Lesions with significant necrotic component or concomitant palliative radiotherapy should be excluded.
Boundary	Lesion with hypervascular component, that component must be included in the measurement. Hypervascular component is viable tumour.
Measurement rules	Tumour measurement performed on CT chest, abdomen, and pelvis. The longest diameter of the lesion should be measured even if the actual axis is different from the one used initially. If TL cannot be measured because of incomplete imaging, the TL will be limited "unknown" or "progressive disease." Changes on pre-existing bone scan lesion will only have influence over OR. Only new bone lesions will be indicative of progressive disease.
Nontarget lesion (NTL)	Change on each lesion will be recorded as: Unequivocal progression (requires retrospective measurements and at least a doubling in LD from nadir for lesion < 2 cm and an increase by 30% for lesion > 2 cm and inconclusive for progressive disease
New lesions	Will be recorded separately from target/nontarget
	≥ 1 cm in longest diameter and depicts arterial hypervascularisation = Progressive disease
	< 1 cm in longest diameter or not typical enhancement = Inconclusive progressive disease

	New lesions smaller than 10 mm in longest diameter must be considered equivocal
	New lesions 10 mm or larger in longest diameter, but without hypervascularisation must be considered equivocal and inconclusive for progressive disease
Response criteria	
Target lesion (TL)	Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking into account the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Lymph nodules	Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Overall response in NTL	NTL New lesion OR
	CR/No CR
	Incomplete response/SD/No SD
	PD Yes/No PD
	Any/Yes PD
	The appearance of one or more new lesions is also considered progression.
	Unequivocal Progression: There must be an overall level of substantial worsening in nontarget disease such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.
	Modest “increase” in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status.
Confirmation criteria	PR or CR, by CT or MRI scan of the chest, abdomen, and pelvis at least 4wk after. If the subject had evidence of bone disease at baseline, response cannot be confirmed if a bone scan was not performed.
Tools for measuring lesions	
Clinical lesions	Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using callipers.
	When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken because it is more objective and may also be reviewed at the end of the study.
Ultrasound	Will not be used to measure tumour lesion
Endoscopy and laparoscopy	Is not advised for tumour evaluation, but it can be used to confirm CR
Tumour makers	Are not reliable to assess response

Abbreviations: BCLC, Barcelona Clinical Liver Cancer; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumours.

APPENDIX 8 **EQ-5D Quality of Life Questionnaire**

The following four pages contain the Quality of Life questionnaire that is to be used by study participants during the course of the trial. The EQ-5D questionnaire is a tool that has been designed for rapid use in the clinical setting.

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

The EQ-5D is used under license from the EuroQol group. The sample version shown here is the Australian English version. Sirtex has purchased the rights to use this document in all participating countries.

Health Questionnaire

English version for Australia

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around	❑	PLEASE TICK
I have some problems in walking around	❑	ONE BOX
I am confined to bed	❑	

Personal Care

I have no problems with personal care	❑	PLEASE TICK
I have some problems washing or dressing myself	❑	ONE BOX
I am unable to wash or dress myself	❑	

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑	PLEASE TICK
I have some problems with performing my usual activities	❑	ONE BOX
I am unable to perform my usual activities	❑	

Pain/Discomfort

I have no pain or discomfort	❑	PLEASE TICK
I have moderate pain or discomfort	❑	ONE BOX
I have extreme pain or discomfort	❑	

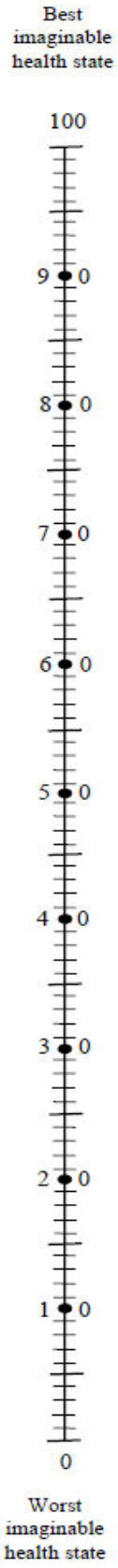
Anxiety/Depression

I am not anxious or depressed	❑	PLEASE TICK
I am moderately anxious or depressed	❑	ONE BOX
I am extremely anxious or depressed	❑	

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 9 World Medical Association Declaration of Helsinki

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in

its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 10 **Abbreviations and Acronyms**

