A FEASIBILITY AND DOSE ESCALATION STUDY OF SELECTIVE INTERNAL RADIATION THERAPY (SIRT) WITH YTTRIUM-90 MICROSPHERES (SIR-Spheres® Y-90 Resin Microspheres) IN PATIENTS WITH PRIMARY OR SECONDARY LUNG MALIGNANCIES

POEM

Clinical study phase:	I	**Version / Date:**	4.1 /18. Feb 2020
Study Reference Number:	LMU-RAD0004	**Status:**	final
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Summary of the revision history

Version no.	Date	Comment / Changes
1.0	18 May 2018	First Version
2.0	13 Nov 2018	Adaption of structure to ISO 14555, adaption of inclusion- and exclusion criteria, revision of the benefit-risk assessment, prolongation of follow-up period, treated lung volume reduced to 40% of total lung volume
3.0	28 Jan 2019	Installation of independent Data Safety Monitoring Board, inclusion time of patients at the same dose level, increase of washout window after completion of prior therapy
4.0	13 Jan 2020	DSMB member definition, definition interims analysis after 4 patients, Secondary endpoint: quality of life
4.1	18 Feb 2020	DSMB safety analysis after 1 and 4 patients

The study will be conducted in compliance with the Clinical Investigation Plan, ICH-GCP and any applicable regulatory requirement.

The approval of this Clinical Investigation Plan is documented in a separate signature document

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List of abbreviations

3D	3 dimensional
5FU	5-Fluorouracil
ADE	Adverse Device Effect
AE	Adverse Event
AIMD	Active Implantable Medical Device
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phophatase
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
ASR	Annual Safety Report
AST	Aspartate Transaminase
ATCC	American Type Culture Collection
BAE	Bronchial Artery Embolization
BACE	Bronchial Artery Chemoembolization
BfArM	Bundesamt für Arzneimittel und Medizinprodukte
CCL-1	CC-motif ligand 1
CEA	Carcinoembryonic Antigen
CEC	Competent Ethics Committee
cm	centimeter
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTCAE	Common Terminology Criteria for Adverse Events
DL	Dose Level
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DLT	Dose Level Toxicity
DM	Data Manual
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
e.g.	for example (latin: exempli gratia)
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram.
eCRF	Electronic Case Report Form
EEC	European Economic Community
EF	Ejection Fraction
EGFR	Endothelial growth factor receptor
ESMO	European Society for Medical Oncology
etc.	et cetera
EU	European Union

FACT-L	Functional Assessment of Cancer Therapy questionnaire
FAS	Full Analysis Set
^{18}F -FDG	Fludeoxyglucose (18F)
FEF	Forced Expiratory Flow
FEV1	Forced Expiratory Pressure in 1 Second
FIF_{25-75}	Forced Inspiratory Flow 25-75%
FOV	Field of View
FU/LV	Fluorouracil/ Leucovorin Calcium
FVC	Forced Vital Capacity
G	Gauge
GBq	Gigabecquerel
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	Gamma-glutamyltransferase
GY	Gray
h	Hour
HCC	Hepatocellular Carcinoma
HCO_3	Hydrogencarbonate
^{125}I	Iodine-125
IATA	International Air Transport Association
i.e.	id est
ICH	International Conference on Harmonization
IMRT	Intensity modulated radiation therapy
INR	International normalized ratio
ISCN	International Standard of Cytogenetic Nomenclature
ISO	International Organization for Standardization
ITF	Investigator Trial File
ITT	Intent-To-Treat
kg	Kilogram
LDH	Lactate Dehydrogenase
MBq	Megabecquerel
MEM	Minimum Essential Medium
MFD	Maximum Feasible Dose
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
MPSV	Medizinprodukte-Sicherheitsplanverordnung
MTD	Maximum Tolerated Dose
n/a	not applicable
NCI	National Cancer Institute
NCTC	National Collection of Type Cultures
no.	Number
NSCLC	Non-Small Cell Lung Cancer

OECD	Organisation for Economic Co-operation and Development
OSTB	Organ-specific tumourboard
pO_2	Partial Pressure of Oxigen
PAPsys	Systolic pulmonary artery pressure
pCO2	Partial Pressure of of Carbon Dioxide
PEF	Peak Expiratory Flow
PET	Positron-Emission Tomography
pH	Potential of Hydrogen
PP	Per-Protocol Population
PVC	Polyvinyl chloride
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency Ablation
RT	Radiation therapy
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SaO_2	Oxygen saturation
SBRT	Stereotactic body radiation therapy
SDV	Source Data Verfication
SIRT	Selective internal radiation therapy
SPECT	Single-photon Emission Computed Tomography
^{99m} TC-MAA	Technetium-99m macro aggregated albumin
TLC	Total Lung Capacity
TMF	Trial Master File
TV	Tidal Volume
ULN	Upper Limit of Normal
v	Version
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
v/v	Volume Fraction
WBC	White Blood Cells
WHO	World Health Organization
w/v	Weight per Volume
^{90}Y	Yttrium-90
^{90}Zr	Zirconium-90

1 Study administrative structure

Sponsor	Klinikum der Universität München – Großhadern Marchioninistr. 15, 81377 München, Germany Represented by Sponsor Delegated Person: Prof. Dr. Jens Ricke Marchioninistr. 15, 81377 München phone +49 89 4400-72750 fax +49 89 4400-78895 email: Jens.Ricke@med.uni-muenchen.de
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2 Synopsis

Study title	A FEASIBILITY AND DOSE ESCALATION STUDY OF SELECTIVE INTERNAL RADIATION THERAPY (SIRT) WITH YTTRIUM-90 MICROSPHERES (SIR-Spheres® Y-90 Resin Microspheres) IN PATIENTS WITH PRIMARY OR SECONDARY LUNG MALIGNANCIES
Short title	POEM
Clinical study phase	I
Study objectives	primary objective: • feasibility secondary objectives: • Safety and Toxicity (according to CTCAE v5.0) • Tumour Response Rate • Time-to-progression in the targeted lesions • Overall Survival • Quality of Life
Test product	SIR-Spheres® ^{90}Y resin microspheres Sirtex Medical Europe GmbH
Reference product	n/a
Indication	primary or secondary lung malignant tumour
Diagnosis and main criteria for inclusion	Inclusion criteria (list not complete; for a complete list of inclusion criteria, see 9.1.1): • Primary carcinoma of any origin (except from the central nervous system and lung) with histologically proven pulmonary metastases, or primary non-small cell lung carcinoma • Unequivocal and measurable CT evidence of either pulmonary metastases from a primary carcinoma, or primary non-small cell lung carcinoma • Stage IV disease in oligometastatic pulmonary disease state that is not suitable for treatment by surgical resection, local ablation, radiation therapy, or other conventional techniques, and is either unsuitable or has failed all conventional systemic treatment options such as chemotherapy, immunotherapy or targeted therapy • Suitable for protocol therapy as determined by a multidisciplinary team, e.g. interventional radiologist, thoracic surgeon, pulmonologist, medical oncologist and radiation oncologist Investigators • WHO performance status 0 – 2 • Adequate hematological and renal function • Estimated life expectancy of at least 3 months without any active treatment
Study design	prospective, single arm
Methodology	This is a prospective, single arm, dose escalation study of selective internal radiation therapy (SIRT) using SIR-Spheres® ^{90}Y resin microspheres as a treatment for patients with primary or secondary lung tumours who have failed all available, or are not suitable for any anti-tumour treatment, both locally and systemically. The objective of this clinical study is feasibility. Safety, toxicity, potential effectiveness and the impact on quality of life are secondary endpoints in the study. Patients will be recruited into five cohorts comprising the

	following radiation doses to the targeted tumour-containing lung segment(s): • Cohort 1: 38Gy • Cohort 2: 44Gy • Cohort 3: 50Gy • Cohort 4: 56Gy • Cohort 5: 62Gy Treatment will be limited to 40% of the total lung volume (in other words, treatment will not be limited to either the left lung or the right lung).	
Type of control	n/a	
Planned study dates	first patient first visit	01 Mar 2020
	last patient first visit	28 Feb 2021
	last patient last visit	01 Apr 2026
Planned number of study centers	2	
Planned number of countries	1 (Germany)	
Number of patients	Dose-escalation study, theoretical minimum number of patients: 3 theoretical maximum number of patients: 30	
Primary endpoint	Feasibility: Pulmonary SIRT will be regarded as feasible if the first dose level can be completed without reaching dose-limiting toxicity in more than 1/3 patients or imminent stasis in more than 3/6 patients. A patient is regarded to have reached imminent stasis if more than 50% of targeted segment/s present with imminent stasis.	
Secondary endpoints	Safety and Toxicity Tumour Response Rate Quality of Life	
Plan for statistical analysis	Descriptive statistics will be used to tabulate outcome measures. Given the small size of this feasibility study, no other statistical tests will be performed.	

3 Flowchart

	Screening Assessments	**Baseline Assessments**	**Follow-up Assessments: First 30 Days Post-SIRT**			**Follow-up Assessments: 3 – 12 months Post-SIRT**	**Follow-up Assessments: 24 – 60 months Post-SIRT**
Schedule	≤30 days prior to study entry	≤ 28 days prior to protocol SIRT treatment	Day 0: SIRT	Day 14	Day 30	Month 3, 6, 9, 12	Month 18, 24,30,36,42,48, 54, 60
Informed consent	✓						
Demographics	✓						
Medical history, including - concurrent illnesses - concomitant meds.	✓					✓	✓
Physical examination, including - height, weight, vital signs - WHO performance status		✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]
ECG		✓	✓	✓	✓	✓	✓
Hematology & biochemistry		✓	✓[b]	✓[b]	✓[b]	✓[b]	✓[b]
Tumour markers[c]		✓		✓	✓	✓	✓
Pregnancy test for females[d]		✓			✓		
Pulmonary function tests		✓			✓	✓	
Screening CT[e]	✓						
Registration fax to sponsor for assignment of enrolment number and dose level		✓					
Contrast CT scan chest with 3D CTA		✓[f]			✓[g]	✓[g]	✓[g]
^{18}F-FDG PET/CT scan chest, abdomen, pelvis		✓[f]				✓[h]	
Mapping bronchial angiography		✓[f]					
^{99m}Tc-MAA study		✓[f]					
SIRT			✓				
Post-SIRT ^{90}Y PET/CT study			✓[i]				
Adverse events			✓	✓	✓	✓	✓
Quality of life[j]		✓			✓	✓	✓
Survival			✓	✓	✓	✓	✓

Notes to the Study Calendar:

a) Physical examination to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Height to be measured at baseline only.
b) Clotting profile and troponin T are not required at these assessments.
c) Tumour markers relevant to the primary or secondary lung tumours, if such markers exist. For example, if the patient has primary colorectal cancer with lung metastases, then carcinoembryonic antigen (CEA) should be assessed.
d) Premenopausal female patients must have a negative serum or urine pregnancy test at study entry. This test should be repeated if pregnancy is suspected during the study. Inform the study Sponsor immediately if pregnancy is confirmed during the study.
e) Screening CT may be used for baseline assessment if performed ≤28 days prior to start of SIRT treatment and the corresponding 3D CTA is available.
f) Procedure/s to be performed after assignment of enrolment number and dose level.
g) 3D CT angiography is not required at these assessments.
h) F-18-FDG PET/CT scan at 3 months only.
i) The post-SIRT ^{90}Y -PET/CT study may be performed either on the same day as SIRT or day 1 following SIRT. A second scan will be performed between 12 to 24 h after the first scan.
j) The Functional Assessment of Cancer Therapy (FACT-L) questionnaire should be completed at baseline, 30 days, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months and 60 months.

The acceptable tolerances in the time points are:

- Day 0 assessments must be performed on day 0
- Day 14, 30 assessments may be performed +/- 5 days
- Month 3, 6, 9, 12 assessments may be performed +/- 2 weeks
- Month 18, 24,30,36,42,48,54,60 assessments may be performed +/- 4 weeks.

4 Background

4.1 NSCLC

Lung cancer is the leading cause of cancer death globally. The annual incidence of non-small cell lung cancer (NSCLC) in Europe and North America is estimated to be 613,700 (1) and in the United States alone, an estimated 226,000 new cases were diagnosed in 2012. Only 16% of all patients developing NSCLC are alive 5 years or more after diagnosis.

Surgery, radiation therapy and chemotherapy, including the biologic (i.e. targeted) therapies, comprise the three main modalities employed to treat patients with NSCLC. These options may be used either alone or in combination, depending on disease status. Locally ablative therapy (e.g. radiofrequency ablation) may also be an option in selected patients.

In general, surgery provides the best chance for cure in patients with Stage I and II NSCLC. The surgical procedure employed depends primarily on the histology of the tumour the extent of disease and on the patient's cardiopulmonary reserve. Lobectomy or pneumonectomy should usually be undertaken if physiologically feasible. Of these two options, lung-sparing lobectomy is usually preferred over pneumonectomy, if anatomically amenable and if margin-negative resection can be achieved. Further lung-sparing sub-lobular resection, either segmentectomy or wedge resection may be appropriate in selected patients. However, controversy remains whether lung-sparing surgeries such as segmentectomy or wedge resection are useful in patients with severely reduced pulmonary function who are otherwise not candidates for surgery. Mediastinal lymph node dissection is an essential part of surgical treatment of lung cancer. Stereotactic ablative radiotherapy may be more appropriate for these patients.

Radiation therapy (RT) may be employed as: 1) adjuvant therapy in patients with resectable disease undergoing surgery; 2) primary local treatment, i.e. for patients with unresectable or medically inoperable disease; and 3) palliative therapy for patients with incurable disease.

Several advanced RT technologies exist including 3D-conformal RT, intensity modulated RT (IMRT), image guided RT, motion management strategies, and proton therapy, all of which have been shown to reduce toxicity and increase survival in non-randomized trials (2) (3) (4) (5).Currently, CT-planned 3D-conformal RT is considered to be the minimum standard.

Stereotactic body RT (SBRT) has been shown to be particularly useful for patients with inoperable Stage I disease or for those who decline surgery (6) (7). For patients with Stage I disease, SBRT may yield a median survival of 32 months and a 3-year overall survival of approximately 43% (8).

Numerous systemic chemotherapy agents are available for the treatment of NSCLC, including platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, vinblastine, etoposide, pemetrexed and gemcitabine.

Platinum containing doublet regimens such as cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/vinorelbine, cisplatin/pemetrexed, gemcitabine/cisplatin and docetaxel/cisplatin have demonstrated superiority compared to single agent therapy. Commonly used first-line chemotherapy regimens for non-squamous NSCLC include: 1) cisplatin (or carboplatin)/pemetrexed; and 2) carboplatin/paclitaxel (± bevacizumab). Gemcitabine/cisplatin is commonly used for patients with squamous NSCLC (9) (10).

The anti-angiogenic agent bevacizumab has demonstrated an improvement in both progression-free and overall survival when added to carboplatin, compared to carboplatin alone, achieving 6.2 months versus 4.5 months and 12.3 months versus 10.3 months, respectively (10). However, the addition of bevacizumab carried a significantly increased rate of bleeding (4.4% versus 0.4).

The EGFR inhibitor gefitinib may be used in patients with advanced, recurrent or metastatic NSCLC who possess an EGFR mutation. The approval of gefitinib was based on the IPASS study (11) that demonstrated that patients with EGFR mutations who received gefitinib experienced increased response rates, progression-free survival and quality of life with fewer side effects when compared to paclitaxel/carboplatin chemotherapy.

The EGFR inhibitor cetuximab may be added to cisplatin/vinorelbine in patients with advanced NSCLC to achieve a moderate increase in median overall survival (11.3 months versus 10.1 months) (12). The FLEX study demonstrated that cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC without EGFR mutations or ALK rearrangements, regardless of histology. Unfortunately, patients typically have a poorer tolerance to the cetuximab containing regimen as a consequence of its toxicity. Therefore cetuximab has not been approved for lung cancer treatment.

The protein kinase inhibitor crizotinib is currently approved in the United States and several other countries for patients with locally advanced or metastatic NSCLC who are positive for the EML4-ALK gene rearrangement. The approval of crizotinib was based on studies that demonstrated high response rates (>80%) in patients who had previously progressed on standard therapies (13) (14).

Radiofrequency ablation (RFA) may be an option for node negative patients who either decline surgery or who cannot tolerate surgery due to poor performance status, reduced cardiopulmonary reserve, or other comorbidities. Optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm in diameter. RFA may be considered for previously irradiated tissue and for palliation (15). Lencioni and collaborators showed that RFA in 33 patients yielded an overall survival of 70% (95% CI, 51% – 83%) at 1 year and 48% (95% CI, 30% – 65%) at 2 years. A 2-year overall survival of 75% (95% CI, 45% – 92%) was reported in patients with Stage I disease who received RFA (16).

In the overall population of patients presenting with primary NSCLC, a significant proportion of patients with locally advanced disease may be: 1) unresectable; 2) unable to tolerate concurrent chemo-radiotherapy; 3) present with diffuse disease compromising treatment with external beam radiotherapy or other local ablative therapy or 4) provided with best supportive care but otherwise left untreated. Consequently, there is a clear need for further research and the identification of new treatment approaches that may be offered to patients with primary NSCLC.

4.2 Secondary Lung Malignancy – Pulmonary Metastases

Pulmonary metastases are a frequent finding in solid tumours. The lung is one of the most common organs to which cancer metastases and approximately 30% of all cancer patients will develop pulmonary metastases at some time (17). Generally, pulmonary metastases are treated using a systemic therapy and with a palliative intent, with chemotherapy being the mainstay of treatment. External beam RT may also be used to provide some local control to pulmonary lesions.

Nevertheless, there is a subset of patients who may be candidates for pulmonary metastastectomy based on accepted selection criteria for surgery (18). These criteria may be summarized as: 1) primary tumour is controlled; 2) no extra-thoracic lesions are present (with the exception of hepatic lesions that are able to be addressed definitively); 3) the metastases are technically resectable; and 4) the general and functional risks are tolerable. However, in patients with multiple lung lesions, surgical resection is limited by residual lung capacity. Since a significant proportion of patients have pulmonary metastases that are diffuse or involve multiple lung segments, most presenting patients are unsuitable candidates for resection.

Despite the many refinements in surgical techniques, radiation therapy, chemotherapy, the newer targeted therapies, and locally ablative therapies, adequate control of pulmonary metastases is also often limited. Hence, there is also a clear need for new treatment approaches for patients with pulmonary metastases from distant solid cancers.

<u>Selective internal radiation therapy (SIRT) in pulmonary metastases:</u>
The following presents a discussion of the treatment options for patients with pulmonary metastases from primary colorectal cancer and primary renal cell carcinoma. While this study does not restrict patients to those with pulmonary metastases from colorectal or renal cell cancer, it was in these tumours that Ricke and collaborators reported the first use of selective internal radiation therapy delivered via the bronchial arteries in humans (19).

Patients with metastatic solid cancers in which the liver is the dominant site of disease – e.g. metastatic colorectal cancer – who have received several systemic chemotherapy regimens, commonly eventually develop diffuse pulmonary metastases. While the primary tumour and liver metastases may often remain adequately controlled via a combination of systemic and liver-directed therapy(ies) these patients' disease commonly progresses in the lung. In this group of patients, who are usually not candidates for pulmonary metastectomy or RFA, there is a lack of alternative treatment options.

Selective internal radiation therapy, which is the intra-arterial delivery of radioactive microspheres to tumours, has an established therapeutic role in the management of inoperable primary and metastatic liver tumours (20). Bronchial arterial embolization for the prevention or control of pulmonary hemorrhage utilizes the same endovascular principles and techniques as SIRT. However, the utility of SIRT for the management of primary and secondary lung tumours remains largely unexplored.

Ricke and collaborators reported the first-in-human use of SIR-Spheres® ^{90}Y resin microspheres delivered via the bronchial artery in two patients exhibiting diffuse pulmonary metastases from primary colorectal and primary renal cell cancer (19). For a detailed case description, please refer to section 6.2.1.

From the 2 cases, the authors concluded that SIRT delivered via the bronchial arteries was technically feasible and that further evaluation of this technique as a potential treatment for pulmonary metastases

and locally advanced NSCLC, that are not suitable for curative therapy by conventional means is warranted in a prospective dose escalating clinical study.

4.3 Selective internal radiation therapy (SIRT)

SIR-Spheres® ^{90}Y 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 within 11 days, leaving only background radiation with no therapeutic value. SIR-Spheres® ^{90}Y 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® ^{90}Y 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). This allows the required patient specific yttrium-90 activity to be manipulated as a volume.

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 (21) (22) (23).

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

1. **Embolisation:** injection into the arterial tumour-feeding vessels of permanently embolic microspheres (SIR-Spheres® ^{90}Y 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® ^{90}Y resin microspheres deliver high dose beta irradiation to the tumour microvascular plexus and to tumour cells directly.

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 (21).
SIR-Spheres® ^{90}Y 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 tumours, with small amounts within the vasculature of normal parenchyma. The device is not phagocytized 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® ^{90}Y 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-tumouros cells.

5 Study device

5.1 Summary description of the investigational device and its intended purpose

SIR-Spheres® is a medical device consisting of biocompatible microspheres containing yttrium-90 with a size range of 20 to 60 microns in diameter. Yttrium-90 is a high energy pure beta radiation emitting isotope with no primary gamma emission. SIR-Spheres® microspheres themselves are a permanent implant. The device is provided in water for injection to allow measurement of desired activity as a volume in a syringe.

In the European Union (EU) SIR-Spheres® ^{90}Y 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'.

The planned study is the first clinical study which systematically assesses if SIRT is a feasible approach for local tumour therapy in the lung (feasibility study).

5.2 Manufacturer of the investigational device

Sirtex Medical Limited
Level 33, 101 Miller Street
North Sydney NSW 2060
Australia

5.1 Name of model/type for full identification

SIR-Spheres® Yttrium-90 Resin Microspheres with associated Delivery Apparatus

5.2 Traceability of the investigational device during and after the clinical investigation

The SIR-Spheres® ^{90}Y resin microspheres being supplied for this clinical study will be from batches of product approved for supply for the treatment of hepatic tumours, manufactured under the approved Sirtex Quality Management System processes and at the approved locations.

A detailed description of device accountability during this clinical trial is included in section 14.3 of this CIP.

5.3 Intended Purpose of the investigational device in the clinical investigation

The planned study is the first clinical study which systematically assesses if SIRT is a feasible approach for local tumour therapy in the lung (feasibility study). One of the questions addressed with the planned protocol relates to the feasibility of implanting the total prescribed radiation dose.

5.4 Populations and indications

SIR-Spheres® microspheres are an implantable therapeutic radioactive device that has been designed to treat patients presenting with liver cancer by delivering a cytocidal level of radiation to tumour cells in the liver while sparing the normal hepatic parenchyma.

In this clinical study the studied population will consist of patients with pulmonary metastases from histologically proven primary carcinoma of any origin (except from the central nervous system and lung), or primary non-small cell lung carcinoma. Patients present with stage IV disease in a oligometastatic pulmonary disease state that is not suitable for treatment by surgical resection, local ablation, radiation therapy, or other conventional techniques, and is either unsuitable or has failed all conventional systemic treatment options such as chemotherapy, immunotherapy or targeted therapy.

The ultimate decision to offer study inclusion based on oncological reasoning must be taken by the independent multidisciplinary, organ-specific tumourboard, for example the GI tumourboard for metastatic GI tumours, the sarcoma board for metastatic sarcoma, the lung tumourboard for bronchial cancer, and more.

5.5 Description of the investigational device

5.5.1 SIR-Spheres® Microspheres

SIR-Spheres® 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. This is a brachytherapy sealed source device.

The yttrium-90 has a purity specification of 999,900 ppm at reference, at (or after) time of manufacture of SIR-Spheres® microspheres. With a physical half-life of 64.1 hours, it decays to stable ^{90}Zr. In use requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days leaving only decaying radiation with no therapeutic value. SIR-Spheres® microspheres themselves are a permanent implant. Each device is for single patient use.

SIR-Spheres® ^{90}Y 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® ^{90}Y resin microspheres are classified as a sealed source brachytherapy device.

5.5.2 Packaging

Each device consists of sufficient microspheres to provide 3 GBq (+/-10%) at the equivalent time to 0900 hours, Australian Eastern Standard Time on the day of calibration (as shown on the label). The microspheres are suspended in sterile water for injection. Each vial of 3GBq is dispatched in a 10mL vial with a volume of 5mL (microspheres and water together).

The vial is contained in a lead pot which is further contained in an IATA-approved Type A bucket for shipping purposes.

The medical device accessory components are a Delivery Set plus V-Vial, both of which are sterile accessories that facilitate delivery.

5.5.3 Delivery Set

Designed to facilitate delivery, the delivery set is supplied as a sterile single use product. Made entirely from biocompatible materials, it consists of two separate pieces packaged together.
One is comprised of connected components as follows:

- three (3) clear tubes made from PVC with luer-lock connectors
- 1 x 21G x 7cm non-coring vascular access needle with an acrylic LL hub and siliconised stainless-steel shaft and protector cover
- 1 x three-way stopcock with a clear housing and rotating collar made from polycarbonate, handle made from polyethylene
- 1 x one-way normally-closed back check valve with a clear polycarbonate housing with silicone rubber diaphragm

The second piece is comprised of

- 1 clear PVC tube with Luer-lock connectors
- 1 x 21G x 7cm non-coring vascular access needle with an acrylic LL hub and siliconised stainless-steel shaft and protector cover
- 1 x one-way normally-closed back check valve with a clear polycarbonate housing with silicone rubber diaphragm

The assembled Delivery Set is placed in a poly bag and then packed in the medical grade clear low density polyethylene fronted pouch with an opaque polyester backweb and labelled “STERILE” with

lot number, date of manufacture and expiry date. The product label is attached to the opaque backweb of the pouch and Instructions for Use are placed in the pouch which is then heat sealed with an adequate peel tab at one end. The packaged product is then sterilized by gamma irradiation and packed into a shelf box.

5.5.4 V-Vial

Designed to facilitate delivery by assisting in the suspension of the microspheres, the V-Vial comprises the following biocompatible components:

- l x 10mL vial made from polycarbonate
- stopper made from neoprene
- aluminium crimp seal
- drawing-up needle (capped)

The assembled V-Vial is placed in a poly bag with the needle and then packed in the medical grade clear low density polyethylene fronted pouch with an opaque polyester backweb and labelled "STERILE" with lot number, date of manufacture and expiry date. The product label is attached to the opaque backweb of the pouch and Instructions for Use are placed in the pouch which is then heat sealed with an adequate peel tab at one end. The packaged product is then sterilized by gamma irradiation and packed into a shelf box. It is packaged separately from the delivery set to allow it to be used in a Nuclear Medicine (or equivalent) department for dose dispensing in advance of use.

5.5.5 Personal protection accessory devices

These include the following components made from acrylic as a beta- radiation blocking material:

- Delivery Box
- V-Vial holder
- Syringe shield

5.6 Summary of the training and experience needed to use the investigational device

Only interventional radiologist investigators with extensive experience in (super) selective bronchial artery angiography and radioembolization will deliver SIR-Spheres® ^{90}Y resin microspheres within this study.

Extensive experience in (super) selective bronchial artery angiography is required in order to:

1) perform meticulously the bronchial angiography and reliably identify any aberrant bronchial or other thoracic vessels that may be present and that may supply non-pulmonary tissues or organs; and
2) possess the necessary catheter expertise to prevent microsphere delivery to these aberrant vessels.

All investigators performing SIRT must be interventional radiologists with >10 years of work experience. A standard procedure protocol for the intervention will be described in a separate document ("SIRT Training Manual"). Compliance with the procedures will be mandatory.

In summary, physicians who conduct pulmonary SIRT must have as minimum the following qualifications:

- being specialized in radiology
- more than 10 years of work experience in interventional radiology

- having completed the Sirtex liver SIRT training program
- having conducted at least 30 liver SIRT therapies
- having conducted at least 30 selective bronchial artery catheterizations

A detailed description of pulmonary SIRT is contained in the document "SIR spheres microspheres training program – lung specific".

5.7 Specific medical or surgical procedures involved in the use of the investigational device

The treatment planning and implementation of ^{90}Y radioembolisation to the lung comprises several steps including assessment of bronchial artery anatomy, FDG PET/CT imaging to evaluate the baseline metabolic status of lung lesions, planning angiography evaluation, ^{99m}Tc-MAA and SPECT CT to assess the predicted distribution of ^{90}Y microspheres, dosimetry and dose calculation preparatory to ^{90}Y resin microsphere infusion, angiographic methodology during treatment and the measurement of post-treatment residual ^{90}Y activity. For a detailed description please refer to section 10.

6 Justification for the design of the clinical investigation

6.1 Preclinical assessment

Sirtex (manufacturer of SIR spheres® microspheres) studied the safety of the microspheres for tissue implantation in seven studies: four in vitro studies and three animal studies. All of these studies were conducted in compliance with GLP and the OECD Principles of GLP.

The non-radioactive product is considered to have permanent implantable characteristics for the microspheres themselves, with tissue contact. It is introduced initially using blood contact. The studies were selected to demonstrate that the implanted microspheres do not cause adverse reactions when in contact with tissues. The mutagenicity and chromosomal studies were undertaken as the microspheres are left in situ permanently. Hemocompatibility was required as spheres are delivered intra-arterially and therefore have initial contact with blood. Cytotoxicity was required to ensure that the microspheres themselves or anything possibly leaching from them were not toxic to cells.

The animal tests were conducted to evaluate local and systemic toxicity in intact animals (biological systems). The possibility of sensitization also required investigation.

The following table describes the 7 studies and their results:

1	**Mutagenicity: Bacterial Reverse Mutation Test (in vitro)(OECD 471 & 472)** Mutagenicity was assessed using the Bacterial Reverse Mutation Test utilising the strains Salmonella typhimurium TA 1535, TA1537, TA 98 and TA 100, and Escherichia coli WP2 uvrA. This test assesses the mutagenicity of a substance by its ability to revert specified bacterial strains from auxotrophic growth to prototrophy. It was conducted according to the requirements of the OECD regulatory guideline for testing chemicals, OECD 471 and 472 adopted May 26th, 1983. Positive controls consisted of direct acting mutagens and those that require metabolic activation. Direct mutagens were sodium azide, 9-aminoacrindine, 2-nitrofluorene and cumene hydroperoxide for S. typhimurium and 4-nitroquinoline-N-oxide for E. coli. The metabolically activated mutagen was 2-aminoanthracene for both bacterial strains. Rat cytochrome P450 mitochondrial fraction was the metabolic activation system used. The first experiment was by the plate incorporation method. If this was positive the second experiment would also be by the plate incorporation method. If the first experiment was negative the second experiment would be by the pre-incubation method. The mean and the

	standard deviation of the plate counts for each experiment were calculated and statistically assessed using a Dunnett's test. A positive result was a statistically significant increase in the numbers of revertants scored in two separate experiments. A negative result was no greater increases in revertants than would be expected from normal variation for any strain in either experiment. All positive controls gave results in the expected ranges indicating the strains used were sensitive to mutagens. *There were no statistically significant increases in revertants from SIR-Spheres® microspheres, thus this device is not mutagenic under the conditions of this test.*
2	**Mammalian Cell Cytogenicity (in vitro) (Chinese Hamster Ovary Cells)** Mutagenicity was also assessed using an in vitro cytogenetic test, which determines if mutagenicity (if present) is due to structural chromosomal damage. This was performed in mammalian cells (Chinese Hamster Ovary Cells). Mutagenicity after metabolic activation of the test substance was also assessed by using the rat cytochrome P450 mitochondrial fraction. Positive controls were mitomycin C (direct mutagen), and benzo(a)pyrene and cyclophosphamide were the metabolically activated mutagens. Scoring of chromosomal damage was by the ISCN classification. Any increase in number of aberrations was compared to negative control using a Fisher's Exact test. The positive controls caused statistically significant increases in aberrations scored, indicating sensitivity of the test system. *Under the conditions of this test SIR-Spheres® microspheres are not clastogenic.*
3	**Cytotoxicity (in vitro) (tested to ISO 10993-5)** Cytotoxicity was assessed by an in vitro cytotoxicity test, which assessed the potential cytotoxicity of leachable endogenous or extraneous substances on the microspheres in accordance with ISO 10993 Part 5. The cell lines used were mouse fibroblast L929 (ATCC, CCL1, NCTC clone 929). Phenol was the positive control and neat minimum essential medium (MEM) was the negative. Cells were examined microscopically after incubation with dilutions of the supernatant (water for injection) from the microspheres. The dilutions of supernatant used were 0.5%-2% v/v. *Under the conditions of this test, the microspheres leached no substance that altered cell morphology or caused any cytotoxic effects at concentrations of 0.5, 1 and 5 mg/mL.*
4	**Hemocompatibility (in vitro) (tested to ISO 10993-4)** Hemocompatibility was assessed according to ISO 10993 Part 4 'Selection of Tests for Interactions with Blood'. Potential endogenous or extraneous substances present in or on the Yttrium phosphate coated microspheres were tested, in vitro, for hemolytic activity against human erythrocytes. Both the negative and positive controls gave results within expected ranges. The test article vessels showed no significant hemolysis. The osmolality of microspheres, compared to 0.9% (w/v) sodium chloride, indicates that this has no effect on the hemolytic potential of the microspheres. Responses to the negative and positive controls were within expected ranges for the hemolysis test. All concentrations of the test article returned a hemolysis value below the 5% level. Hemolysis values below 5% are not considered indicative of hemolytic activity. *Under the experimental conditions employed, any potential leachable substances present in or on the microspheres demonstrated no hemolytic activity against human erythrocytes.*
5	**Intracutaneous Toxicity (Reactivity) (Rabbit) (tested to ISO 10993-10)** This was assessed with the Intracutaneous Injection Test in the Rabbit (ISO 10993 Part 10, March 1995). This test was conducted with a 50% v/v dilution of the microspheres in water, as the standard presentation will not traverse an intradermal needle. Three female New Zealand white rabbits were used. Each rabbit had 5 x 0.2 mL of the test device injected intradermally on one side of the midline of the back and 5 x 0.2 mL of water for injection as the controls on the other side. At the completion of the observation period (72 hours) the

	primary irritation scores and the primary irritation index were calculated as per ISO 10993-10. *There was negligible response to the device indicating that it is not locally irritant or toxic.*
6	**Systemic Toxicity of Potential Leach Products (Mouse) (Tested to ISO 10993-11)** This was assessed with the Systemic Injection Test in the Mouse. The methodology was from ISO 10993 Part 11 Biological evaluation of medical devices, Tests for systemic toxicity and also the United States Pharmacopoeia 23 1995 for assessment of biological reactivity, in vivo, Monograph <88>, page 1699. This test was conducted to evaluate systemic responses to extracts of the microspheres following intravenous and intraperitoneal injection. Polar (water for injection) and non-polar (cottonseed oil) extracts were prepared. Blanks of both extracts were also prepared. A fifth solution (Solution A), being neat supernatant from centrifuged microspheres was also used. The four extract preparations were each tested in five mice, all of which received only a single systemic injection. Solution A was tested in four mice. Doses were all 50 mL/ kg. Animals were observed over a 72 hour period for signs of toxicity. There were no differences between blanks and extracts and all animals in all groups maintained weight and a healthy appearance throughout. *Intravenous administration of the water for injection in which the microspheres are supplied failed to produce apparent toxic effects. Under the conditions of this study, SIR-Spheres® microspheres do not leach or produce any toxic substances that are released systemically.*
7	**Maximum Sensitisation (Guinea Pig) (tested to ISO 10993-10)** Sensitising ability was assessed with the maximum sensitisation test in the guinea pig. This test evaluates the potential of the device to cause a delayed dermal hypersensitivity/Type 1V immune response. The procedures used were based on the methods described in ISO 10993 Part 10 Biological Evaluation of Medical Devices: Test for Irritation and Sensitisation of March 1995. In the main study, 30 female albino guinea pigs were allocated to a group of 20 test animals and a group of 10 control animals. The topical range finding study in four animals indicated that the microspheres were non-irritant. The lack of primary irritancy allowed assessment for delayed sensitivity. Following challenge with undiluted test article, 3 of the 20 animals in the test group gave positive skin responses (scores of 1) at either the 24 or 48 hour examinations, giving a response incidence of 15%. None of the animals in the control group responded positively to undiluted test article at any examination, giving a response incidence of 0%. None of the animals in the test or control group exhibited positive responses to water. The lack of response in control animals to dermal application of undiluted microsphere suspension confirmed that the test article was not a primary skin irritant. The weak positive responses in the test group were therefore indicative of a delayed dermal hypersensitivity immune response according to the criteria described in ISO 10993. *The device is therefore considered a mild sensitizer under the condition of this study.*

Two independent animal studies from Switzerland came to comparable results after radioembolisation of the porcine kidney with ^{90}Y labelled resin particles (to note: these studies did not use the marketed SIR spheres® microspheres). Schubiger et al. (24) studied ^{90}Y labeled resin particles which were suspended in a glucose/dextran solution and infused into the kidneys of 3-month-old pigs (tumour model). Both kidneys of each animal were embolized with particles, but only one with active (^{90}Y loaded) particles and the other, for comparison, with inactive particles. There was a clear shrinkage of the ^{90}Y -treated kidneys with a reduction in weight of up to 50%. Histologically, the ischemic lesions

(infarcts and atrophy) were clearly more pronounced and extensive in the ^{90}Y -embolized kidneys than in the non-radioactive embolized kidneys. Furthermore, severe arterial wall changes and fibrotic necrosis due to radiation damage were observed in the ^{90}Y -treated kidneys. The authors concluded that with intra-arterially applied particles a dose of about 100 Gy is sufficient to completely destroy tissue-specific structures. Complications due to acute necrosis or inflammatory reactions were not observed.

Zimmermann et al. (25) performed an experimental study using superselective administration of ^{90}Y particles to deliver up to 100 Gy to the porcine kidney. Patterns and severity of damage in test organs were compared with controls, and the feasibility of this model is discussed. Bio-Rex 70 particles were applied via selective catheterization of the renal artery. Four pigs received inactive particles and four pigs received active particles. Organ distribution and shunting of yttrium-90 were determined, and kidney damage patterns were histologically analyzed. In addition to tissue shrinkage from mechanical obstruction, considerable damage ensued mainly by radiation-induced arterial necrosis and arteritis.

In summary, the preclinical studies show SIR-Spheres® ^{90}Y resin microspheres are hemocompatible, non-cytotoxic, non-mutagenic, non-toxic locally or systemically and are a mild sensitizer in the guinea pig under the conditions of the test.

After systemic IV injection in mice, no toxic effects of the non-radioactive resin microspheres were observed.
In the mouse experiment, the microspheres were trapped in the first microvascular bed after injection. (after IV injection the first microvascular bed is the the pulmonary artery tree of the lung).
Although, in the planned clinical study, the microspheres will be injected into the bronchial artery (and not into the pulmonary artery), the results of the preclinical studies are assumed to be transferable to the planned clinical study and to provide sufficient evidence of the non-toxic effect of the resin microspheres in the lung.

6.2 Clinical data

6.2.1 Data on ^{90}Y labeled SIR spheres microspheres in the Lung

The SIRT concept is based on the injection of microspheres into the arterial system with embolization of the capillaries. Once located in the distal microvasculature, SIR-Spheres® microspheres deliver high dose beta irradiation from decay of ^{90}Y which is attached to the microspheres. Preferential localization of the microspheres in tumour is due to (super-) selective injection techniques and the higher perfusion of tumour (compared to normal tissue).

Ricke and collaborators reported the first-in-human use of SIR-Spheres® ^{90}Y resin microspheres delivered via the bronchial artery in two patients exhibiting diffuse pulmonary metastases from primary colorectal and primary renal cell cancer (19):

- Case 1
  A 45-year-old female patient was initially diagnosed with colorectal cancer in 2009. Following a right hemicolectomy she developed lung only metastases in 2010 and received FOLFIRI and cetuximab as well as 5FU/LV and panitumumab. A resection of lung metastases in 2011 was complicated by sepsis and multi-organ failure. She recovered but presented with progressive lung disease in both lobes in 2012. In this chemotherapy-refractory (i.e. salvage) setting, the multi-disciplinary team decision was to offer loco-regional therapy with SIRT to the part of the lung that was affected most. The remaining lesions in the untreated areas could undergo local ablation afterwards, and the lung segments not treated with SIR-Spheres® ^{90}Y resin microspheres were intended to serve as reserve capacity in case radiation pneumonitis developed.

  Pulmonary function tests (including vital capacity and forced expiratory volume FEV1) revealed values within normal limits. The patient was evaluated for SIRT by applying 21

MBq ^{99m}Tc-MAA via the left bronchial artery supplying segments 1 – 3 and the upper proportion of segment 6. The anatomical work-up of the bronchial arterial system was identical to a search in patients with suspected bronchial artery bleeding. For the identification of the bronchial arterial anatomy, a standard 5F guiding catheter was used. For the selective catheterization of the bronchial arteries, a hydrophilic 0.018 inch microcatheter was used. SPECT-CT demonstrated strong uptake of ^{99m}Tc-MAA in the lung nodules of these segments ranging from 4 mm to 5 cm maximum diameter.

Dosimetry for SIRT assumed a conservative scenario of homogenous dose distribution in the targeted lung, i.e. tumour uptake ratio of 1:1. Following the recommendations of Ho and collaborators, the maximum dose exposure of one lung was limited to 30 Gy (26). CT-based volumetry served to determine the appropriate prescribed activity of SIR-Spheres® ^{90}Y resin microspheres. Subsequently, 180 MBq of SIR-Spheres® ^{90}Y resin microspheres was injected into the feeding bronchial artery of the targeted segments. However, in contrast to the conservative dosimetric assumptions of a tumour uptake ratio of 1:1, post-SIRT ^{90}Y -PET and bremsstrahlung SPECT revealed a dose uptake that was visually limited to the metastases. Pronounced yttrium-90 activity was detected in neither lung parenchyma nor the chest wall.

Physical examination and lung function tests remained unchanged and within normal limits at 4 weeks follow-up. CT between 4 and 12 weeks revealed no signs of radiation pneumonitis. The lung nodules treated with SIR-Spheres® ^{90}Y resin microspheres showed stable disease or partial remission according to RECIST 1.1 criteria, whereas the untreated nodules in the contralateral lung showed progressive disease. The patient received local ablations of the remaining tumours and was alive however, progressive with new metastases, 9 months after her initial presentation.

- Case 2

  A 69-year-old male patient was initially diagnosed with renal cell carcinoma in 2006 and subsequently developed lung metastases in 2008. He had undergone systemic treatments with sunitinib and sorafenib but due to severe side effects these therapies were discontinued. A brain metastasis was resected surgically. After local ablations of lung metastases in 2009 and 2011, the patient presented with diffuse lung metastases in both upper lung lobes not amenable to further local ablation or surgery. The patient declined further systemic therapies due to his history of toxicities from targeted agents. The multi-disciplinary team decision was to offer cytoreduction as indicated by the ESMO guidelines specifically for renal cell cancer with lung only disease, using a combination of a loco-regional therapy with SIRT and further local ablation if necessary.

  The patient was evaluated for SIRT of the lung. Respiratory function tests were normal, and angiography revealed strongly hyperperfused lung metastases. Angiographic work-up and the assumptions for dosimetry were the same as described in case 1. 41 MBq ^{99m}Tc-MAA was injected via a microcatheter into the right bronchial artery feeding segments 4 – 6, as well as a minor proportion of the mediastinum. One week later, SIRT was performed by injecting 195 MBq of SIR-Spheres® ^{90}Y resin microspheres into the feeding bronchial artery.

  Lung function tests and CT imaging 4 weeks post-SIRT revealed no functional impairment or signs of radiation pneumonitis. Subsequently, evaluation of the left upper lung lobe segments 1 – 3 with 80 MBq ^{99m}Tc-MAA was undertaken. This was followed by treatment with a further 180 MBq of SIR-Spheres® ^{90}Y resin microspheres a week later. Clinical examinations as well as CT follow-up 4 weeks post-second-SIRT did not show any signs of functional or morphological impairment in either lung. The lesions treated with SIR-Spheres® ^{90}Y resin microspheres remained stable or displayed partial remission according to RECIST 1.1, whereas the lesions not treated with SIRT were slowly progressive. Before further local

ablations were scheduled as initially intended, the patient died of unknown causes 6 months after SIRT.

From the 2 cases, the authors concluded that SIRT delivered via the bronchial arteries was technically feasible and that further evaluation of this technique as a potential treatment for pulmonary metastases and locally advanced NSCLC, that are not suitable for curative therapy.

The rationale for the planned study has been developed on the basis of the following considerations:

a) the concept of vascular embolization is universal and works in all human tissues
b) clinical evidence is available on the safety of non-radioactive human bronchial artery embolization for the treatment of hemoptysis
c) chemoembolization together with ^{125}I seed implantation has been reported as efficacious and safe in human patients
d) data on the radiosensitivity of the lung are available from external beam radiation and the inadvertent deposition of ^{90}Y microspheres in the lung as a complication of hepatic radioembolization

Below, these aspects are discussed in more detail:

a) The concept of capillary blockade works whenever the injected microsphere is larger than the diameter of the smallest vessels, irrespective of the tissue type. The principle of capillary blockade by microspheres has been introduced into research in 1967 by Rudolph and Heymann (27) for examining regional blood flow in sheep fetuses in utero, and, thereafter, became an essential tool in cardiovascular research. In research, microsphere distribution is an accepted gold standard method for measurement of local perfusion, the deposition of microspheres blocking the microvasculature accurately mirrors the distribution of regional blood flow.

b) Embolization of bronchial arteries with different technologies is an effective and safe therapeutic procedure in patients with hemoptysis. Its use was first reported by Remy et al. in 1973 (28). Since then, bronchial artery embolization (BAE) has emerged as a standard therapy of hemoptysis (29). In 2002, Yu-Tang Goh et al. (30) reviewed their 6 years' experience with BAE. In their series, 134 patients were treated for hemoptysis; of these, 116 were followed up for 1- 66 months (median 9.5 months), and 103 required embolization. Embolization was done with polyvinyl alcohol particles alone or in combination with gelfoam. Sixteen patients required multiple embolization sessions. No major complications were encountered. The authors conclude that embolization is effective for treatment of moderate to massive hemoptysis.

Maleux et al. (31) conducted a retrospective study of patients referred for *repeat* BAE to manage recurrent hemoptysis after initial successful embolization. BAE was performed in 223 patients; 36 (16.1%) of these patients underwent 59 repeat BAE procedures because of recurring symptoms. Most patients (64%) underwent 2 embolization procedures owing to vessel recanalization (71%) as the most frequent pathophysiologic mechanism of recurrent hemoptysis. No serious adverse events requiring prolonged hospital stay were noted. The authors conclude repeat BAE for recurrent hemoptysis after initial successful BAE is safe and efficacious, especially in patients with bronchiectasis as the underlying lung disease. Other authors were able to show that BAE can be safely done with different embolization material (32) (33) (34)

Yoon et al. (35), in their review article, summarize the reported knowledge of BAE complications: According to their review, chest pain is the most common complication, with a reported prevalence of 24%–91%. The authors regard chest pain as likely related to an ischemic phenomenon caused by embolization; chest pain was usually transient. In addition, dysphagia due to embolization of esophageal branches was encountered with a reported prevalence of 0.7%–18.2%. Dysphagia also regresses spontaneously. Subintimal dissection of the aorta or the bronchial artery during BAE is a minor complication, with a reported prevalence of 1%–6.3%. There are usually no symptoms or

problems related to the subintimal dissection. Comparable complication rates were published more recently by Panda et al. (36).

The most disastrous complication of BAE is spinal cord ischemia due to the inadvertent occlusion of spinal arteries. The prevalence of spinal cord ischemia after BAE is reported to be 1.4%–6.5%. According to Yoon et al. (35), the visualization of radicular branches on bronchial or intercostal angiograms is not an absolute contraindication for BAE; however, when the anterior medullary artery (artery of Adamkiewicz) is visualized at angiography, embolization should not be performed. In this study, these patients will be excluded.

Other rare complications include aortic and bronchial necrosis, bronchoesophageal fistula, non–target organ embolization (e.g., ischemic colitis), pulmonary infarction, referred pain to the ipsilateral forehead and orbit, and transient cortical blindness. It is hypothesized that cortical blindness develops because of embolism to the occipital cortex, either via a bronchial artery–pulmonary vein shunt or via collateral vessels between the bronchial and vertebral arteries. Despite the complications, the authors conclude that bronchial and non-bronchial systemic artery embolization is a safe and effective nonsurgical treatment for patients with massive hemoptysis.

c) Recently, Chen et al. (37) investigated the short-term efficacy and safety of bronchial artery chemoembolization (BACE) combined with radioactive iodine-125 seed implantation in the treatment of non-small cell lung cancer (NSCLC). Sixty-two (62) stage III-IV NSCLC patients were divided into Groups A and B. Thirty patients were treated with BACE combined with radioactive iodine-125 seed implantation in the Group A, and 32 patients were treated with BACE alone in the Group B until disease progression. Efficacy, incidence rate of adverse drug reactions, and survival rate were compared between the two groups. In their study, the local control rates of Groups A and B were 90% and 59.3%, respectively ($P < 0.05$). The progression-free survival of the study group and the control group was 12.6 and 8.2 months, respectively; the median survival time of the Groups A and B was 644 and 544 days, and the difference was statistically significant ($P = 0.034$). The authors conclude that BACE combined with radioactive iodine-125 seed implantation was safe and effective in the treatment of advanced NSCLC, with an efficacy superior to that of single BACE.

d) Data on radiosensitivity of the lung are important in the context of the planned study to avoid potentially life-threatening pulmonary radiation damage. The maximum tolerated dose to lung tissue can be extrapolated from EBRT (external beam radiation therapy) data. In a recent publication, Cremonesi et al. [14] provided such extrapolations for the lung: for homogeneous irradiation of 1/3 of the lungs by EBRT, TD5/51 and TD50/5 were reported as 44 Gy (Gray) and 65 Gy, respectively. For radioembolization, their extrapolation provided values of 47 Gy (TD5/5) and 62 Gy (TD50/5). For radioembolization of the total lung, the respective values are 23 Gy and 30 Gy.

The calculation from Cremonesi et al. (38) can be compared to clinical data from the use of SIRT for treatment of primary and secondary liver malignancies. In the treatment of liver malignancies, shunted microspheres may be trapped in the lung and result in pulmonary toxicity. This type of pulmonary toxicity is rare. Leung et al. (39) reported the occurrence of radiation pneumonitis in three patients for lung doses (total lung irradiation) between 25 Gy and 36 Gy. The same authors reported signs of radiation pneumonitis in three further patients after treatment with a combination of SIR-Spheres® microspheres and inert particles (total lung dose=10 – 25 Gy). These values are in good agreement with the data from Cremonesi et al. (38).

Further data are available for another type ^{90}Y microsphere based on glass (40). From a series of 403 patients receiving liver SIRT, 58 received >30 Gy cumulative lung dose. Lung imaging was available in 53 of these 58 patients. Ten (10) of the 53 patients exhibited lung imaging findings like pleural effusions, atelectasis, and ground glass attenuation. Absorbed doses to the lungs higher than 100 Gy

[1] tissue tolerance dose; TD 5/5 defines the dose that leads to serious complications within 5 years in a maximum of 5% of patients; TD 50/5 leads to serious complications in a maximum of 50% of treated patients

were tolerated in individual cases without clinical evidence of adverse events. The data from Salem et al. (40) suggest that the lung may be more radiation resistant in clinical SIRT than presumed by Cremonesi et al. (38) from the extrapolation of EBRT data based on the assumption of homogeneous lung irradiation.

In summary, the available data show that the concept of bronchial artery embolization has a positive benefit-risk ratio in patients with hemoptysis. The combination of bronchial artery chemoembolization with ^{125}I radioactive seed implantation has been successfully used in patients with non-small cell lung cancer. Available data allow estimating irradiation to the lung during pulmonary SIRT, and to exclude to the extent possible radiation-associated pulmonary failure.

Together, the available evidence is regarded as sufficient to justify the planned clinical study using radioembolization in patients with lung tumours.

6.3 Benefit-risk assessment

6.3.1 Anticipated clinical benefits

Patients for whom no additional anti-tumour treatment is indicated oncologically from the perspective of a multi-disciplinary organ-specific tumourboard (for example, sarcoma board, GI board, lung board for bronchial cancer) will be included into this clinical study. Participation in this clinical study may provide an additional treatment alternative beyond current standard therapy.

It is possible, that pulmonary SIRT effectively reduces tumour volume in the lung and contributes to an improvement of symptoms and quality of live in the treated patients. It is further possible that the reduction of tumour mass may contribute to longer overall survival.
Only patients who are considered appropriate by the respective tumourboard will be included. The patients will be presented in the tumourboard and whether a patient can be included doesn´t depend solely on whether or not there is any standard therapy for this patient, but rather by oncological reasoning. Patients will only be included if the tumourboard judges that the potential reduction of tumour mass in the lung as a consequence of study participation is expected to provide clinical benefit to the patient. The tumourboard provides written consent that the patient is suitable for study inclusion (see also 8.2).

6.3.2 Anticipated adverse device effects

- **Frequent:**
  - Symptoms of mild post embolisation syndrome:
    - fever, nausea, vomiting; pain which can radiate typically to chest, back or neck. Also includes associated symptoms such as discomfort, hypertension, tachycardia, diaphoresis
- **Probable**
  - Symptoms of mild post embolisation syndrome:
    - confusion, fatigue, weakness
  - Radiation pneumonitis, radiation-induced lung fibrosis, progressive pulmonary insufficiency (Probable in case of unselective administration into bronchial arteries.)
  - Spinal Cord Injury (Anticipated if SIR-Spheres® are inadvertently implanted through anastomoses or reflux into anterior spinal artery. Frequency estimate inferred from experience with bronchial artery embolisation, where the frequency of spinal cord ischaemia was 0.6-6.5% (35) (36). Risk in POEM study is considered even lower than for bronchial artery embolisation due to smaller amount of administered material.)
  - Pleural effusion; hemoptysis; lung infection (e.g., pneumonia, abscess, empyema)
  - Pericarditis, pericardial effusion (Anticipated if SIR-Spheres® are inadvertently implanted through anastomoses to coronary arteries.)
- **Occasional**

  - Symptoms of mild post embolisation syndrome:
    - Dehydration with sequelae including acute renal failure
  - Hematological complications (transient and reversible lymphopenia or neutropenia (including febrile neutropenia), pancytopenia as a result of bone marrow suppression
  - Injury to other organs, e.g. stomach, liver (Anticipated only in case of inadvertent implant of SIR-Spheres® through anastomoses or due to reflux)
- **Improbable**
  - Transient ischemia / stroke (stroke is a very rarely reported complication of bronchial artery embolisation (41). Risk in POEM study is considered even lower than for bronchial artery embolisation due to smaller amount of administered material.)

6.3.3 Residual risks associated with the investigational device

All identified unacceptable hazards have been addressed and control strategies are in place to render the hazard acceptable. It is concluded that there are no unacceptable hazards remaining and the hazards are expected to be acceptable for the patient population concerned if benefits of treatment can be demonstrated. Therefore, the benefits of SIRT (using SIR-Spheres® microspheres plus Delivery Set and V-Vial) are expected outweigh the risks in relation to the patient population being treated.

6.3.4 Risks associated with participation in the clinical investigation

- **Probable**
  - Bronchial artery via brachial artery angiographies are required as part of SIRT procedure with potential for adverse events such as: vessel dissection or rupture, site infection, contrast allergy, thrombosis, artery spasm, nerve damage etc.
- **Occasional**
  - Series of CT Scans required post-SIRT to assess tumour response which gives additional patient radiation exposure
  - Cancer patients are pre-disposed to lower limb DVT with related potential for pulmonary embolus
  - ^{99m}Tc-MAA scan is required during patient work-up. This has the potential to cause systemic reactions such as fever, hypotension, rash, allergic reactions

6.3.5 Possible interactions with concomitant medical treatments

Possible interactions include (1) anticoagulation, e.g. caused by platelet aggregation inhibitors, (2) an increase of radiosensivity caused by chemotherapeutic substances and (3) an antiangiogenic effect of chemotherapeutic therapy.

(1) In order to prevent a hemorrhage at the puncture site for the catheter due to anticoagulation, platelet aggregation inhibitors will be discontinued 8 days bevor the SIRT intervention. If necessary, a risk-adapted change to prophylactic low molecular weight heparin therapy will be initiated.
The described procedure corresponds to the recommendations of the “Guidelines for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery“ of the European Society of Cardiology (42).

(2) An increase of radiosensivity has been described for different chemotherapeutic substances as Zysplatin, 5FU, Irinotecan, and Erbitox. According to the experiences with SIRT in the liver indication, a 14 day washout phase is standard in clinical routine procedures.
In this study, a washout window of at least 45 days after completion of prior therapy and start of SIRT treatment has to be respected to exclude interaction of the local radiation with any remaining previous medical treatment. The multidisciplinary team may recommend a washout period prolongation (see section 9.1).

(3) The antiangiogenic effect of vascular endothelial growth factor (VEGF) inhibitors, can be seen after e.g. Bevacizumab (Avastin) therapy. In order to avoid an effect on SIR-sphere location in the tumour, a washout window of 6 weeks (42 days) has to be warranted. In this study, the determined washout window of 45 days after completion of prior therapy and start of SIRT exceeds this recommended wash-out period and therefore meets this recommendation.

6.3.6 Steps that will be taken to control or mitigate the risks

In order to mitigate the possible risk of unintended (i.e. non-targeted) delivery of SIR-Spheres® ^{90}Y resin microspheres to excessive normal lung parenchyma or to organs or tissues outside the lung, only interventional radiologist investigators with extensive experience in (super)selective bronchial artery angiography and radioembolisation will deliver SIR-Spheres® ^{90}Y resin microspheres within this study. Extensive experience in (super)selective bronchial artery angiography and radioembolisation is required in order to: 1) perform meticulously the bronchial angiography and reliably identify any aberrant bronchial or other thoracic vessels that may be present and that may supply non-pulmonary tissues or organs; and 2) possess the necessary catheter expertise to prevent microsphere delivery to these aberrant vessels.

In order to mitigate the risk from radioembolistion for patients, the study SPONSOR regards a pre-SIRT "simulation" of microsphere blockade using ^{99m}Tc-MAA (macro-aggregated albumin) scintigraphy as indispensable. During this scintigraphic study, the effect of microsphere blockade is studied in the same patient who will later receive pulmonary SIRT. In contrast to SIRT, vascular blockade by ^{99m}Tc-MAA is reversible and does not result in persistent side effects (^{99m}Tc-MAA of the lung is a routine nuclear medicine procedure in patients with, e.g., suspected lung embolism).

The distribution of ^{99m}Tc-MAA will be used to assess the extent of uptake in the tumour(s) and normal lung parenchyma in the target lung segment, and the presence of any uptake in non-target lung segments or other non-pulmonary structures (e.g. the chest wall, spinal cord) through undetected micro branches of the targeted bronchial artery, downstream of the micro-catheter position. Any increased risk for non-target delivery will be assessed for every individual patient which in some cases may result in exclusion of this patient from SIRT. The pre-SIRT ^{99m}Tc-MAA scintigraphy will provide the required information regarding the integrity of the lung vessels in tumour lesions for each individual patient. Additionally, dynaCT examinations will be performed in case of untypical arterial supply and coil embolization of aberrant bronchial arteries will be performed.

Another strategy to control the risk of possible risk of unintended (i.e. non-targeted) delivery of SIR-Spheres® ^{90}Y resin microspheres to normal lung parenchyma are the limitation of treatment to max. 40% of total lung volume to ensure adequate margin of safety to prevent fatal outcome even in case of total functional loss of treated lung volume plus injury of some adjacent tissue.
The intervention is done under sight control and with a "sandwich technique" of sequential spheres application.

The validity of these approaches has been demonstrated in one publication presenting the compassionate use of SIR-Spheres® microspheres in the lung for 2 patients with advanced renal or colorectal metastases in the salvage situation [17]. As illustrated in the ^{90}Y -PET images following the administration of SIRT, there was exquisite uptake of microspheres to the tumour, with no exposure to normal lung parenchyma.

The required CT scans, Tc-MMA scans and bronchial artery angiography as part of the clinical investigation are routine non-unique procedures with established risk profiles.
The increased risk of venous thromboembolism (VTE) is a standard risk of patients with advanced cancer. VTE prophylaxis will be performed according to clinical standards.

In this study, the mentioned risks are expected to be acceptable for the patient population concerned if benefits of treatment can be demonstrated.

7 Study Objectives and Hypotheses

7.1 Primary objective

- Feasibility

Pulmonary SIRT will be regarded as feasible if the first dose level can be completed without reaching dose-limiting toxicity in more than 1/3 patients or imminent stasis in more than 3/6 patients.

A patient is regarded to have reached imminent stasis if more than 50% of targeted segment/s present with imminent stasis.

7.2 Secondary objectives

- Safety and Toxicity (according to CTCAE v5.0)
- Tumour Response Rate
- Time-to-progression in the targeted lesions
- Overall Survival
- Quality of Life

8 Overview of methodology and design

8.1 Study design

The study will be organized as multi-center, single arm clinical trial in one country.

It is a prospective, feasibility and dose escalation study of selective internal radiation therapy (SIRT) using SIR-Spheres® ^{90}Y resin microspheres as a treatment for patients with primary or secondary lung tumours who have failed or are not suitable for any standard-of-care anti-tumour treatment, both locally and systemically.

The primary endpoint of this clinical study is feasibility. Safety, toxicity, potential effectiveness and the impact on quality of life are secondary endpoints in the study. The study aims to recruit a minimum of 18 patients.

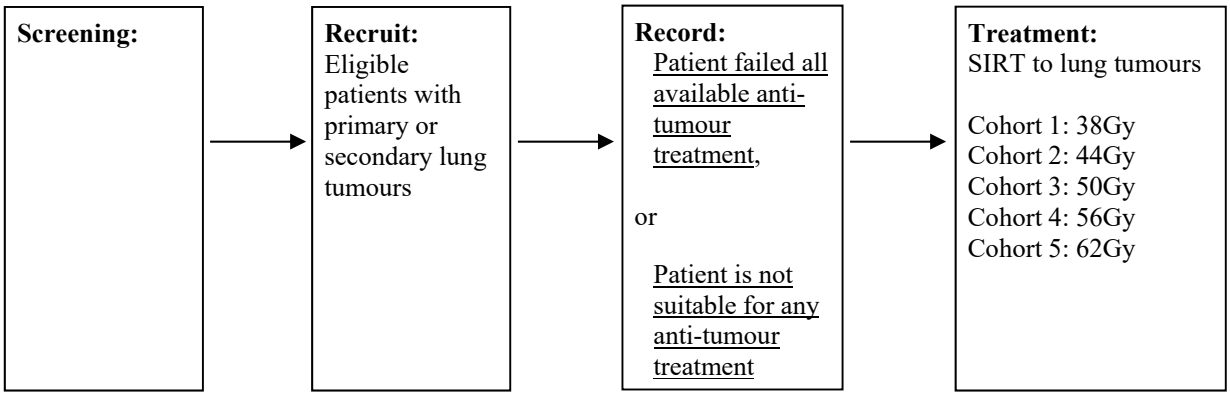
There will be no comparator nor will any blinding or randomization be applied.

Patients will be recruited into five cohorts comprising the following radiation doses to the targeted tumour-containing lung segment(s):

- Cohort 1: 38Gy
- Cohort 2: 44Gy
- Cohort 3: 50Gy
- Cohort 4: 56Gy
- Cohort 5: 62Gy.

Treatment will be limited to 40% of the total lung volume (in other words, treatment will not be limited to either the left lung or the right lung).

If a lesion could not be safely treated according to the investigator at an assigned dose level, this lesion should not be considered for treatment in the study.



This clinical study is a feasibility and dose escalation study of SIRT using SIR-Spheres® ^{90}Y resin microspheres as a treatment for patients with primary or secondary lung tumours. One of the questions addressed with this Clinical Investigation Plan relates to the feasibility of implanting the total planned radiation dose. Safety and efficacy of pulmonary SIRT will be assessed in an exploratory way to provide data on a potential clinical usefulness of the method. The results from this clinical study are required for planning of future clinical studies which will address safety and effectiveness systematically.

The study will be conducted as a radiation dose escalation study and will recruit patients into five dose escalating cohorts of 3 – 6 patients, depending on the toxicities observed in each cohort.

8.2 Radiation Dose Escalation Plan

Maximum dose in pulmonary SIRT is expected to be limited by 2 factors: (1) dose-limiting toxicity, and (2) imminent stasis which prevents the injection of the prescribed activity.

Based on these factors, the guiding principles for the dose-escalation scheme are as follows:

- The Maximum Tolerated Dose (MTD) is the highest dose level at which less than 1/3 of patients experience dose-limiting toxicity.
- The Maximum Feasible Dose (MFD) is the dose level at which at maximum 50% of patients present with imminent stasis.

A patient is regarded to have reached imminent stasis if more than 50% of targeted segment/s present with imminent stasis.

The rules for MTD follow the 3+3 design frequently used in cancer studies:

Patients will be recruited into five dose escalating cohorts: 38Gy, 44Gy, 50Gy, 56Gy and 62Gy radiation dose to the targeted tumour-containing lung segment(s).

The following table describes how the radiation dose will be escalated in successive cohorts:

Cohort Number	Planned Radiation Dose to Targeted Lung Segment	Number of Patients in Cohort
1	DL -2: 38Gy	3 – 6
2	DL -1: 44Gy	3 – 6
3	DL 0: 50Gy	3 – 6
4	DL +1: 56Gy	3 – 6
5	DL +2: 62Gy	6

- At least three patients will be recruited to each dose level, the time period between inclusion of consecutive patients at the same dose level will be at least 1 week,
- Protocol treatment will begin with cohort number 1,
- If 0/3 patients experience DLT within the first 30 days after SIRT, then 3 patients will be recruited at the next highest dose level,
- If 1/3 patients experience DLT within the first 30 days after SIRT, then 3 additional patients will be recruited to that dose level for a total of 6 patients in the cohort. If 1/6 patients experience DLT, then dose escalation will continue. If ≥ 2/6 patients experience DLT, then that radiation dose will exceed the maximum tolerated dose (MTD),
- If 2/3 patients experience DLT within the first 30 days after SIRT, then that radiation dose will exceed the MTD.
-

Additional criteria related to MFD:

- The target is to study at minimum 3 patients without imminent stasis at each dose level,
- For each patient with imminent stasis, one additional patient will be recruited into the same dose level (up to a maximum of 6 patients per dose level),
- Recruitment at a given dose level will be stopped and the next dose level started if 3 patients were treated without imminent stasis and without reaching MTD,
- If 1 of 3 patients without imminent stasis exhibits DLT while the remaining (up to) 3 patients at the same dose level show imminent stasis, then this dose level is defined as MFD/MTD.
- If more than 3 of 6 patients present with imminent stasis at a given dose level, then this dose level exceeds MFD.

In order to ensure that a sufficient number of patients is included into this study to gain experience on feasibility, safety, and effectiveness of pulmonary SIRT, the following additional rule has been added:

- If, at the first dose level, 4 or more patients develop imminent stasis without reaching the criteria for DLT, then another 6 patients shall be studied at the same dose level.

Dose limiting toxicity will be defined as any ≥ grade 3 toxicities occurring during the first 30 days after the administration of SIR-Spheres® ^{90}Y resin microspheres that are judged as possibly, probably, or definitely related to SIRT. AE grading will follow the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version (CTCAE v5.0).

In hepatic radioembolisation with ^{90}Y resin microspheres, common side effects relating to a form of post-embolisation syndrome (pain related to catheterisation, fatigue, nausea, fever) is common and self-limiting. Given the patient population and the known side effects of the application of the treatment, these are exempted in the definition of dose limiting toxicity as a false negative conclusion might be obtained as the known side effects might potentially incorrectly conclude the study treatment as negative (if self-limited).

For a better comprehension of different study scenarios the number of patients per dose level as a function of stasis and dose-limiting toxicity (DLT) is summarized in Table 1; the different scenarios for MTD and MFD are summarized in Table 2.

Table 1: number of patients per dose level as a function of stasis and DLT

scenario	number of patients with stasis (of all patients treated at the respective dose level)	number of patients with DLT (of all patients treated at the respective dose level)	number of patients at the respective dose level
1	0	0	3
2	1	0	4
3	2	0	5
4	3	0	6
5	0	1	6
6	1	1	6
7	2	1	6
8	3	1	6
9	0-3	2	2-6*
10	4	any	4-6#

* the study is stopped once 2 patients exhibit DLT at the same dose level
# the study is stopped once 4 patients exhibit stasis at the same dose level

Table 2: Scenarios for MTD and MFD

scenario	number of patients with stasis*	number of patients with DLT	result
1	0-3	0 of 3-6 patients	go to next dose level
2	0-2	1 of 3-6 patients	go to next dose level
3	3	1 of 3 patients with stasis	go to next dose level
4	3	1 of 3 patients without stasis	study stop (MFD/MTD)
5	0-3	≥2 of 3-6 patients	study stop (MTD)
6	4#	0-1 of 6 patients	study stop (MFD)
7	4#	≥2 of 6 patients	study stop (MTD)

* for each patient with stasis, one additional patient is included at the same dose level (until the maximum of 6 patients per dose level is reached)
# the study is stopped once 4 patients exhibit stasis at the same dose level

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be installed. The DSMB will be composed of 1 nuclear medicine physician, 1 pulmonologist (Prof. Dr. Rudolf Huber), 1 interventional radiologist, 1 radiotherapist and 1 medical ethicist. Members of the DSMB must be independent. No investigator of the POEM trial and no member of any local POEM study team is allowed to serve as member of the DSMB.

The tasks of the DSMB are

- to continuously monitor safety and toxicity
- to determine at each dose level if Maximum Tolerated Dose (MTD) or Maximum Feasible Dose (MFD) has been reached. If MTD/MFD has been reached the study will be stopped.
- to determine at each dose level, if an additional 3 patients have to be studied at the same dose level
- to determine that progression to the next dose level is justified.
- to stop the study once 2 patients exhibit DLT at the same dose level
- to stop the study once 4 patients exhibit stasis at the same dose level

Details, e.g. frequency and method of meetings, documentation, etc., will be stated in a separate document (Study Management Committee Charter).

Before the second patient will be enrolled in the POEM study all safety data from the first patient will be submitted to the DSMB. The DSMB will issue a statement on safety and efficacy of the study and will recommend the inclusion of additional patients. After the treatment of the first four patients all safety event data will be forwarded again to the DSMB and the DSMB will give a statement concerning the inclusion of further patients.

The DSMB will review the data whenever additional patients have completed their first 30 days after SIRT.

Organ-specific tumourboard
The treatment of patients with cancer is typically organized and planned by a dedicated specialized tumourboard handling disease entities (e.g. sarcoma board, GI-board, a.s.o.). This respective tumourboard is referred to as "OSTB", in this Clinical Investigation Plan. The OSTB is expected to oversee all aspects of patient treatment and to decide on additional treatment options. The OSTB is, therefore, expected to be aware of (and have been responsible for) oncological pre-treatment of included patients.

The inclusion of patients into this clinical study is to be proposed by an investigator, and confirmed by the OSTB. This confirmation must be recorded in writing. No POEM investigator and no member of a POEM study team is allowed to participate and influence the OSTB decision to include patients into the POEM trial. The OSTB confirms that a patient can be included in the clinical study if the patient is no longer suitable for any "standard" anti-tumour treatment (except best supportive care) and the potential reduction of tumour mass in the lung is expected to provide clinical benefit to the patient. In addition, the OSTB confirms that the patient, according to his physical state, is not in a "palliative situation".

If the tumourboard at the study site has not been responsible for the patient's pre-treatment, the investigator has to ensure that the OSTB reviews the full history of the patient and seeks advice from physicians who treated the patients for their cancer before referring to the study site's OSTB, where necessary.

8.3 Investigational device(s) and comparator(s)

An elaborate description of the investigational device is to be found in section 5. There will be no comparators.

9 Study population

9.1 Eligibility / description

Patients of either sex are eligible for this trial provided they meet all in- and exclusion criteria.

9.1.1 Inclusion criteria

1. Willing, able and mentally competent to provide written informed consent
2. Aged 18 years or older
3. Histologically proven primary carcinoma of any origin (except from the central nervous system and lung) **with pulmonary metastases**, or primary non-small cell lung carcinoma (Note: HCC patients might be enrolled without histology in accordance with current guidelines).

4. Unequivocal and measurable CT evidence of either pulmonary metastases from a primary carcinoma, or primary non-small cell lung carcinoma
5. Stage IV disease in oligometastatic pulmonary disease state that is not suitable for treatment by surgical resection, local ablation, radiation therapy, or other conventional techniques, and is either unsuitable or has failed all conventional systemic treatment options such as chemo-therapy, immunotherapy or targeted therapy.

   The determination that all available "standard-of-care" treatment options are no longer indicated must be made by the respective tumourboard (OSTB) responsible for patient treatment. The oncological rationale has to be documented accordingly.

   Note: A combination of local therapy (surgery, ablation, radiation) and SIRT is allowed within this Clinical Investigation Plan if deemed appropriate by the OSTB. Pulmonary SIRT

and other local interventions will be performed as sequential procedures. The remaining total lung volume of all procedures may not be below 60%.

Note: Measurable disease is defined as lung lesions that can be accurately measured in at least one dimension with longest diameter ≥10mm using CT.

6. Suitable for protocol therapy as determined by a multidisciplinary team, e.g. interventional radiologist, thoracic surgeon, pulmonologist, medical oncologist and radiation oncologist investigators
7. All imaging evidence used as part of the screening process must be less than or equal to 30 days old at the time of study entry
8. In case of previous systemic anti-tumour treatment, a washout window of at least 45 days after completion of prior therapy and start of SIRT treatment has been respected to exclude interaction of the local radiation with any remaining previous medical treatment. The multidisciplinary team may recommend a washout period prolongation.
9. WHO performance status 0 – 2
10. Adequate hematological and renal function as follows:

Hematological	Neutrophils	> 1.5 x 10^9/L
	Platelets	> 100 x 10^9/L
	Hemoglobin	> 10 g/dL
Renal	Creatinine	< 1.5 x ULN

Note: the blood results must be less than 7 days old at the time of study entry.

11. Female patients must either be postmenopausal, sterile (surgically or radiation- or chemically-induced), or - if sexually active - using a highly effective method of contraception (failure rate < 1% / year)
12. Male patients must be surgically sterile or - if sexually active and having a premenopausal partner - must be using an acceptable method of contraception
13. Estimated life expectancy of at least 3 months without any active treatment

9.1.2 Exclusion criteria

1. Manifest respiratory insufficiency, defined as: pO2 <60mmHg or pCO2 >45mm Hg
2. Previous radiotherapy delivered to either lung field
3. Suitable for treatment by surgical resection taking into account the following functional resectability criteria:
    a. FEV1 at least 30% of predicted normal, and/or
    b. Diffusion capacity at least 30% of predicted normal, and/or
    c. Maximum O_2 uptake on ergospirometry at least 15mL/min/kg, and/or
    d. EF at least 30% on echocardiography
4. Intercurrent disease that would render the patient unsuitable for treatment according to this Clinical Investigation Plan, such as, but not limited to: bronchial asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, pulmonary hypertension with PAPsys ≥35 mmHG on echocardiography
5. Uncontrolled cardiovascular disease presently or within the last 6 months (e.g., myocardial infarction, unstable angina pectoris, uncontrolled congestive heart failure, significant uncontrolled cardiac arrhythmia or conduction abnormality, valvular disease with significant compromise in cardiac function, or inadequately controlled hypertension)
6. History of or present deep vein thrombosis
7. Any lung tumour that extends beyond the lung parenchyma, e.g. involvement of mediastinal structures, chest wall or pleura (pleural carcinomatosis)
8. Primary cancers of the central nervous system (CNS) or CNS metastases
9. Equivocal, immeasurable, or unevaluable pulmonary metastases from a primary carcinoma, or primary non-small cell lung carcinoma as sole evidence of lung lesions
10. Known allergies against contrast agents used in the study (e.g. iodized angiographic contrast

agents, F-18 FDG or ^{99m}Tc-MAA)
11. Prior SIRT treatment
12. Pregnant or breast feeding
13. Presently participating in an active part of another clinical study

9.2 Rationale for in-/exclusion criteria

The in- and exclusion criteria are selected to ensure the recruitment of the desired patient population (inclusion criteria 3, 4, 5, 6, 7, 13), and to exclude minors (inclusion criterion 1) and patients with increased risk of adverse events (inclusion criteria 2, 8, 9, 10, 11, and 12 as well as all exclusion criteria).

9.3 Gender-specific considerations

The primary objective of this trial is to assess the feasibility of lung SIRT. No gender-specific effect on these assessments is expected. As well, no gender-specific effect is expected with regard to the side effect profile. Consequently, patients of both genders are included without any effort to control for the percentage of males/females. Gender-specific sub-analyses will be performed as a secondary analysis.

9.4 Withdrawal and replacement criteria for treatment

Protocol deviations will be recorded. Patients with protocol deviations will not be replaced.

Any patient who received pulmonary SIRT and dropped-out before completing the 30 days follow-up assessment, will be replaced. Any patient who entered the study and was allocated with an enrollment number but did not receive SIRT is considered drop out and will be replaced.

No imputation of missing values is planned.

9.5 Withdrawal and replacement criteria for assessment

Primary analysis will be done on the ITT population.

9.6 Recruitment / Point of enrolment

Patients for this study will be identified within the routine oncological clinical conferences as part of a treatment decision by the multi-disciplinary team.

9.7 Patient identification

Each center participating in this trial is assigned a two-digit center number, followed by a two-digit patient number starting with 01. Patients will be allocated the next available patient number in the respective center.
Example: patient 0103 – third patient in center no. 1.

9.8 Therapies other than study device 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 CRF, including any supportive treatment provided for the implantation of SIR-Spheres® ^{90}Y resin microspheres.

Once protocol SIRT has been delivered, the patient should receive the best available care as determined by the treating Investigator. While the typical patient entered onto this study will have no further conventional therapy options available, patients are permitted to receive further therapy of any type commencing no earlier than 60 days post-SIRT, at the discretion of the treating Investigator.

9.9 Duration of the clinical investigation

The total expected duration of the Clinical Investigation is 6 years and one month.
The planned dates are:

First patient first visit	01 Mar 2020
Last patient first visit	28 Feb 2021
Last patient last visit	31 Apr 2026

9.10 Expected duration of each subject's participation

Each subject is expected to stay in the study for a maximum of 61 months from Screening assessment until the end of the 60 months follow-up period.

9.11 Number of subjects required to be included in the clinical investigation

Due to the Dose-escalation recruiting scheme the theoretical minimum number and theoretical maximum of patients differ a lot. The theoretical minimum number of patients is 3 and the theoretical maximum number of patients 30. The determination of the sample size is described in section 12.5.3 of this Clinical Investigation Plan.

9.12 Estimated enrolment period

The estimated time needed to select this number of patients is 12 months.

10 Procedures

10.1 Schedule of evaluations

This study consists of the screening phase, the baseline examinations, the SIRT treatment, the immediate 30 days post treatment phase, and the follow-up period until 60 months (or patient death, whichever occurs first).

10.2 Visit description

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.

After signing the informed consent, and upon documentation of eligibility, the patient will be registered in an enrolment log that is kept by the sponsor. The patient will also be formally allocated to the applicable dose level. The enrolment log will ensure participating patients from potentially different institutions are tracked within the applicable dose level and treatment allocation and treatment initiation is centralized.

All medications taken by the patient including medications that are unrelated to their cancer management should be recorded on the CRF. 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 90 days after SIRT was administered.

Routine medications should be listed in the appropriate section and need only be recorded on the CRF once unless they are changed. Additional routine medications should be recorded on the CRF upon commencement of the new medication. Commencement and cessation dates, dosage and route of administration are required.

10.2.1 Screening

All patients referred for possible participation in this study must be pre-screened by the Investigator. The respective organ-specific tumourboard has to confirm the patient’s eligibility to receive protocol treatment and to confirm the lack of other treatment options.

All documentation supporting the inclusion and exclusion criteria and screening investigation results are to be retained by the Investigators and made available for monitoring by the study sponsor.

Patients failing during work-up angiogram will be considered screen failures and study data up to the timepoint of the angiogram will be captured in the eCRF.

All patients assessed as ineligible to receive protocol treatment by the tumourboard (OSTB) or fail screening for other reasons will have their initials recorded on the Patient Screening Log and no further data will be collected for these patients. The Patient Screening Log will include the reason(s) for the patient's exclusion from receiving protocol treatment and will be maintained by the site and copies retained by the study sponsor.

Patients must have histologically confirmed primary carcinoma of any origin with pulmonary metastases or non-small cell lung carcinoma. Reason for suitability of participating patients for the study will be recorded as either: 1) the patient failed all available systemic and local anti-tumour treatment; or 2) the patient is not suitable for anti-tumour treatment, both locally and systemically, at the time of study entry.

In order to be considered eligible for this study, patients must fulfil the inclusion and exclusion criteria (section 9.1).

All patients must be assessed clinically by the Investigators to determine the patient's eligibility to receive protocol treatment. Clinical assessment includes a comprehensive medical history with concurrent illnesses and concomitant medications. Demographic data of the patients will be recorded, additionally.

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

A written informed consent to participate in the study will be obtained from each patient after detailed oral and written information.

10.2.2 Study entry

Study entry is defined as the date that the enrolment number is allocated. The time period between study entry and the commencement of protocol treatment is not to exceed 28 days. Patients may only commence protocol treatment after all eligibility criteria have been confirmed, the patient is registered in the study and the dose level and start of treatment have been confirmed by the sponsor.

10.2.3 Baseline Assessment

Baseline assessment will start after written informed consent and formal study entry. The following data derived from clinical routine assessments within **28 days** prior to start of SIRT treatment are required:

Physical Examination and WHO performance status	All patients are required to undergo a comprehensive physical examination including height, weight and vital signs (body temperature, blood pressure, heart rate and respiratory rate) to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Also, the WHO performance status has to be assessed by the Investigators.	
Hematological and Biochemical Investigations	Hematology	• Hemoglobin • platelets • WBC • absolute neutrophils

		• absolute lymphocytes • Clotting profile (INR and APTT) • Troponin T
	Renal	• urea • serum creatinine • sodium • potassium • calcium • magnesium • phosphate
	Liver	• total bilirubin • ALT • AST • GGT • ALP • Albumin • LDH
	Tumour markers	Appropriate tumour markers if applicable to the tumour type
	Pregnancy test	Serum or urine pregnancy test in premenopausal female patients
Cardiac and Pulmonary Function Tests	ECG	12 lead ECG
	Spirometry	• forced vital capacity (FVC) • forced expiratory volume in 1 sec (FEV_1) • forced expiratory flow (FEF) • forced inspiratory flow 25-75% (FIF_{25-75}) • Peak expiratory flow (PEF) • tidal volume (TV)
	Body plethysmography	• total lung capacity (TLC) • residual volume (RV)
	Diffusion capacity	DLCO
	Arterial blood gases (blood from the ear lap)	pH, pO_2, pCO_2, HCO_3, SaO_2
^{18}F-FDG PET/CT Scan	An ^{18}F-FDG PET/CT scan of the chest, abdomen and pelvis to evaluate both the primary cancer (if relevant) and the lung lesion(s) in terms of location, extent and metabolic activity.	
Contrast CT Scan of the chest with 3D CTA	A contrast enhanced CT scan of the chest with three-dimensional CT angiography (3D CTA) of the bronchial arteries to evaluate the bronchial arterial anatomy of the target lung segment(s).	
Mapping Bronchial Angiography and ^{99m}Tc-MAA Study	All patients must undergo mapping bronchial angiography to determine the bronchial arterial anatomy of the target lung segment(s) and to perform a ^{99m}Tc-MAA study to assess the extent of uptake in the tumour(s) and normal lung parenchyma in the target lung segment(s). The mapping bronchial angiography must be performed in order to: • Fully identify and define all relevant bronchial arterial vasculature, including determining whether the bronchial artery(ies) supply any non-pulmonary structures, • Assess the bronchial arterial supply to the tumour(s), • Assess the flow characteristics in the bronchial artery(ies),	

	• Confirm the ability to selectively catheterize the bronchial artery(ies), • Perform a ^{99m}Tc-MAA study via injection into the bronchial artery(ies) to assess the extent of uptake in the tumour(s) and normal lung parenchyma in the target lung segment, and the presence of any uptake in non-target lung segments or other non-pulmonary structures (e.g. the chest wall, spinal cord).
Quality of Life questionnaire	FACT-L

10.2.4 SIRT Treatment (Day 0)

Patients should begin SIRT treatment as soon as possible, and not later than 28 days after study entry.

10.2.4.1 Protocol Treatment: SIR-Spheres® ^{90}Y Resin Microspheres

The treatment planning and implementation of ^{90}Y radioembolisation to the lung comprises several steps including

- contrast-enhanced computed tomography angiography (delineation of bronchial artery blood supply)
- dynaCT in case of untypical arterial supply
- coil embolization of aberrant bronchial arteries
- ^{99m}Tc-MAA study (simulation of the implantation pattern, identification of segments at risk for non-target deposition; to be done after coil embolization of aberrant arteries, if applicable)
- dosimetry and dose calculation preparatory to ^{90}Y resin microsphere infusion
- angiographic methodology during treatment and the measurement of post-treatment residual ^{90}Y activity

SIRT will only be performed if non-target implantation of microspheres is excluded based on these measures.

Further technical details and associated equipment will be specified and supplied to the investigators in a separate document. Summaries of the various steps in the treatment process are provided below.

10.2.4.2 Calculation of Prescribed Activity of SIR-Spheres® ^{90}Y Resin Microspheres

Patients will be recruited into five dose escalating cohorts, with each dose implanted into the target segment(s) of the lung. Treatment will be limited to 40% of total lung volume.

The dose level (DL) of each cohort is defined as follows:

- **Cohort 1:** DL -2: dose leading to 38Gy exposure to the target segment(s)
- **Cohort 2:** DL -1: dose leading to 44Gy exposure to the target segment(s)
- **Cohort 3:** DL 0: dose leading to 50Gy exposure to the target segment(s)
- **Cohort 4:** DL +1: dose leading to 56Gy exposure to the target segment(s)
- **Cohort 5:** DL +2: dose leading to 62Gy exposure to the target segment(s)

If a lesion could not be safely treated according to the investigator at an assigned dose level, this lesion should not be considered for treatment in the study.

The prescribed activity of SIR-Spheres® ^{90}Y resin microspheres will be calculated based on the intended radiation dose to be delivered to that segment(s), in accordance with the cohort that the patient is recruited to.

10.2.4.3 Administration of SIR-Spheres® ^{90}Y Resin Microspheres

SIR-Spheres® ^{90}Y resin microspheres will be implanted via a temporary trans-femoral bronchial arterial micro-catheter. However, in some patients micro-catheter access via alternative arterial routes

may be preferable. The details of the SIR-Spheres® ^{90}Y resin microspheres prescribed and actually implanted activity will be recorded in the CRF.

Microspheres injection into a territory will only be *done* at positions (at least) 2 cm distal to the previous vascular branching point (safety margin) using the "sandwich technique" with separate sequential administration of contrast medium and small fractions of microspheres; this technique allows to identify stasis early and to avoid "backwash" of microspheres.

The number of treated lesions is not specified in this Clinical Investigation Plan. Patients meeting the inclusion and exclusion criteria (which include criteria on functional resectability) will receive SIRT of all technically accessible tumour lesions as long as the total treated lung volume is smaller than or equal to 40% of total lung volume.

The pre-determined end-points for the administration of SIR-Spheres® ^{90}Y resin microspheres into the bronchial arterial circulation are either:

1) Administration of the entire prescribed activity of SIR-Spheres® ^{90}Y resin microspheres, or

2) Administration of SIR-Spheres® ^{90}Y resin microspheres to the point of sluggish antegrade bronchial arterial flow, at which point further infusion of SIR-Spheres® ^{90}Y resin microspheres could result in completed embolic occlusion of the tumour micro-vascular bed. This point is referred to as 'imminent stasis'. The stopping point for the infusion of SIR-Spheres® ^{90}Y resin microspheres is at the discretion of the treating interventional radiologist.

Further details on the technique for delivery of SIR-Spheres® ^{90}Y resin microspheres is provided in a separate document ("SIR-Spheres microspheres Training Program – lung specific").

As indicated above there is a possibility that imminent stasis will preclude the administration of the prescribed dose for a given patient, as specified. Factors that may result in this phenomenon may include: 1) potentially small treatment volumes that may be encountered with resulting limited capacity for the uptake of ^{90}Y microspheres to the tumour bed; 2) presence or absence of collateral vessels which will affect the deposition of ^{90}Y microspheres within the treatment volume; 3) presence or absence of vessels that may result in non-target deposition of ^{90}Y microspheres outside the treatment field; 4) other variables.

Given individual patient variability in bronchial artery anatomy and presentation of the above mentioned factors, there is no method to reliably identify or assess whether imminent stasis will occur prior to the actual infusion of microspheres during the treatment procedure. However, if imminent stasis does occur, this is an indicator that pulmonary lesions within the treatment field have reached maximum possible, and presumed optimal exposure to ^{90}Y resin microspheres, according to the applicable dose level. The resulting tumour response and occurrence of any Dose Limiting Toxicities (as specified in Section 8.2) for patients who reach imminent stasis will be documented. Given the exclusive uptake in lung lesions documented for the two cases treated with ^{90}Y radioembolization with no observed pulmonary toxicities (19), there is preliminary evidence for the feasibility of this therapy in the lung application.

10.2.4.4 Measurement of Residual Activity Post-Treatment

Once the pre-determined end-point for the administration of SIR-Spheres® ^{90}Y resin microspheres into the bronchial arterial circulation has been reached, the micro-catheter will be removed from the patient and the amount of activity remaining in the SIR-Spheres® ^{90}Y resin microspheres V-Vial, Delivery Set and micro-catheter must be assayed, in order to determine the amount of activity that was actually administered to the patient.

10.2.5 Immediate 30 days post treatment period

Following the administration of SIR-Spheres® ^{90}Y resin microspheres, a same day or day 1 post-SIRT ^{90}Y -PET/CT study of the chest which covers the entire lung must be performed. A second scan will be performed between 12 to 24 h after the first scan. These two studies detect the positron emission from the yttrium-90 and are performed in order to confirm the placement of SIR-Spheres® ^{90}Y resin microspheres in the target lung segment(s) and to exclude non-targeted delivery of SIR-Spheres® ^{90}Y resin microspheres to other non-pulmonary structures (e.g. chest wall, spinal cord). The ^{90}Y-PET studies must be performed with prolonged scan duration (e.g. equivalent to 20 min per bed position on a Siemens mCT with an extended axial FOV).

Further follow-up assessments are planned at day 14 and day 30 after SIRT treatment (+/- 5 days).

Additional procedures within the immediate 30 days post treatment period are summarized in the following table:

Physical Examination and WHO performance status	All patients are required to undergo a comprehensive physical examination including weight and vital signs (body temperature, blood pressure, heart rate and respiratory rate) to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Also, the WHO performance status has to be assessed by the Investigators. Height is to be measured at baseline only.	
Hematological and Biochemical Investigations	Hematology (days 0, 14, and 30)	• Hemoglobin • platelets • WBC • absolute neutrophils • absolute lymphocytes
	Renal (days 0, 14, and 30)	• urea • serum creatinine • sodium • potassium • calcium • magnesium • phosphate
	Liver (days 0, 14, and 30)	• total bilirubin • ALT • AST • GGT • ALP • Albumin • LDH
	Tumour markers (days 14 and 30)	Appropriate tumour markers if applicable to the tumour type
	Pregnancy test (only if pregnancy is suspected)	Serum or urine pregnancy test in premenopausal female patients

Pulmonary Function Tests	Spirometry (day 30)	• forced vital capacity (FVC) • forced expiratory volume in 1 sec (FEV_1) • forced expiratory flow (FEF) • forced inspiratory flow 25-75% (FIF_{25-75}) • Peak expiratory flow (PEF) • tidal volume (TV)
	Body plethysmography (day 30)	• total lung capacity (TLC) • residual volume (RV)
	Diffusion capacity (day 30)	DLCO
	Arterial blood gases (blood from the ear lap) (day 30)	pH, pO_2, pCO_2, HCO_3, SaO_2
Contrast CT Scan of the chest	A contrast enhanced CT scan of the chest	
Quality of Life questionnaire (at day 30)	FACT-L	

10.2.6 Follow-up period 3-12 months

All patients will be followed for a period of 60 months or until death (whichever occurs first).

During the first 12 months of the follow-up period, 4 visits are planned (month 3, 6, 9, 12 +/- 2 weeks). Changes in concurrent illnesses and/or concomitant diseases will be recorded in the eCRF.

The following examinations are to be performed at each visit during the first 12 months of the follow-up period (assessments every 3 months):

Physical Examination and WHO performance status	All patients are required to undergo a comprehensive physical examination including weight and vital signs (body temperature, blood pressure, heart rate and respiratory rate) to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Also, the WHO performance status has to be assessed by the Investigators.	
Hematological and Biochemical Investigations	Hematology	• Hemoglobin • platelets • WBC • absolute neutrophils • absolute lymphocytes
	Renal	• urea • serum creatinine • sodium • potassium • calcium • magnesium • phosphate
	Liver	• total bilirubin • ALT • AST • GGT

		• ALP • Albumin • LDH
	Tumour markers	Appropriate tumour markers if applicable to the tumour type
Pulmonary Function Tests	Spirometry	• forced vital capacity (FVC) • forced expiratory volume in 1 sec (FEV_1) • forced expiratory flow (FEF) • forced inspiratory flow 25-75% (FIF_{25-75}) • Peak expiratory flow (PEF) • tidal volume (TV)
	Body plethysmography	• total lung capacity (TLC) • residual volume (RV)
	Diffusion capacity	DLCO
	Arterial blood gases (blood from the ear lap)	pH, pO_2, pCO_2, HCO_3, SaO_2
^{18}F-FDG PET/CT Scan (at 3 months follow-up only)	An ^{18}F-FDG PET/CT scan of the chest, abdomen and pelvis to evaluate both the primary cancer (if relevant) and the lung lesion(s) in terms of location, extent and metabolic activity.	
Contrast CT Scan of the Chest	A contrast enhanced CT scan of the chest	
Quality of Life questionnaire	FACT-L	

10.2.7 Follow-up period 18-60 months

During the following 4 years of follow-up, a total of 8 visits are planned (month 18, 24, 30, 36, 42, 48, 54, 60 +/- 4 weeks). Changes in concurrent illnesses and/or concomitant diseases will be recorded in the eCRF.

The following examinations are to be performed at each visit during the following 4 years of the follow-up period (assessments every 6 months):

Physical Examination and WHO performance status	All patients are required to undergo a comprehensive physical examination including weight and vital signs (body temperature, blood pressure, heart rate and respiratory rate) to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Also, the WHO performance status has to be assessed by the Investigators.	
Hematological and Biochemical Investigations	Hematology	• Hemoglobin • platelets • WBC • absolute neutrophils • absolute lymphocytes
	Renal	• urea • serum creatinine • sodium • potassium • calcium • magnesium • phosphate
	Liver	• total bilirubin • ALT • AST • GGT • ALP • Albumin • LDH
	Tumour markers	Appropriate tumour markers if applicable to the tumour type
Contrast CT Scan of the chest	A contrast enhanced CT scan of the chest	
Quality of Life questionnaire	FACT-L	

10.3 Flowchart

	Screening Assessments	**Baseline Assessments**	**Follow-up Assessments: First 30 Days Post-SIRT**			**Follow-up Assessments: 3 – 12 months Post-SIRT**	**Follow-up Assessments: 24 – 60 months Post-SIRT**
Schedule	≤30 days prior to study entry	≤ 28 days prior to protocol SIRT treatment	Day 0: SIRT	Day 14	Day 30	Month 3, 6, 9, 12	Month 18, 24,30,36,42,48, 54, 60
Informed consent	✓						
Demographics	✓						
Medical history, including - concurrent illnesses - concomitant meds.	✓					✓	✓
Physical examination, including - height, weight, vital signs - WHO performance status		✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]
ECG		✓	✓	✓	✓	✓	✓
Hematology & biochemistry		✓	✓[b]	✓[b]	✓[b]	✓[b]	✓[b]
Tumour markers[c]		✓		✓	✓	✓	✓
Pregnancy test for females[d]		✓			✓		
Pulmonary function tests		✓			✓	✓	
Screening CT[e]	✓						
Registration fax to sponsor for assignment of enrolment number and dose level		✓					
Contrast CT scan chest with 3D CTA		✓[f]			✓[g]	✓[g]	✓[g]
^{18}F-FDG PET/CT scan chest, abdomen, pelvis		✓[f]				✓[h]	
Mapping bronchial angiography		✓[f]					
^{99m}Tc-MAA study		✓[f]					
SIRT			✓				
Post-SIRT ^{90}Y PET/CT study			✓[i]				
Adverse events			✓	✓	✓	✓	✓
Quality of life[j]		✓			✓	✓	✓
Survival			✓	✓	✓	✓	✓

Notes to the Study Calendar:

a) Physical examination to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators. Height to be measured at baseline only.
b) Clotting profile and troponin T are not required at these assessments.
c) Tumour markers relevant to the primary or secondary lung tumours, if such markers exist. For example, if the patient has primary colorectal cancer with lung metastases, then carcinoembryonic antigen (CEA) should be assessed.
d) Premenopausal female patients must have a negative serum or urine pregnancy test at study entry. This test should be repeated if pregnancy is suspected during the study. Inform the study Sponsor immediately if pregnancy is confirmed during the study.
e) Screening CT may be used for baseline assessment if performed ≤28 days prior to start of SIRT treatment and the corresponding 3D CTA is available.
f) Procedure/s to be performed after assignment of enrolment number and dose level.
g) 3D CT angiography is not required at these assessments.
h) F-18-FDG PET/CT scan at 3 months only.
i) The post-SIRT ^{90}Y PET/CT study may be performed either on the same day as SIRT or day 1 following SIRT. A second scan will be performed between 12 to 24 h after the first scan.
j) The Functional Assessment of Cancer Therapy (FACT-L) questionnaire should be completed at baseline, 30 days, 3 months, 6 months, 9 months and 12 months, 18 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months and 60 months.

The acceptable tolerances in the time points are:

- Day 0 assessments must be performed on day 0
- Day 14, 30 assessments may be performed +/- 5 days
- Month 3, 6, 9, 12 assessments may be performed +/- 2 weeks
- Month 18, 24,30,36,42,48,54,60 assessments may be performed +/- 4 weeks.

10.4 Post-study therapy

Post-study therapy will follow routine clinical care.

10.5 End of study

End of study is defined as the last visit of the last patient. In this study this would be the 60 months Follow-Up visit or death of the last active patient, whichever happens first.

11 Monitoring

Monitoring procedures include one visit designed to clarify all prerequisites before the study commences. One or more interim monitoring visits will take place on a regular basis according to a schedule fixed by mutual agreement. During these visits, the CRA will check the entries on the eCRFs for completion, their compliance with the Clinical Investigation Plan and with Good Clinical Practice, will compare the eCRF entries with the source data, and will check the correct handling of study devices. Further details regarding monitoring activities will be summarized in the "Monitoring Manual".

The CRA will determine whether all AEs and SAEs have been appropriately reported within the time periods required (SAEs only).

12 Statistical Considerations

12.1 Primary analysis set

The full analysis set (FAS) includes all patients who received any dose of pulmonary SIRT. The intent-to-treat (ITT) population includes all patients who underwent pulmonary SIRT and completed at least 3 months follow-up. The ITT population will be the primary population for the analyses of efficacy endpoints and all baseline characteristics. Patients will be analyzed as treated. The per-

protocol population (PP) of patients with no major protocol deviations will be used as secondary analysis set for efficacy. Safety will be assessed in the FAS.

12.2 Subgroup analysis

No subgroup analyses are planned.

12.3 Primary target variables

Pulmonary SIRT will be regarded as feasible if the first dose level can be completed without reaching dose-limiting toxicity in more than 1/3 patients or imminent stasis in more than 3/6 patients. A patient is regarded to have reached imminent stasis if more than 50% of targeted segment/s present with imminent stasis.

12.4 Secondary target variables

12.4.1 Safety and Toxicity

Safety and toxicity will be assessed using the NCI Common Terminology Criteria for Adverse Events version 5.0. Patients are to be followed for safety and toxicity from the time of providing informed consent until 12 months post-SIRT. Definitions and the requirements for reporting adverse events (AE) and serious adverse events (SAE) are detailed in section 15.

12.4.2 Tumour Response Rate

The response across all lung lesions will be determined using modified response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) (43).

Evaluation of the tumour response rate by means of the sum of largest diameters of target lesions will be applied to assess if the effect of pulmonary SIRT treatment (which may not cover all lesions present in the lungs) can be assessed sufficiently accurately following the RECIST principle (RECIST – response evaluation criteria in solid tumours; the RECIST principle uses the sum of target lesion diameters for response assessment). The volumetric assessment of the treatment effect on individual lesions will serve as a comparator to the RECIST principle.

12.4.3 Quality of Life assessment

The functional assessment of cancer therapy-lung (FACT-L) developed by the American Thoracic Society is a tool to assess QoL of lung cancer patients. The questionnaire includes 5 subscale scores (Physical, social/family, emotional, functional well-being and lung cancer subscale (symptoms, cognitive function, regret of smoking). Each of the multi-item sub-scales includes a different set of items – no item occurs in more than one scale.
The “Total score” is the sum of subscale scores.
An alternative scoring is the Trial Outcome Index (TOI) = sum of the Physical, Functional, and Lung Cancer Subscales.
All of the above subscale scores, as well as total score and Trial Outcome Index (TOI) will be tabulated for each dose level as well as overall. Pairwise differences in TOI between the different dose levels will be compared using Mann-Whitney U test.

12.5 Statistical Methods

Descriptive statistics will be used to tabulate outcome measures. Given the small size of this feasibility study, no other statistical tests will be performed.

12.5.1 List of variables and population characteristics

- Patient demographic data (gender, year of birth, height, weight)
- Baseline findings
- Medical and surgical history
- Concomitant medication
- AE's / SAE's
- vital signs
- Laboratory evaluations
- Clinical follow-up information
- Tumour Response Rate
- Time-to-progression in the targeted lesions
- Overall Survival
- Quality of Life

12.5.2 Interim analyses

No interim analysis is planned.
After the first 4 patients all adverse event data will be forwarded to the lead ethics committee for review. In addition, study safety will be monitored by the independent DSMB (time intervals see chapter 8.2).

12.5.3 Determination of sample size

The study will be conducted as a feasibility and radiation dose escalation study and will recruit patients into five dose escalating cohorts of 3 – 6 patients, depending on the toxicities observed and imminent stasis in each cohort.

The following table provides patient numbers for different possible scenarios. Not all theoretically possible scenarios are listed, but the table covers the scenario with the lowest and the highest number of included patients (without drop-outs).

	Scenario	**number of patients in study**
1	Dose-limiting toxicity in 2 or 3 of the first 3 patients included into this study (first dose level; =theoretical minimum number of patients)	3
2	Imminent stasis in 4 or more of the first 6 patients included into this study	12
3	dose level 1: 3 patients without DLT; dose level 2: 6 patients, 1 patient with DLT dose level 3: 6 patients, 4 patients with imminent stasis	15
4	Six patients studied at each dose level (= theoretical maximum number of patients)	30

DLT – dose limiting toxicity

12.5.4 Randomization/Stratification

Not applicable

13 Data handling and quality assurance

13.1 Data recording

Data required according to this Clinical Investigation Plan are to be recorded on the electronic CRFs in a timely manner.

Any documents related to the study must be archived at the study site or in a central archive. This includes the careful listing of the identities of the patients involved in the study. This list and the signed informed consent statements are key documents in the files to be stored by the investigator.

For purposes of source data verification (SDV), the following variables are to be captured in the investigator's patient file:

- Demographics
- The fact that the patient is in the study (including date of providing informed consent)
- Any study procedures (SIRT)
- Study device administration
- Visit dates
- SAEs
- Medical history (including diagnosis of indication being treated)
- AEs (the CRF may contain more details than the patient file)
- Concomitant medication (the CRF may contain more details than the patient file)

13.2 Data processing

A Data Manual (DM) will be maintained specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing). This DM will be stored in the TMF.

For data coding (e.g., AEs, baseline findings, medication, medical/surgical history), internationally recognized and accepted dictionaries will be used.

13.3 Auditing

A member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to visit the investigator in order to audit the performance of the study at the study site and the study documents originating there. The auditor(s) will usually be accompanied by the CRA. The investigator will be informed about the outcome of the audit.

In addition, inspections by health authority representatives – including foreign authorities – and CEC(s) are possible at any time. The investigator is to notify the sponsor of any such inspection immediately.

13.4 Archiving

The sponsor and the investigator/medical institution shall, in every case, retain essential documents relating to this trial for at least 15 years after its completion. They shall retain the documents for a longer period if required by other applicable regulatory requirements or by a separate agreement between the sponsor and the investigator. Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The ITF (investigator's trial file) is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study center.

14 Ethical and regulatory aspects

14.1 Amendments to the CIP

Substantial amendments are only implemented after approval of the CEC and CA, respectively.

All non-substantial amendments are communicated to the CA as soon as possible (if applicable) and to the CEC within the Annual Safety Report (ASR).
Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to implementation.

14.2 Deviations from clinical investigation plan

Strict adherence to all specifications laid down in this Clinical Investigation Plan is required for all aspects of the study conduct; the investigator may not modify or alter the procedures described in this clinical investigation plan. If clinical investigation plan modifications are necessary, all alterations that are not solely of an administrative nature require a formal clinical investigation plan amendment (see section 14.1 for the involvement of CEC(s).

Under emergency circumstances, deviations from the clinical investigation plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA, as soon as possible.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved clinical investigation plan.
Investigators are responsible for recording and reporting clinical investigation plan deviations as soon as they are identified.

It is the responsibility of the sponsor to analyze, grade (observation / protocol violation), and document each deviation from the clinical investigation plan. If deviations from the clinical investigation plan occur, the sponsor has to initiate that immediate steps to correct the problem are being taken.
Furthermore, the step-by-step procedure and study workflow have to be reviewed regularly by the sponsor to help identify root cause of deviations from the clinical investigation plan and to protect from re-occurrence.
If an investigator repeatedly and deliberately deviates from the clinical investigation plan, he will be removed from the study.

14.3 Device accountability

SIR-Spheres® will be shipped directly from the manufacturer and delivered to the participating sites upon receipt by Sirtex of a "SIR-Spheres Clinical Trial Order Form". Regulatory and local radiation usage guidelines should be followed concerning storage, dose preparation, implantation and post-implantation care. The SIR-Spheres® vial and its contents should be stored inside the delivered transportation container at room temperature (15-25ºC). The calibration date (for radioactive contents) and the expiry information are on the vial label. SIR-Spheres® is usable up to 24 hours from the time of calibration. Any unused SIR-Spheres® will be stored within the radioactive waste storage facility at the participating site until decayed to the limits set by local regulatory authorities that are safe for disposal. Disposal is in the responsibility of the local investigator.

The investigator or pharmacists at the study site will confirm receipt of the study device in writing and will use the study device only within the framework of this clinical study and in accordance with the Clinical Investigation Plan. He/she will keep a record of the study device dispensed, preferably on the eCRF.

Receipt, distribution and disposal/return of study device must be properly documented on the forms provided by the sponsor giving the following information: Clinical Investigation Plan number, sender, receiver, date, mode of transport, quality, batch number, expiration date and retest date, if applicable.

A complete record of batch numbers and expiry dates of all study devices will be maintained in the TMF.

The administration of SIR-Spheres® is carried out by the investigator. The investigator ascertains and documents that the patient received the treatment according to the Clinical Investigation Plan.

14.4 Ethical Conduct of the Study / Statement of compliance

The study will be carried out in accordance to the Clinical Investigation Plan and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, ISO 14155, the national law and German regulatory authority's requirements.
The CEC will receive annual safety reports and be informed about study stop/end in agreement with local requirements.
The clinical investigation shall not begin until the required approval/favorable opinion from the CEC and competent authority have been obtained.
Any additional requirements imposed by the CEC or competent authority shall be followed.

14.5 Compensation for health damage of patients / insurance

Insurance of patients against health impairment occurring as a result of participation in the study will be set up in accordance with said laws and regulations. All relevant documentation regarding such insurance will be filed in the TMF and/or ITF, as appropriate

14.6 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information and consent sheet provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this Clinical Investigation Plan.

Based on this patient information sheet, the investigator will explain all relevant aspects of the study to each patient, before his / her entry into the study (i.e., before examinations and procedures associated with selection for the study are performed).

The investigator will also mention that written approval of the CEC has been obtained.
Each patient will have ample time (minimum 24 hours) and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
Following this informative discussion, the patient will be asked if he / she is willing to sign and personally date a statement of informed consent, which includes consenting to the processing of his / her data as explained in the patient information sheet. Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he / she enter the study. Additionally, the investigator will personally sign and date the form, too. The patient will receive a duplicate of the signed and dated form.

The signed informed consent statement is to remain in the ITF or, if locally required, in the patient's note / file of the medical institution.

The investigator will document on the CRF the time and date of obtaining informed consent.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the Clinical Investigation Plan which necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the CEC's approval / favourable opinion in advance of use.

15 Safety

15.1 Data Safety Monitoring Board

The safety of trial subjects on this study will be reviewed by both the coordinating investigator and an independent data safety monitoring board (DSMB). For details, please refer to section 8.2.

15.2 Definitions

- Incident: Any occurrence of a malfunction, failure, change in the characteristics or performance, or improper labeling or instructions for use of a medical device which, directly or indirectly, have led to the death or serious deterioration of the health of a patient, user or other person. A malfunction is also a defect of serviceability which causes misapplication.
- Recall: a corrective action that initiates the return, replacement, conversion or refitting, disposition or destruction of a medical device or provides users, operators or patients with instructions for the continued safe use or operation of medical devices.
- Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medical (investigational) product.
- Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.
- Serious adverse event (SAE): any adverse event which could have resulted in or could result in any unintentional event occurring in a clinical trial or performance-based performance test subject to authorization that has resulted, directly or indirectly, in the death or serious deterioration of the health status of a subject, user or other person without consideration whether the event was actually caused by the medical device.
  The above applies accordingly to serious adverse events that have occurred in a clinical trial or performance evaluation examination for which an exemption from the licensing requirement under section 20(1)(2) of the Medical Devices Act has been granted.
  Medical and scientific judgment should be exercised in deciding whether it is appropriate to report an AE as serious also in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse.
- Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

15.3 Reporting

Reporting will be done to the Bundesamt für Arzneimittel und Medizinprodukte (BfArM) according to the German Medical Devices Act (MPSV).

The investigator or principal investigator must submit within 24 hours a complete SAE Report for all serious adverse events, regardless of a possible causal relationship, to the study sponsor or the sponsor delegated person.

The investigator is required to document in full the course of the SAE and any therapy given, including any relevant findings / records in the report. The investigator will also inform the sponsor, or

the sponsor delegated person, of the relevant follow-up information and the outcome of the SAE as soon as possible (follow-up report).

Details on safety reporting will be documented in the current "Safety Flow Chart" and a separate "Safety Plan", issued to the investigators.

The sponsor, or the sponsor delegated person, must report serious adverse events to the responsible competent authority. This also applies if they occurred outside of Germany.

An immediate report from the sponsor to the authorities is necessary if there is a possible causal relationship of the SAE to the study device or the SAE needs to be reported to foreign authorities in the European Economic Area.

The "Report form for reporting of serious adverse events (SAE) in clinical trials or performance evaluations for use by sponsors according to section 3 (5) of the Ordinance on the Medical Device Safety Plan" will be used to report SAEs to the competent authority in electronic form. The Form is to be found on the internet page of the CA. (BfArM.de /Medizinprodukte/ Klinische Prüfung).

All other SAEs will be documented by the sponsor and reported as a summary every 3 months (or on demand) to the CA using the respective template, issued by the CA.

The necessary steps for the risk analysis must be performed immediately and be reported to the CA.

There will be a regular assessment of all SAEs in the study by the DSMB (see section 15.1).

The sponsor, or the sponsor delegated person, will report incidents that have occurred in Germany as well as recalls in Germany to the responsible competent authority.

If a serious adverse event also constitutes an incident, then the sponsor may also fulfill his obligation to report incidents by submitting a report in accordance with Section 5 of the Medical Devices Act. The notification must indicate that the obligation to report an incident under section 1 of the Medical Devices Act has been fulfilled.

15.3.1 Reporting Timelines

Serious adverse events have to be reported immediately. This also applies to reports of serious adverse events for which a link with the medical device under test, a reference product or the therapeutic or diagnostic measures used in the clinical trial or the other conditions for carrying out the clinical trial cannot be excluded.
All other serious adverse events must be fully documented and reported quarterly or at the request of the competent authority in summary form.

The sponsor, or the sponsor delegated person, has to report incidents according to the urgency of the risk assessment to be carried out, but at the latest within 30 days after he has become aware of this. In the event of imminent danger, the notification must be made immediately. Recalls must be reported at the latest when the measures are implemented

15.4 Assessments and documentation of adverse events

15.4.1 Categories for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

<u>Seriousness</u>
For each AE, the seriousness must be determined according to the criteria given in Section 8.5.1.

Intensity
The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event:

- Mild
- Moderate
- Severe
- Optional category

Causal relationship to study device
The possible causal relationship between the AE and the administration of the investigational product will be classified by the investigators into the following categories:

- None
- Unlikely
- Possible
- Probable
- Definite

'Related' AEs comprise the categories 'possible', 'probable' and 'definite'.

The definitions for the categories are specified in the "Safety Plan". The "Safety Plan" will be issued to the investigators in a separate document to this Clinical Investigation Plan.

Causal relationship to study conduct
The possible causal relationship between the AE and any study-conduct-related procedures and activities required by the Clinical Investigation Plan will be classified by the investigators into the following categories:

- None
- Unlikely
- Possible
- Probable
- Definite

'Related' AEs comprise the categories 'possible', 'probable' and 'definite'.

The definitions for the categories are specified in the "Safety Plan". The "Safety Plan" will be issued to the investigators in a separate document to this Clinical Investigation Plan.

Outcome
The outcome of the AE is to be documented as follows:

- Recovered / resolved
- Recovering / resolving
- Not recovered / not resolved
- Recovered / resolved with residual effects
- Fatal
- Unknown.

15.4.2 Documentation of adverse events

All assessments of AEs and the respective documentation are to be done by the investigator. The determination of expectedness is the responsibility of the sponsor.

15.5 Expected adverse events

15.5.1 Expected disease-related AEs

Please refer to section 6.3.2.

15.5.2 Expected conduct-related AEs

Please refer to section 6.3.4.

15.6 Further safety

15.6.1 Pregnancies

Pregnant patients are not to be included in this study. In the case a pregnancy occurs during the course of the study, it has to be reported to the Sponsor within a maximum of 24 hours of becoming aware of it. The patients will be withdrawn from the study and followed-up according to routine clinical standards. The sponsor will record pregnancy outcome and follow-up on the status of the infant until 1 year of age.

15.6.2 Laboratory evaluations

Elaborate hematological and biochemical investigations will be performed at baseline and at each follow-up visit. Please refer to section 10.2 for details. Any relevant, abnormal laboratory values will be treated as Adverse Events.

15.6.3 Physical examination and vital signs

A comprehensive physical examination including weight and vital signs (body temperature, blood pressure, heart rate and respiratory rate) to be performed by the Pulmonologist and/or by the Interventional Radiologist and/or by the Nuclear Medicine Investigators at baseline and at each follow-up visit. Height to be measured at baseline only
WHO performance status will be assessed by the investigators at baseline and at each follow-up visit.

15.6.4 ECG

A 12-lead electrocardiogram will be obtained at baseline and at each follow-up visit.

16 Premature termination of study

The Sponsor may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

In case of premature termination the investigators, CECs and regulatory authorities will be informed by the sponsor or CRO.

In case of premature termination, all patients who received a SIRT treatment of the lung following this CIP will have all follow-up visits, as per protocol. For details see sections 10.2.5 -10.2.7.
The patients´ further therapy will follow routine clinical care.

17 Publication policy

Information concerning the study drug and patent applications, scientific data, or other pertinent information is confidential and remains the sole property of the sponsor. The Investigator is not allowed to disclose or publish any information without express permission from the sponsor.

The results of this trial will be published respecting patient's data confidentiality.

18 Financing

Each investigator (including principal and/or any sub-investigators; as well as their spouses and dependent children) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the TMF and/or ITF, as appropriate.

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APPENDIX 1 WHO Performance Status (Definitions)

WHO Performance Status	Patient Description
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable only of limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

APPENDIX 2 World Medical Association Declaration of Helsinki

The full World Medical Association Declaration of Helsinki can be found on the following website:

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Alternatively the document can be obtained from the study Sponsor.

APPENDIX 3 NCI CTCAE v5.0 Recommendation for Grading of Adverse Events

The full Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published 27 Nov 2017 can be obtained at the following website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Alternatively the document can be obtained from the study Sponsor.

APPENDIX 4 FACT-L FACIT Questionnaire

FACT-L (Fassung 4)

Nachfolgend finden Sie eine Liste von Aussagen, die von anderen Personen mit Ihrer Krankheit für wichtig befunden wurden. **Bitte geben Sie jeweils an, wie sehr jede der folgenden Aussagen im Laufe der letzten 7 Tage auf Sie zugetroffen hat, indem Sie die entsprechende Zahl ankreuzen.**

	KÖRPERLICHES WOHLBEFINDEN	Über-haupt nicht	Ein wenig	Mäßig	Ziem-lich	Sehr
GP1	Mir fehlt es an Energie	0	1	2	3	4
GP2	Mir ist übel	0	1	2	3	4
GP3	Wegen meiner körperlichen Verfassung habe ich Schwierigkeiten, den Bedürfnissen meiner Familie gerecht zu werden	0	1	2	3	4
GP4	Ich habe Schmerzen	0	1	2	3	4
GP5	Die Nebenwirkungen der Behandlung machen mir zu schaffen	0	1	2	3	4
GP6	Ich fühle mich krank	0	1	2	3	4
GP7	Ich muss zeitweilig im Bett bleiben	0	1	2	3	4

	VERHÄLTNIS ZU FREUNDEN, BEKANNTEN UND IHRER FAMILIE	Über-haupt nicht	Ein wenig	Mäßig	Ziem-lich	Sehr
GS1	Ich stehe meinen Freunden nahe	0	1	2	3	4
GS2	Ich bekomme seelische Unterstützung von meiner Familie	0	1	2	3	4
GS3	Ich bekomme Unterstützung von meinen Freunden	0	1	2	3	4
GS4	Meine Familie hat meine Krankheit akzeptiert	0	1	2	3	4
GS5	Ich bin damit zufrieden, wie wir innerhalb meiner Familie über meine Krankheit reden	0	1	2	3	4
GS6	Ich fühle mich meinem Partner/meiner Partnerin oder der Person, die mir am nächsten steht, eng verbunden	0	1	2	3	4
G1	*Beantworten Sie bitte die folgende Frage unabhängig davon, inwieweit Sie zurzeit sexuell aktiv sind. Wenn Sie die Frage lieber nicht beantworten möchten, kreuzen Sie das nebenstehende Kästchen an* ☐ *und fahren Sie mit dem nächsten Abschnitt fort.*					
GS7	Ich bin mit meinem Sexualleben zufrieden	0	1	2	3	4

FACT-L (Fassung 4)

Bitte geben Sie jeweils an, wie sehr jede der folgenden Aussagen im Laufe der letzten 7 Tage auf Sie zugetroffen hat, indem Sie die entsprechende Zahl ankreuzen.

	SEELISCHES WOHLBEFINDEN	Über-haupt nicht	Ein wenig	Mäßig	Ziem-lich	Sehr
GW1	Ich bin traurig	0	1	2	3	4
GW2	Ich bin damit zufrieden, wie ich meine Krankheit bewältige	0	1	2	3	4
GW3	Ich verliere die Hoffnung im Kampf gegen meine Krankheit	0	1	2	3	4
GW4	Ich bin nervös	0	1	2	3	4
GW5	Ich mache mir Sorgen über den Tod	0	1	2	3	4
GW6	Ich mache mir Sorgen, dass sich mein Zustand verschlechtern wird	0	1	2	3	4

	FUNKTIONSFÄHIGKEIT	Über-haupt nicht	Ein wenig	Mäßig	Ziem-lich	Sehr
GF1	Ich bin in der Lage zu arbeiten (einschließlich Arbeit zu Hause)	0	1	2	3	4
GF2	Meine Arbeit (einschließlich Arbeit zu Hause) füllt mich aus	0	1	2	3	4
GF3	Ich kann mein Leben genießen	0	1	2	3	4
GF4	Ich habe mich mit meiner Krankheit abgefunden	0	1	2	3	4
GF5	Ich schlafe gut	0	1	2	3	4
GF6	Ich kann meine Freizeit genießen	0	1	2	3	4
GF7	Ich bin derzeit mit meinem Leben zufrieden	0	1	2	3	4

FACT-L (Fassung 4)

Bitte geben Sie jeweils an, wie sehr jede der folgenden Aussagen im Laufe der letzten 7 Tage auf Sie zugetroffen hat, indem Sie die entsprechende Zahl ankreuzen.

	ZUSÄTZLICHE FAKTOREN	Über-haupt nicht	Ein wenig	Mäßig	Ziem-lich	Sehr
H 1	Ich leide unter Atemnot	0	1	2	3	4
C 2	Ich verliere an Gewicht	0	1	2	3	4
L 1	Ich kann klar denken	0	1	2	3	4
L 2	Ich habe Hustenanfälle	0	1	2	3	4
H 5	Haarausfall macht mir zu schaffen	0	1	2	3	4
C 6	Ich habe einen guten Appetit	0	1	2	3	4
L 3	Ich verspüre einen Druck im Brustkorb	0	1	2	3	4
L 4	Das Atmen fällt mir leicht	0	1	2	3	4
Q8	Haben Sie jemals geraucht? Nein___ Ja___ Wenn ja:					
L 5	Ich bereue es, geraucht zu haben	0	1	2	3	4