3D-CRT	Three-dimensional Conformal Radiation Therapy
5FU	5-fluorouracil
AASLD	The American Association for the Study of Liver
AE	Adverse Event
ADE	Adverse Device Effect
AFP	Alpha-Fetoprotein
AIMD	Active Implantable Medical Device
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate Aminotransferase
AVM	Arterio-Venous Malformations
BSA	Body Surface Area
BTC	Biliary Tract Cancer
CA 19-9	Carbohydrate antigen 19-9
CA 125	Cancer antigen 125
CEA	Carcinoembryonic Antigen
CIP	Clinical Investigation Plan
CIS	Cisplatin
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reaction Protein
CSG	Clinical Study Group
CT	Computed Tomography
EASL	The European Association for the Study of Liver
EBRT	External Beam Radiation Therapy
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EC	Ethics Committee
EE	Efficacy Evaluable
ERC	Endoscopic Retrograde Cholangiography
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
ESMO	European Society for Medical Oncology
EU	European Union
FBC	Full Blood Count
FOLFOX	Oxaliplatin + leucovorin + 5-fluorouracil systemic chemotherapy
FOLFOX6m	modified FOLFOX6
FOV	Field of View
FU	Follow up
FUDR	Floxuridine
GCP	Good Clinical Practice
GD	Gastric-Duodenal
GEM	Gemcitabine
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transpeptidase
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma

HCV	Hepatitis C Virus
HEENT	Head, Eye, Ear, Nose and Throat
ICC	Intrahepatic Cholangiocarcinoma
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSA	Infectious Disease Society of America
IDSMC	Independent Data Safety Monitoring Committee
IGRT	Image Guided Radiotherapy
IHAC	Intra-Hepatic Arterial Chemotherapy
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
IRCP	International Commission on Radiological Protection
ISO	International Standards Organization
ISO 14155	Clinical Investigation of Medical Devices for Human Use
ITT	Intention To Treat
mITT	modified Intention To Treat
IWRS	Interactive Web Response System
LC	Local Control
LD	Longest Diameter
LG	Left Gastric
LH	Left Hepatic
LLN	Lower Limit of Normal
LN	Lymph Node
LPFS	Liver-Progression Free Survival
LV	Leucovorin (folinic acid)
MAA	Macro-Aggregated Albumin
METAVIR	Meta-analysis of Histological Data in Viral Hepatitis
MIRD	Medical Internal Radiation Dose
MRI	Magnetic Resonance Imaging
NCIC CTC	National Cancer Institute of Canada Common Toxicity Criteria
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Care Excellence
NTL	Nontarget Lesion
ORR	Overall Response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PMA	Pre-Market Approval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTC	Percutaneous Transhepatic Cholangiography
PTCD	Percutaneous Transhepatic Cholangio-Drainage
RE	Radioembolisation
RECIST	Response Evaluation Criteria In Solid Tumours
REILD	Radioembolisation Induced Liver Disease
RH	Right Hepatic
ROI	Region of Interest
RT	Radiotherapy
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SIRT	Selective Internal Radiation Therapy

SLD	Sum of Longest Diameter
SMA	Superior Mesenteric Artery
SPECT	Single Photon Emission Computed Tomography
SPL	Splenic
TGA	Therapeutic Goods Administration
TL	Target Lesion
TNC	Too Numerous to Count
TR	Treatment Received = Safety Population
TTP	Time To Progression
ULN	Upper Limit of Normal
WBC	White Blood Count
WHO	World Health Organisation
WMA	World Medical Association

RECIST outcome abbreviations

CR	Complete response
NE	Not Evaluable
PR	Partial response
SD	Stable disease
PD	Progressive disease

Units of measurement

GBq	gigabequerel
Gy	Gray
dL	decilitre
hr	hour
kg	kilogram
L	litre
mg	milligram
mL	millilitre
mSv	millisieverts
µSv	microsieverts
v	volume

APPENDIX 11 NETHERLANDS SPECIFIC SAFETY REPORTING PROCEDURES

Netherlands specific safety reporting procedures in accordance with the Medical Research Involving Human Subjects Act, Wet medisch-wetenschappelijk onderzoek met mensen (WMO) in the Netherlands.

The sponsor will report all SAEs through the web portal Toetsing Online to the accredited METC (Medisch Ethische Toetsings Commissie) that approved the protocol, at the following timeframes:

1. SAEs that result in death or are life threatening will be reported through the web portal Toetsing Online within 7 days after the sponsor has first knowledge of the serious adverse event, followed by a period of maximum of 8 days to complete the initial preliminary report.

2. Unanticipated SAEs which are or are suspected to be related to a study procedure or to the medical device will be reported through the web portal Toetsing Online within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse event.

3. Anticipated SAEs which are or are suspected to be related to a study procedure or to the medical device will be reported periodically through the annual report.

4. SAEs which are definitely not related to a study procedure or to the medical device will be reported periodically through the annual report

The sponsor will submit a summary of the progress of the study (Annual progress report) to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/ serious adverse reactions, other problems, and amendments.

Temporary halt for reasons of subject safety
In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC with undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed.