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STATISTICAL AND ANALYSIS PLAN

PROTOCOL TITLE: A MULTICENTRE, OPEN-LABEL PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIODISTRIBUTION AND ANTI-TUMOUR ACTIVITY OF ^{177}LU-OPS201 WITH COMPANION IMAGING ^{68}GA-OPS202 PET/CT IN PREVIOUSLY TREATED SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC CANCERS EXPRESSING SOMATOSTATIN RECEPTOR 2 (SSTR2)

PROTOCOL VERSION AND DATE: VERSION 2.0 – 07 MARCH 2019

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STUDY NUMBER:	D-FR-01072-002
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SAP VERSION:	Final Version 2.0
SAP DATE:	03 January 2020

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
10, 11, 12, 25, 26, 29, 31, 33, 54, 56	1, 2, 3			Changes to be consistent with protocol amendment (version 2, dated 07 March 2019)
57	5	No changes affecting the statistical analysis defined in the protocol are made.	Due to Premature Closure of this study, the statistical analysis for the Clinical Study Report was revised, This revision was to generate key listings identified in Section 5 of this SAP	Study was terminated prematurely per Sponsor decision.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
Ae	Cumulative amount (of unchanged drug) excreted into the urine
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate amino transferase
AUC	Area under the curve
BC	Breast cancer
BM	Bone marrow
BOR	Best overall response
Bq	Becquerel, SI unit of radioactivity
CDK	Cyclin-dependent kinase
ceCT	Contrast enhanced CT
ceMRI	Contrast enhanced MRI
CI	Confidence interval
Cmax	Maximum observed concentration
CMR	Complete metabolic response
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria Adverse Event
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA-DSB	Deoxyribonucleic acid-double strand breaks
DOM	Dosimetry operational manual
DoR	Duration of response
DOTA	Tetraxetan (INN), a chemical chelator group
DRB	Data review board
DRR	Durable response rate
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Extensive disease
eCRF	Electronic case report form

ABBREVIATION	Wording Definition
eGFR	Estimated glomerular filtration rate
EOAC	End of additional cycles
EOCT	End of core trial
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQoL 5-dimension 5-level
EU	European Union
EW	Early withdrawal
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
Gy	Gray, SI unit of absorbed radiation dose
GST	Alpha-glutathione S-transferase
GSTP1	Glutathione S-transferase P1
HCG	Human chorionic gonadotrophin
HER2-	Human epidermal growth factor receptor 2 negative
HR+	Hormone receptor positive
KIM-1	Kidney injury molecule-1
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ICL	Imaging core laboratory
IHC	Immunohistochemistry
IIP	Investigational Imaging Product
IRPP	Investigational radiopharmaceutical product
ITT	Intent to treat
i.v.	Intravenous
LD	Limited disease
MACA	Maximum administrable cumulative activity
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mL	Millilitre
mGa-PERCIST	Modified gallium PERCIST
mGa-RECIST	Modified gallium RECIST
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume

ABBREVIATION	Wording Definition
MRI	Magnetic resonance imaging
MTCA	Maximum tolerated cumulative activity
MTSA	Maximum tolerated single activity
NCI	National Cancer Institute
NET	Neuroendocrine tumours
OPS301	Ipsen's amino acid solution
ORR	Objective response rate
OS	Overall survival
PARP	Poly adenosine diphosphate ribose polymerase
PERCIST	Positron emission tomography response criteria in solid tumours
PET	Positron emission tomography
PFS	Progression free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PP	Per protocol
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QC	Quality control
QoL	Quality of life
RBC	Red blood cell(s)
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SCLC	Small cell lung cancer
SMD	Stable metabolic disease
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SoC	Standard-of-care
SOC	System organ class
SOP	Standard Operating Procedure
SOT	Standard-of-Truth

ABBREVIATION	Wording Definition
SPECT	Single Photon Emission CT
sstr2	Somatostatin receptors subtype 2
SUL	SUV normalised by lean body mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake volume
t½	Elimination half life
TEAE	Treatment emergent adverse event
tmax	Time to maximum observed concentration
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
Vd	Apparent volume of distribution
WBC	White blood cell(s)
µg	Microgram
^{68}Ga	Gallium-68, positron-emitting isotope of gallium
^{68}Ga-OPS202	Study medication; 68Ga-radiolabelled somatostatin analogue for diagnostic imaging
^{177}Lu	Lutetium-177, beta- and gamma-emitting isotope of lutetium
^{177}Lu-OPS201	Study medication; 177Lu-radiolabelled somatostatin analogue for PRRT

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

Phase I

To evaluate the safety and tolerability and to define the maximum tolerated cumulative activity (MTCA) of fractionated intravenous (i.v.) administration over two cycles of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing somatostatin receptors (sstr2) as identified by ^{68}Ga-OPS202 positron emission tomography (PET)/computed tomography (CT) scans.

Phase II

To evaluate the objective response rate (ORR) of fractionated i.v. administration of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans.

1.1.2 Secondary objectives

Phase I

- To determine the whole-body distribution and pharmacokinetics (PK) of ^{177}Lu-OPS201 after each administration.
- To determine the radiation dosimetry of ^{177}Lu-OPS201 (organ exposure to radiation) after each administration.
- To determine the PK of OPS201 in plasma and urine.
- To describe the preliminary anti-tumour activity of ^{177}Lu-OPS201.
- To evaluate progression free survival (PFS) until Long-term Follow-up Visits up to 2 years after the End of Core Trial (EOCT) Visit.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 SPECT/CT.
- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT and tumour response to ^{177}Lu-OPS201.

Phase II

- To evaluate the efficacy of ^{177}Lu-OPS201 using Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 and/or Positron Emission Tomography Response Criteria In Solid (PERCIST) v1.0 criteria, volumetric CT and modified PERCIST using ^{68}Ga-OPS202 PET scans and modified RECIST using the ^{68}Ga-OPS202 avid lesions.
- To evaluate PFS until long-term follow-up visits up to 2 years after the EOCT Visit.
- To estimate the 1-year overall survival (OS) rate.
- To further evaluate the safety profile of ^{177}Lu-OPS201.
- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT with tumour response to ^{177}Lu-OPS201 therapy.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 SPECT/CT.
- To evaluate the impact of ^{177}Lu-OPS201 on the health-related quality of life of treated subjects.

- To estimate the proportion of sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by standardised uptake volume (SUV) in subjects screened for ^{177}Lu-OPS201 treatment.
- To further assess some PK and dosimetry parameters of ^{177}Lu-OPS201 based on the phase I results.

1.1.3 Exploratory Objectives

Phase I/II

- To explore renal and haematological safety by measuring urinary specific biomarkers and deoxyribonucleic acid-double strand breaks (DNA-DSB) and DNA repair in peripheral lymphocytes (at selected centres).
- To evaluate the tumour microenvironment, transcriptomics, DNA repair, gene mutation in tumour as compared to germinal mutation and other markers of interest through assessment of tumour biopsies.
- To collect biobank samples for future analysis of circulating markers (optional, additional informed consent required).
- To evaluate the association between the tumour uptake of ^{68}Ga-OPS202 and sstr2 expression on tumours as determined by immunohistochemistry (IHC).
- To generate a model integrating PK, pharmacodynamics, dosimetry, anti-tumour activity and safety data if warranted by the data.

1.2 Study design

This study is a phase I/II, multicentre, open-label study of ^{177}Lu-OPS201 therapy with companion diagnostic imaging product ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic solid tumour expressing sstr2 who progressed under or after, failed to respond to, or are intolerant or having a contraindication to available standard-of-care (SoC) treatment options and are deemed suitable for treatment with ^{177}Lu-OPS201 as per the investigator's clinical assessment and/or their individual disease state. More specifically:

- Subjects who had extensive disease-small cell lung cancer (ED-SCLC) at presentation who have progressed on or after one line of standard chemotherapy. If a subject had limited disease-small cell lung cancer (LD-SCLC) at presentation and received surgery and/or radiotherapy as first line treatment (with or without chemotherapy) and has localised relapse, further local treatment (such as surgery) should be considered in addition to the chemotherapy options.

  For subjects with either ED-SCLC or LD-SCLC, if subjects relapse more than 6 months after first-line treatment, re-treatment with their initial regimen is recommended. Subjects may have received prior immunotherapy.
- Subjects with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (BC) after failure of prior standard-of-care treatments and who have received, if indicated, at least one line of hormonal therapy, cyclin-dependent kinase 4/6 (CDK4/6) inhibitor for advanced or metastatic disease and at least one line of chemotherapy for metastatic disease; subjects with *BRCA*-mutated metastatic disease who may have received a poly adenosine diphosphate ribose polymerase (PARP) inhibitor, if available, are eligible; prior adjuvant hormonal treatment and prior adjuvant chemotherapy are allowed.

Once the maximum tolerated cumulative radioactivity is reached and the appropriate peptide mass determined, additional subjects may be treated at this radioactivity/peptide dose, per tumour type cohort.

A clinical research Master Protocol in selected indications (basket design) will encompass this biomolecular target study protocol together with other study protocols targeting the same receptor (sstr2) and will describe the overall background, rationale, objectives, design, methodology and organisation of the overall sstr2-positive cancer research project for OPS201 and OPS202.

Pre-treatment Period

A subject that qualifies will receive ^{68}Ga-OPS202 and will be imaged on PET/CT. Subjects with at least two sstr2 avid lesions of ≥20 mm in the longest diameter on ^{68}Ga-OPS202 PET/CT scan, confirmed by central read and having ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reader will then be treated with ^{177}Lu-OPS201.

Treatment Period - Phase I

Phase I is a multicentre, open-label, single-arm study designed to primarily investigate the safety and tolerability of ^{177}Lu-OPS201 following fractionated i.v. administrations in pretreated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans. This phase will encompass both radioactivity escalation and peptide mass dose evaluation.

Treatment Period - Phase II

Phase II is a multicentre study with open-label multiple single arm cohorts using Simon's optimal two-stage design to evaluate the efficacy, as assessed by ORR, of treatment with ^{177}Lu-OPS201 in subjects with locally advanced or metastatic SCLC, or metastatic HR+/HER2- BC expressing sstr2, as identified by ^{68}Ga-OPS202 PET/CT scans.

Approximately 76 subjects with locally advanced or metastatic SCLC and approximately 96 subjects with metastatic HR+/HER2- BC deemed sstr2-positive on ^{68}Ga-OPS202 PET/CT scans will receive the ^{177}Lu-OPS201 treatment regimen recommended based on the results of the phase I. It is expected that two cycles of ^{177}Lu-OPS201 will be administered in subjects enrolled in phase II.

For phase I and phase II studies, up to four additional cycles might be administered in subjects who tolerate the treatment well and show clinical benefit (CR, PR, or stable disease) after the first two cycles.

These additional cycles will be administered at radioactivity adjusted based on dosimetry results, provided limiting organ radiation dose levels have not been exceeded.

Additional cohorts could be added to the study according to evidence based on preclinical and clinical work and data on ^{68}Ga-OPS202 and ^{177}Lu-OPS201, sstr2 expression and candidate diseases.

Post-treatment Period

Subjects in each phase of the study will have 2-year follow-up after the end of the last ^{177}Lu-OPS201 Cycle, with a visit every 3 until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first.

The phase I schedule of assessment during the study is summarised in Table 4 of the protocol for the core treatment phase and in Table 5 of the protocol for the additional cycles. The phase

II schedule of assessment will be based on the phase I results and documented as part of a protocol amendment.

1.2.1 Study population

This study will be conducted at approximately 30 global clinical sites. Eight of these sites will participate in phase I and all sites in phase II. Participating regions are planned to be North America, Europe and Asia-Pacific. Additional sites may be added.

During phase I, up to 30 subjects will be enrolled for treatment with ^{177}Lu-OPS201. Based on the current knowledge on the proportion of subjects presenting with sstr2-positive tumours, it is anticipated that approximately 55 to 60 subjects will need to be administered ^{68}Ga-OPS202. Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with all the other inclusion/criteria met, the administration of ^{68}Ga-OPS202 and subsequent PET imaging will be stopped. Selection of sstr2-positive tumours for the treatment with ^{177}Lu-OPS201 will be revised in a protocol amendment.

During phase II, approximately 172 subjects (76 subjects with SCLC and 96 with BC) are planned to be enrolled for the Simon's optimal two-stage design. In this study phase, it is anticipated that approximately 340 subjects will need to be administered ^{68}Ga-OPS202 for PET imaging screening. However, recruitment will be stopped once the number of required evaluable subjects (i.e. 76 subjects with SCLC and 96 with BC) is reached.

Further cohorts of subjects with other tumours expressing sstr2 could be added in this protocol according to the advances in the preclinical and clinical knowledge on ^{68}Ga-OPS202 and ^{177}Lu-OPS201 and emerging published data on the diseases. In this case, the additional number of subjects will be estimated based on standard of care historical response (e.g. ORR/best overall response (BOR)) of the corresponding disease.

1.2.2 Study exposure

In phase I, for subjects receiving only two treatment cycles of ^{177}Lu-OPS201, this study will consist of up to 3-week screening period and a 12-week dosing period (+ up to additional 4 weeks in case of adverse events (AEs) that need to be adequately recovered). A treatment cycle is defined as the timeframe of 6 (up to 10) weeks between two administrations or the timeframe of 6 weeks following the last administration. In case of logistical issues, the cycle could be extended by up to additional 2 weeks. Dosing period can be extended up to 36 weeks in case subjects receive up to four additional cycles. Subjects are thus expected to participate in this study for a minimum of 15 weeks and up to 39 weeks (+ up to additional 4 weeks in case of AEs that need to be adequately recovered). In all cases, a long-term follow-up lasting 24 months will start after the end of the last ^{177}Lu-OPS201 cycle.

For phase II, it is anticipated that the duration of the study will be identical to the duration in phase I; however, pending the results of phase I on recommended treatment regimen (doses and intervals) the study duration will be refined.

The subject’s participation in the treatment period of the study will be considered to have ended at the end of core trial (EOCT) or end of additional cycles (EOAC) visit. The subject’s participation in the 24-month follow-up period of the study will be considered to have ended when the subject dies, withdraws consent to the follow-up period, or ends the 24-month follow-up, whichever occurs first.

The overall duration of the study will be approximately 5.5 years. The study will be considered to have started when the first site has been initiated.

The study will be considered to have ended after the last subject has completed the last follow-up visit in the study.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

This is an open-label, single arm trial. After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. Following confirmation of eligibility for the treatment, subjects will be considered as enrolled and allocated to one of the cohorts. Evaluable subjects will be enrolled in cohorts to receive ^{177}Lu-OPS201 therapy at a nominal radioactivity level and peptide mass dose.

1.3.2 Subjects assessments

1.3.2.1 Pharmacodynamics/efficacy assessments

Phase I

Secondary tumour activity endpoints and evaluations planned in phase I are summarised in Table 1. All tumour endpoints will be evaluated by a central imaging core laboratory (ICL).

Table 1 Secondary Tumour Activity Endpoints and Evaluations in Phase I (Core Treatment)

Measure	Timepoints	Variable	Endpoint
Tumour size (longest diameter)	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Tumour response according to RECIST v1.1	ORR BOR DCR PFS
Tumour size (longest diameter)	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour response according to mGa-RECIST*; Metabolic tumour response by ^{18}F-FDG-PET using PERCIST v1.0 and ^{68}Ga-OPS202 by mGa-PERCIST*	ORR BOR
Tumour volume	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Mean change (%) in tumour volume assessed by Volumetric CT (or MRI)	% change from baseline in tumour volume
Event of death	1 and 2 years	Death count	OS
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour-to-background ratio by ^{18}F-FDG-PET using PERCIST v1.0	Quantitative changes in tumour-to-background ^{18}F-FDG-PET uptake
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	sstr2 targeted tumour uptake by ^{68}Ga-OPS202 PET/CT.	Changes in tumour uptake on ^{68}Ga-OPS202 PET/CT

Measure	Timepoints	Variable	Endpoint
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	^{68}Ga-OPS202 uptake and ^{177}Lu-OPS201 therapy response	Change in ^{68}Ga-OPS202 uptake on PET scan in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and BOR
SUV_{max} and SUV_{mean}	Screening[a] for ^{68}Ga-OPS202 PET/CT; Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Uptake on ^{68}Ga-OPS202-PET/CT and ^{177}Lu-OPS201 therapy response (using ceCT/MRI – RECIST v1.1)	Correlation between change (%) in tumour uptake on ^{68}Ga-OPS202 PET/CT at screening[a] with tumour response to ^{177}Lu-OPS201 therapy.
Lesion count	For ^{68}Ga-OPS202 at screening For ^{177}Lu-OPS201 at 24 hours after first administration (Cycle 1)	Uptake on ^{68}Ga-OPS202-PET/CT and uptake on ^{177}Lu-OPS201 SPECT/CT	Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT

Abbreviations: BOR=Best overall response; ce= Contrast enhanced; CT=Computed tomography; DCR=Disease control rate; FDG=Fluorodeoxyglucose; mGa= Modified gallium; MRI=Magnetic resonance imaging; ORR=Objective response rate; OS=Overall survival; PERCIST=Positron emission tomography response criteria in solid tumours; PFS= Progression free survival; PET= Positron emission tomography; RECIST=Response evaluation criteria in solid tumours; SUL=SUV normalised by lean body mass; SUV=Standardised uptake volume.
a. Screening=Baseline scan

Imaging Assessments and Evaluations

Expression of the target receptor (sstr2) will be determined using PET/CT imaging with the companion diagnostic imaging product ^{68}Ga-OPS202. Radiographic response and disease progression will be determined using RECIST v1.1 (CT/MRI) and PERCIST v1.0 (^{18}F-FDG-PET), tumour volume (as assessed by volumetric analysis from CT/MRI), "mGa-RECIST" (CT/MRI and OPS202 PET scan) and mGa-PERCIST evaluating PET ^{68}Ga-OPS202 for sstr2-positive lesions (see details in the IRC).

For each subject, the same imaging methods should be used throughout the study (e.g. ceCT or ceMRI for RECIST v1.1 tumour response assessment). Imaging parameters and approach used at screening should remain consistent throughout the study.

The same PET scanner for all the ^{68}Ga-OPS202 and scans must be used for each subject and likewise for the ^{18}F-FDG-PET.

^{68}Ga-OPS202 scans are anticipated to be identified on lesions that may or may not be seen by FDG-PET scans due to the different metabolic pathways. Therefore, PERCIST, which is based on evaluating the most avid lesion, is likely to be different than one selected by ^{68}Ga-OPS202 and hence the need for evaluation by the modification (mGa-PERCIST). Likewise, RECIST requires the identification of the five largest lesions, which are generally selected by ceCT and a fused PET image. ^{68}Ga-OPS202 may provide an alternative radiological interpretation, which will be evaluated using the modification (mGa-RECIST).

Tumour Response Using RECIST v1.1

For phase I, tumour response will be evaluated using the revised RECIST guideline v1.1 (see IRC). Only subjects with measurable disease at baseline, who have received at least two

administrations of ^{177}Lu-OPS201 and reached the end of Cycle 2 or EOCT visit would be considered evaluable for response.

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

A modified version of RECIST ("mGa-RECIST") will also be assessed. In this second evaluation, tumours will be assessed for reading based on ^{68}Ga-OPS202 and CT. There will be a tumour mapping, so that RECIST can be determined on ^{68}Ga-OPS202 positive lesions. Since there is a possibility for a different set of lesions to be identified by ^{68}Ga-OPS202, this provides the direct response of ^{177}Lu-OPS201 on these tumours to be evaluated.

Tumour response of each subject will be graded as complete response, partial response, stable disease or progressive disease and unevaluable according to RECIST version 1.1. Based on this classification, the following endpoint will be calculated as defined by RECIST v1.1 and "mGa-RECIST":

- ORR: proportion of subjects with a BOR characterised as either CR or PR relative to the total number of evaluable subjects.
- DCR: proportion of subjects with a BOR characterised as CR, PR or stable disease relative to the total number of evaluable subjects.
- PFS will be evaluated as defined per RECIST version 1.1.
- Tumour response using volumetric CT/MRI assessment

The same tumours identified as target lesions and assessed by "mGa-RECIST" will also be evaluated by the percentage change in volume.

Tumour Response Using PERCIST v1.0

For phase I, tumour response will be evaluated using the PERCIST guideline v1.0 (see IRC). Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-OPS201 and reached EOCT visit will be considered evaluable for response.

Key elements of PERCIST include performance of PET scans in a method consistent with the NCI recommendations (UPICT) and those of The Netherlands multicentre trial group on well calibrated and well-maintained scanners. A baseline PET scan will be obtained at approximately 1 hour (50 to 70 minutes) after ^{18}F-FDG injection. At EOCT, the PET scan will be obtained with the same interval (between ^{18}F-FDG-injection and acquisition time) reported at baseline ±15 minutes, but never less than 50 minutes from the injection. All scans will be performed on the same PET scanner with the same injected dose ±20% of radioactivity.

A PERCIST evaluation will also be performed using the ^{68}Ga-OPS202 scans (mGa-PERCIST). This will provide a different set of analyses and support the possibility of using ^{68}Ga-OPS202 as a surrogate endpoint in future studies.

Tumour metabolic response of each subject will be defined based on quantitative changes (SUL_{max} and SUL_{mean}) in tumour-to-background after two cycles versus baseline and will be graded as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD) or unevaluable according to PERCIST v1.0. The grading scale for "mGa-PERCIST" will be evaluated.

Sstr2 Targeted Tumour Uptake

Sstr2 targeted tumour uptake will be determined using PET/CT molecular imaging with the companion diagnostic imaging product ^{68}Ga-OPS202.

The change in ^{68}Ga-OPS202 PET/CT tumour uptake will be computed as a change in SUV_{max} and SUV_{mean} from baseline to EOCT/EOAC visit. These changes will also be compared to clinical outcome and ORR and to ^{177}Lu-OPS201 tumour uptake on SPECT/CT.

Phase II

The primary endpoint is ORR over the two treatment cycles of the core study. Objective response is defined using RECIST v1.1 measured by CT or magnetic resonance imaging (MRI). Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. Radiological interpretation for subject management will be performed at the site, whereas efficacy evaluation will be conducted by the ICL.

Primary and secondary tumour activity endpoints and evaluations are summarised in Table 2.

Table 2 Primary and Secondary Tumour Activity Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Tumour response according to RECIST v1.1	• ORR • BOR • PFS (complemented with events of death) • DRR (CR or PR lasting ≥6 months) • DCR • TTP • TTR • DoR
Tumour size (longest diameter)	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour response according to mGa-RECIST; Metabolic tumour response by ^{18}F-FDG-PET – PERCIST v1.0 and ^{68}Ga-OPS202 by mGa-PERCIST*	• ORR • BOR
Tumour volume	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Mean change (%) in tumour volume assessed by volumetric CT/MRI	% change from baseline in tumour volume
Event of death	1 and 2 years	Death count	OS
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	sstr2 targeted tumour uptake by ^{68}Ga-OPS202-PET/CT	Change in tumour uptake on ^{68}Ga-OPS202 PET/CT scan

Measure	Timepoint	Variable	Endpoint
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour-to-background ratio by ^{18}F-FDG-PET using PERCIST v1.0	Quantitative changes in tumour-to-background ^{18}F-FDG-PET uptake
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	^{68}Ga-OPS202 uptake and ^{177}Lu-OPS201 therapy response	Change in ^{68}Ga-OPS202 uptake on PET scan in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR
SUV_{max} and SUV_{mean}	Screening[a] for ^{68}Ga-OPS202 PET/CT; Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Uptake on ^{68}Ga-OPS202 PET/CT and ^{177}Lu-OPS201 therapy response (using ceCT/MRI – RECIST v1.1)	Correlation between the uptake on ^{68}Ga-OPS202 PET/CT at baseline[a] with tumour response to ^{177}Lu-OPS201 therapy
Lesion count	For ^{68}Ga-OPS202 at screening For ^{177}Lu-OPS201 at 24 hours after first administration (Cycle 1)	Uptake on ^{68}Ga-OPS202-PET/CT and uptake on ^{177}Lu-OPS201 SPECT/CT	Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
Identification of avid lesions	Screening[a]	Number of subjects with avid lesions	Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT

Abbreviations: ce= Contrast enhanced; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DoR=Duration of response; DRR=Durable response rate; FDG=Fluorodeoxyglucose; MRI=Magnetic resonance imaging; OS=Overall survival; PERCIST=Positron emission tomography response criteria in solid tumours; PET=Positron emission tomography; PFS=Progression free survival; PR=Partial response; RECIST=Response evaluation criteria in solid tumours; SUL=SUV normalised by lean body mass; SUV=Standardised uptake volume; TTP=Time to progression; TTR=Time to response.
[a] Screening=Baseline scan

Patient Reported Outcomes (PROs) will be assessed in phase II using the following questionnaires: the EuroQoL 5-dimension 5-level (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

The EQ-5D-5L questionnaire is a 2-page, generic preference-based Quality of Life (QoL) measure comprised of a 5-item health status measure and a visual analogue scale and is used to generate two scores. The EQ-5D utility score is based on answers to five questions to evaluate mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problem, slight problems, moderate problems, severe problems, unable to/extreme.

The EQ-5D-5L visual analogue scale generates a single health status index, the analogue scale ranges from 0 to 100 in which subjects are asked to rate their current health state by drawing a line from a box marked.

The EORTC QLQ-C30 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumour types. It assesses 15 domains consisting of five functional domains (physical, role, emotional, cognitive, social), nine symptom domains (fatigue, nausea and

vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and a global health status or QoL scale as shown below. Missing data will be handled using the method described in the scoring guidelines for EORTC QLQ-C30. If at least half of the items from a scale are answered, it is assumed that the missing items have values equal to the average of those items that are present for that respondent.

Table 3 Scoring EORTC QLQ-C30 version 3.0

	Number of items	Item range	Item numbers
Global health status/QoL			
Global health status/QoL	2	6 (1-7)	29, 30
Functional scales			
Physical functioning	5	3 (1-4)	1-5
Role functioning	2	3 (1-4)	6, 7
Emotional functioning	4	3 (1-4)	21-24
Cognitive functioning	2	3 (1-4)	20, 25
Social functioning	2	3 (1-4)	26, 27
Symptom scales / items			
Fatigue	3	3 (1-4)	10, 12, 18
Nausea and vomiting	2	3 (1-4)	14, 15
Pain	2	3 (1-4)	9, 19
Dyspnoea	1	3 (1-4)	8
Insomnia	1	3 (1-4)	11
Appetite loss	1	3 (1-4)	13
Constipation	1	3 (1-4)	16
Diarrhoea	1	3 (1-4)	17
Financial difficulties	1	3 (1-4)	28

The PK of ^{177}Lu-OPS201 and OPS201, as well as the dosimetry assessments and timepoints are related to the phase I of the study. PK and dosimetry assessments will also be included in phase II. However, the timepoints might be revised based on the phase I results and document as part of a protocol amendment.

1.3.2.2 Safety assessments

The primary safety variable is the occurrence of Dose-Limiting Toxicities (DLTs) during Cycle 1 or Cycle 2.

The DLTs are defined for any of the following Investigational Radio-Pharmaceutical Product-related (IRPP-related) AEs according to National Cancer Institute Common Terminology Criteria Adverse Event (NCI-CTCAE) scale version 5.0 that occur during the defined DLT assessment period (from the first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration):

- Grade 4 neutropenia lasting for seven or more consecutive days.
- Grade 3 and 4 febrile neutropenia.
- Grade 4 thrombocytopenia for seven or more consecutive days.
- Grade 3 thrombocytopenia complicated by a bleeding event.
- Grade 4 anaemia.

- Grade 3 anaemia requiring transfusion.
- Grade 3 or higher laboratory abnormalities of aspartate amino transferase/alanine amino transferase (AST/ALT) and/or bilirubin, with the following exceptions:

  for subjects with Grade 1 AST/ALT at baseline (>upper limit of normal (ULN) to 3xULN), a AST/ALT level of >7.5xULN will be considered a DLT.

  for subjects with Grade 2 AST/ALT at baseline (>3xULN to 5xULN), a AST/ALT level > 10xULN will be considered a DLT.
- any Grade 3 or higher acute kidney injury (creatinine >3x baseline or >4.0 mg/dL).
- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate supportive care
  - Grade 3 fatigue lasting less than a week
  - Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, is not clinically complicated and resolves spontaneously or with conventional medical interventions
  - Grade 3 or higher amylase or lipase not associated with symptoms or clinical manifestations of pancreatitis
- any toxicity related to ^{177}Lu-OPS201 resulting in a treatment delay of more than 4 weeks due to delayed recovery to baseline or resolution of any AE of Grade 2 or more (exception of alopecia and lymphopenia).
- Grade 5 toxicity (death)

DLT Assessment: During the DLT assessment period (from first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration), two assessments over 6 weeks each will be performed. The first, between first and second administration and the second, between second administration and EOCT visit.

DLT Population: Subjects will be evaluable for DLT if received Cycle 1 and Cycle 2 administrations and completed DLT assessment period (i.e. 6 weeks after second administration) or stopped treatment because of a DLT during DLT assessment period.

Other safety assessments include clinical laboratory haematology, serum chemistry, urinalysis and pregnancy tests, physical examination, vital signs, electrocardiography.

1.3.2.3 Physical Examination

Physical examinations, including body weight will be conducted at Screening, Day 1, Day 15 of Cycle 1 and Cycle 2 and EOCT.

1.3.2.4 Vital Signs

Supine and standing systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate will be measured at Screening, Day 1, Day 2, Day 3, Day 15, Day 22, Day 29, Day 36 of each cycle and EOCT.

For the day of infusion vital signs will be measured prior to infusion and at infusion completion (0 minutes), 30±5 minutes, 60±10 minutes, 4 hours ±10 minutes after the end of infusion.

1.3.2.5 Electrocardiography

An ECG analysis will be included as a safety evaluation/endpoint in this study. Twelve lead-ECG will be recorded at Screening, Day 1 of each cycle and EOCT and 6-hour Holter ECG

will be recorded at Day 1 of each cycle. Twelve lead ECGs will be recorded so that the different ECG intervals (RR, PR, QRS, QT, QTcF) will be measured.

1.3.2.6 Clinical Laboratory Tests

Haematology

Blood samples will be collected to assess the following parameters: RBC count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count.

Blood Biochemistry

Blood samples will be collected to assess the following parameters:

- urea, uric acid, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase
- albumin and total protein, total cholesterol, triglycerides, fasting glucose
- C-reactive protein (CRP)

Estimated glomerular filtration rate (eGFR) will be calculated based on serum creatinine levels using MDRD formula.

Urinalysis

Urine samples will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose. Proteinuria will be performed with dipsticks, in case of positivity, a proteinuria over 24 hours will be performed.

Pregnancy Test

A β human chorionic gonadotrophin (HCG) serum test will be performed for all female subjects of childbearing potential at Screening (visit 1) and if clinically indicated thereafter. Moreover, a HCG urine test will be performed at Day 1 of each cycle before each 177Lu-OPS201 administration.

Hypothalamic-Pituitary-Adrenal Axis Biomarkers

Sample for hormone analysis will be collected at predose Day 1 of each Cycle and at EOCT/EOAC visit. These samples include analysis of cortisol, TSH, parathyroid hormone (PTH), luteinising hormone (LH), follicle-stimulating hormone (FSH), free thyroxine (FT4) and IGF-1.

Hormone analyses will only be analysed in subjects who do not have substitution or therapy impacting one of the respective pituitary axis (e.g. no cortisol sampling in subjects who receive corticosteroids, no thyroid-stimulating hormone and free thyroxine sampling in subjects who have thyroxine substitution.

TSH, cortisol and IGF-1 will be measured at baseline and at end of core trial.

Specific Renal Safety Biomarkers

Renal safety biomarkers include markers specific of the different renal tubule regions toxicity: alpha-glutathione S-transferase (GST), glutathione S-transferase P1 (GSTP1), kidney injury molecule-1 (KIM-1), clusterin, cystatin-C, calbindin, beta-2 microglobulin and creatinine.

Urine samples will be collected at the following timepoints:

- Cycle 1:

- Day 1: early morning, before the infusion (baseline)
- Day 3: early morning (48 hours after the end of 177Lu-OPS201 infusion at the latest)

• End of core trial Visit/Early Withdrawal Visit: early morning.

Specific Pancreatic Function Biomarker

Samples for specific pancreatic function biomarker will include glycosylated haemoglobin HbA1c and glucose. Blood will be collected at Day 1 of each visit before infusion and End of core trial visit / Early Withdrawal.

Testicular Function Biomarkers

Samples for Testicular Function Biomarkers will include testosterone, Inhibin B and sex hormone-binding globulin SHBG. Blood will be collected at Day 1 of each visit before infusion and End of core trial visit / Early Withdrawal.

1.3.2.7 Nuclear Medicine Imaging for Dosimetry

All images will be centralised and analysed by independent readers for dosimetry analysis of the dose limiting organs and tumour lesions.

To determine the biokinetics and perform an absolute quantification, whole body scans (planar scintigraphy) and SPECT/CT will be performed at each cycle at the following timepoint ranges just after the end of ^{177}Lu-OPS201 infusion:

- Day 1: 2 to 4 hours
- Day 2: 16 to 24 hours
- Day 3: 40 to 48 hours
- Day 4 to Day 5: 72 to 96 hours
- Day 6 to Day 7: 144 to 168 hours.

At the timepoint between 16 to 24 hours, SPECT/diagnostic CT will be performed. For all other time points, SPECT/low dose CT will be performed.

For subjects receiving additional administrations (up to four additional cycles), dosimetry assessments will be performed after each additional administration with nuclear medicine imaging described above.

1.3.2.8 Pharmacokinetics of OPS201

Blood Sample Collection

For each subject, OPS201 plasma concentration will be measured. Each subject will have blood samples collected at Cycle 1 only at the following time points:

- Day 1: before the infusion (baseline), at the end of infusion of ^{177}Lu-OPS201 (0), 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes), 6 (±30 minutes), and 10±1 hours after the end of infusion.
- Day 2: 24±2 hours after the end of infusion of 177Lu-OPS201.
- Day 3: 48±2 hours after the end of infusion of 177Lu-OPS201.

Urine Sample Collection

The samples for urine OPS201 concentration analysis will be taken from urine collected during four different periods at Cycle 1: from 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours (0 to 4 and 4 to 8 hours only in US sites) after the start of infusion, with an initial void collection shortly before the infusion (0) and a final collection, 48 hours after the end of ^{177}Lu-OPS201 infusion.

1.3.2.9 Exploratory Biomarkers and Biobanking

DNA-DSB in Peripheral Lymphocytes

DNA-DSB in lymphocytes will be measured using an immunofluorescent method in selected sites. DNA-DSB will be measured in lymphocytes (n=6 per cycle) before the infusion (baseline), at 1, 4, 24, 48 and 72 to 96 hours after the end of ^{177}Lu-OPS201 infusion (Cycle 1 and Cycle 2).

DNA Repair Capacity in Peripheral Lymphocytes

DNA repair capacity in lymphocytes will be measured using an enzymatic method in selected sites.

Germinal Mutation in Blood

Blood sample will be collected in a Paxgen-DNA tube at Cycle 1 Day 1 before infusion from the arm opposite to that of the study drug infusion or from another site.

Tumour Biopsy

Sequential biopsies will be obtained at Screening and EOCT or at disease progression, whichever occurs earlier. Baseline biopsy is mandatory and post-treatment biopsy is optional.

Tumour Micro-environment and Other Markers of Interest

The biopsy will be used to evaluate tumour microenvironment and other markers of interest of the disease, such as: proliferative marker (ki-67), Tumour infiltrating immune cells (TIL/TME), DNA-DSB (gammaH2AX), target receptor evaluation (sstr2), tumour gene expression profile and gene mutations (targeted or TMB).

Specific markers depending on the indication will also be assessed in tumour biopsy (i.e. for BC: ER, progesterone receptor and HER2 protein expression and for SCLC: p53, Rb1, MYC and DLL3 gene expression).

DNA Repair Capacity in Tumour Tissue

DNA repair capacity will be measured in tumour tissue by a specialised laboratory in case sufficient material is available (biopsy larger than 5 mm^3).

Biobanking

Analysis of biobank samples will be performed outside the scope of the main study and will be reported separately. Therefore, this analysis is optional.

1.3.2.10 Withdrawal/discontinuation

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation.

A subject (or a legal representative) has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator at the institution.

The investigator and/or sponsor can decide to withdraw a subject from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the following reasons:

- Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date this decision is to be recorded and every

effort should be made to continue safety evaluations, tumour assessments, and collection of subsequent anticancer treatment information and follow-up information for survival.

- The investigator feels it is not in the best interest of the subject to continue on study.
- Subject participation in another clinical study using an investigational agent or investigational medical device.
- Necessity for treatment with other systemic anticancer therapy (non-protocol defined).
- Necessity for withholding study drug for greater than 6 weeks for study-treatment related AEs.
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilised) to use medically accepted methods of contraception.
- Female subjects who become pregnant.
- Request by the sponsor.
- Subject request to discontinue study treatment (with or without concurrent withdrawal of informed consent).
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the sponsor
- Unacceptable side effects the investigator feels may be due to study treatment.

In addition, if any of the following occur, no further treatment will be administered:

- Cumulative kidney absorbed dose exceeds 23 Gy.
- Cumulative BM absorbed dose exceeds 1.5 Gy during core trial or up to 2 Gy during additional cycles, as determined by dosimetry of peripheral blood samples and imaging.
- Subject has not sufficiently recovered from an adverse event despite extension of the dosing interval by 4 weeks (such as delayed grade 3-4 haematotoxicity)
- Hypersensitivity to the active substance or to any of the excipients of the study drugs
- Radiological disease progression

All cases of discontinuation will be discussed between the investigator and the sponsor.

A subject can also withdraw their consent to the treatment period but agree to take part in 24-month follow-up period.

If a subject is considered Not Evaluable for DLT due to withdrawal during DLT assessment period, he/she will be replaced by another subject.

In phase I, a cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or discontinue early during Cycle 2. If subjects discontinue for any reason other than a DLT (e.g. disease progression) before end of Cycle 2, they might be replaced.

The phase I will be terminated once the MTCA has been determined. The phase II is designed with early stopping criteria, allowing any cohort to be closed early in case of futility.

A specific site or a given cohort can also be discontinued or the entire study may be terminated at any time if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessments for subjects who are still in the study will be performed. Some possible reasons for the closure of a study site may include:

- failure of the investigator staff to comply with the protocol or with the Good Clinical Practice (GCP) guidelines.
- safety concerns.
- inadequate subject recruitment.

In case of premature discontinuation of a site or the complete study, depending on the reason(s) for the discontinuation, the sponsor will notify the investigator(s) affected in writing as to whether the ongoing subjects should continue the remaining IRPP dose administration(s).

Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with all the other inclusion/criteria met, the administration of ^{68}Ga-OPS202 and subsequent PET imaging will be stopped. Selection of sstr2-positive tumours for the treatment with ^{177}Lu-OPS201 will be revised in a protocol amendment.

1.3.3 Schedule of assessments

The phase I study design with and without additional cycles are shown in Figure 1 and Figure 2.

Figure 1 Phase I Study Design Scheme (Without Additional Cycles)

Figure 2 Phase I Study Design Scheme (With Additional Cycles)

Pharmacokinetics, biodistribution and dosimetry endpoints and measurement timepoints for phase II will be defined according to the phase I results.

The current protocol may be amended at the end of the phase I to define the phase II design.

1.3.4 Planned sample size

Sample Size Determination for Phase I

This is primarily a descriptive safety and tolerability study. The total number of subjects is not based on a formal statistical sample size calculation.

The actual sample size required to adequately determine the MTCA/MTSA during phase I depends on the initial activity, rate of radioactivity escalation and the observed radioactivity-toxicity and radioactivity/organ absorbed dose relationships. Simulation studies have been performed to quantify the operational characteristics (ie, precision of the MTCA/MTSA, sample size, number of subjects being over/under dosed) of the adaptive radioactivity-escalation design under a number of plausible escalation-DLT relationship scenarios. Based on experience, the chosen sample size of 3-5 subjects per cohort is considered to be sufficient to fulfil the objectives of the study. It is anticipated that between 15 and 30 subjects will be required to establish the MTCA or maximum administered cumulative activity (MACA).

Sample Size Determination for Phase II

The sample size is calculated using Simon's optimal two-stage design based on the ORR rate (complete response (CR) + partial response (PR)) following ^{177}Lu-OPS201 treatment.

For the Simon's optimal two-stage design, the hypotheses that will be tested for each cohort are:

H_0: ORR$\leq$ORR$_0$ versus the alternative H1: ORR>ORR$_0$ where ORR is the true objective response rate following ^{177}Lu-OPS201 treatment that warrants further clinical development, and ORR$_0$ is the minimum objective response rate to be excluded from further clinical development. The thresholds for ORR and ORR$_0$ may be updated based on results from phase I and the advances in scientific knowledge.

ORR will be analysed at the end of Stage 1 (6 weeks after the second ^{177}Lu-OPS201 administration (Cycle 2) of the core treatment period of the last evaluable subject of the Stage 1 cohort for each type of cancer). If the observed number of responders is below a predefined threshold, the respective study cohort will be stopped for futility. Otherwise, additional subjects will be treated to complete the planned enrolment. At the end of Stage 2, the null hypothesis will be rejected depending on the total observed number of responders based on a predefined threshold.

For the SCLC cohort, with 69 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 23% and an alternative hypothesis ORR rate of 40% at one-sided significance level of α=0.05. The first stage consists of 29 subjects. If seven responses or less are seen in the first 29 subjects then the trial is stopped. Otherwise accrual continues to a total of 69 response evaluable subjects. Approximately 76 subjects are planned to be enrolled to account for 10% study dropout.

For the BC cohort, with 87 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 12% and an alternative hypothesis ORR rate of 25% at one-sided significance level of α=0.05. The first stage consists of 33 subjects. If four responses or less are seen in the first 33 subjects then the trial is stopped. Otherwise accrual continues to a total of 87 response evaluable subjects. Approximately 96 subjects are planned to account for 10% study dropout.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Eligibility screened population

All subjects screened (i.e. who signed the informed consent).

2.2 Efficacy

2.2.1 Intention-To-Treat population (ITT)

All subjects who received at least one dose of ^{177}Lu-OPS201 in the phase II of the study.

2.2.2 Per Protocol population (PP)

All subjects in the ITT population in the phase II of the study who have measurable disease at baseline, have at least one post baseline response assessment and no major protocol deviations occurred that could affect efficacy analysis.

The PP population will be used for the analyses of ORR, DCR, PFS, OS, TTP, TTR and DoR.

2.2.3 ^{68}Ga-OPS202 positive population

All subjects who received ^{68}Ga-OPS202 with at least one readable screening ^{68}Ga-OPS202 PET, at least one readable screening ceCT scan, at least one readable screening ^{18}F-FDG-PET scan, and have at least one lesion identified by central readers on screening ^{68}Ga-OPS202 PET. This population encompasses subjects with sstr2 positive lesion(s) (i.e., avid lesion with ^{68}Ga-OPS202).

2.2.4 ^{68}Ga-OPS202 response evaluable population

All subjects in the ^{68}Ga-OPS202 positive population with the following 6 weeks post second ^{177}Lu-OPS201 administration (second cycle): a readable ^{68}Ga-OPS202 PET, a readable ceCT scan, and a readable ^{18}F-FDG-PET scan.

The ^{68}Ga-OPS202 positive and ^{68}Ga-OPS202 response evaluable populations will be used for the analyses of diagnostic endpoints of ^{68}Ga-OPS202.

2.3 Safety

Safety population is all subjects who received at least one dose of ^{177}Lu-OPS201 or ^{68}Ga-OPS202.

- ^{68}Ga-OPS202 safety population: All subjects who received at least one dose of ^{68}Ga-OPS202.
- ^{177}Lu-OPS201 safety population: All subjects who received at least one dose of ^{177}Lu-OPS201.

2.4 MTCA evaluable population

MTCA evaluable population is all subjects who received at least one dose of ^{177}Lu-OPS201 in the radioactivity escalation of the phase I of the study. The MTCA-evaluable population will be used to determine the MTCA/MTSA/MACA for phase I of the study.

2.5 Dosimetry

2.5.1 Dosimetry population

All subjects who received at least one dose of ^{177}Lu-OPS201 for whom at least one complete set of dosimetry imaging and dosimetry blood sample measurements is available. Dosimetry may be analysed separately for phase I and phase II.

2.5.2 Per protocol dosimetry population

All subjects in the dosimetry population for whom no major protocol violations occurred affecting dosimetry variables. Dosimetry may be analysed separately for phase I and phase II.

2.6 Pharmacokinetics

2.6.1 Radiopharmaceutical pharmacokinetic population

All subjects who received at least one dose of ^{177}Lu-OPS201 and have at least one measured radioactive concentration in blood. Radiopharmaceutical PK may be analysed separately for phase I and phase II.

2.6.2 OPS201 pharmacokinetic population

All subjects who received at least one dose of ^{177}Lu-OPS201 and have no major protocol deviations affecting the PK variables and who have a sufficient number of OPS201 concentrations to estimate the main PK parameters (i.e. maximum observed concentration (C_{max}), time to maximum observed drug concentration (t_{max}) and area under curve (AUC)). OPS201 PK may be analysed separately for phase I and phase II.

2.7 Primary population

For the phase I of the study, the primary analysis based on the primary safety endpoint will be performed on the MTCA evaluable population.

For the phase II of the study, the primary analysis based on the primary efficacy endpoint will be performed on the PP population. In addition, secondary/confirmatory analysis may be performed on the ITT population.

The primary dosimetry analysis will be based on the dosimetry population. A supportive analysis will be based on per protocol dosimetry population.

The assessment of safety and tolerability will be based on the safety population.

The assessment of PK will be based on the radiopharmaceutical pharmacokinetic population and OPS201 pharmacokinetic population.

2.8 Reasons for exclusion from the analyses

Any major protocol deviation will be described and its impact on inclusion in each analysis population for any subject will be specified. The final list of protocol deviations impacting each analysis population will be reviewed prior to interim analysis and database lock. The list may be updated, up to the point of interim analysis and database lock, to include any additional major protocol deviations impacting inclusion in each analysis population.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated.

Statistical analyses will be performed by CCI [redacted] managed by the sponsor's biometry department.

Data from phase I and phase II will be analysed and reported separately. Phase I analyses will be performed by cohort and in total for the applicable population. Phase II analyses will be performed by cancer type for efficacy analyses and by cancer type and in total for safety analyses for the applicable population.

3.1.1 Primary endpoints

Phase I

The primary endpoint is the MTCA or the MACA if the MTCA is not identified during the phase I. The primary variables determining the MTCA will be the incidence of DLTs and the cumulative organ absorbed doses (Gy) during two cycles of treatment. The DLT assessment

period for the determination of the primary endpoint starts from the first administration of ^{177}Lu-OPS201 and ends 6 weeks after the second administration.

The MTCA is defined as the maximum cumulative radioactivity that may be administered following fractionated i.v. administrations of at least 6 weeks apart, so that:

- no more than 33% of the subjects experience a DLT after first or second administration of ^{177}Lu-OPS201 and/or
- no more than 10% of the subjects have cumulative absorbed dose in each target organ exceeding the acceptability limits (1.5 Gy in BM and 23 Gy in kidney) after second administration of ^{177}Lu-OPS201.

The MTSA is defined as the highest single radioactivity that can be given so that no more than 33% of the subjects experience a DLT during Cycle 1. The MTSA will be determined in case of unacceptable toxicity seen after first administration of ^{177}Lu-OPS201.

The MACA will be determined if the MTCA is not reached during the dose escalation.

Phase II

Phase II primary endpoint is to evaluate the ORR of fractionated i.v. administration of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans. The primary endpoint is ORR measure by RECIST 1.1 over the two treatment cycles of the core study. Objective response is defined as the sum of PR and CR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. All images will be sent to an ICL for evaluation and confirmation of response.

3.1.2 Secondary endpoints

All imaging endpoints will be assessed by blinded independent readers managed by the ICL.

Phase I

Pharmacokinetics, biodistribution and dosimetry

For PK, biodistribution and dosimetry of ^{177}Lu-OPS201, the endpoints are:

- C_{max}, t_{max}, maximal uptake (%), AUC at the target lesions, discernible organs and blood and elimination half-life ($t_{½}$) of radioactivity concentrations in blood.
- Highest absorbed dose, Specific absorbed dose to the target lesions (Gy/GBq), Specific absorbed dose per organ (Gy/GBq) and Cumulative absorbed organ doses (Gy).

For PK of OPS201, the endpoints are:

- Pharmacokinetic parameters including, but not limited to, C_{max}, AUC, $t_{1/2}$, total plasma clearance (CL), apparent volume of distribution (V_d), cumulative amount (of unchanged drug) excreted into the urine (A_e), renal clearance, as measured in plasma and urine at defined timepoints.

Pharmacodynamic/efficacy

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration compared to Screening as assessed by CT or MRI:
  - RECIST version 1.1 (tumour size is defined as the sum of the diameters of the target lesion in subjects who received ^{177}Lu-OPS201)
  - volumetric CT
- PFS as determined from start of study treatment until occurrence of tumour progression or death.

- BOR defined as the best response recorded from the start of the treatment until disease progression/recurrence.
- ORR defined as proportion of subjects with a BOR characterised as either CR or PR relative to the total number of evaluable subjects.
- DCR defined as proportion of subjects with a BOR characterised as CR, PR or stable disease relative to the total number of evaluable subjects.
- PFS will be evaluated as defined per RECIST version 1.1.
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause.
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Changes in tumour uptake (assessed based on SUV_{max} and SUV_{mean}) on ^{68}Ga-OPS202 PET/CT from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle) as compared to clinical response and BOR.
- Correlation between change (%) in tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle) using ceCT/MRI – RECIST v1.1.
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT.
- Diagnostic sensitivity of 68Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of 68Ga-OPS202 imaging using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ^{177}Lu-OPS201 SPECT/CT.

Phase II

Efficacy

- Durable response rate (DRR: CR or PR lasting ≥6 months)
- Progression free survival (PFS) as determined from start of study treatment until occurrence of tumour progression or death. Progression will be radiologically assessed by RECIST v1.1 and "mGa-RECIST" as two separate endpoints; for RECIST it will be measured at Screening and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle); for "mGa-RECIST" it will be measured at Screening and 6 weeks after the second ^{177}Lu-OPS201 administration (second cycle).

  PFS (months) = (event or censoring date – first dose date + 1)/30.4375

  PFS will be right-censored for subjects who met one or more of the following conditions:

  - no baseline disease assessment or no evaluable post baseline disease assessments unless death occurred prior to the first planned assessment at post baseline (in which case death will be considered a PFS event).

- amputation or surgical resection of tumour in the absence of documented disease progression.
- subsequent anticancer therapy in the absence of documented disease progression.
- died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
- alive and without documented disease progression on or before the data cutoff date

If a subject meets more than one of these conditions, then the scenario that occurs first will be used for analysis. The progression or censoring date will be determined based on the conventions listed in Table 4:

Table 4 Date of Progression or Censoring for PFS

Situation	Date of progression or censoring	Outcome
Death before first planned disease assessment	Date of death	Event
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
No baseline disease assessment or no evaluable post-baseline disease assessments	Date of first dose of ^{177}Lu-OPS201	Censored
Surgical resection or subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last disease assessment prior to surgery or start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last disease assessment	Censored

- Other response endpoints (same timepoints as for PFS):
  - disease control rate (DCR)
  - time to progression (TTP)
  - time to response (TTR)
  - duration of response (DoR)

TTP or TTR (months) = (event or censoring date – first dose date + 1)/30.4375

TTP does not include deaths. Deaths are censored, either at the time of death or at an earlier visit representing informative censoring.

The progression or censoring date will be determined based on the conventions listed in Table 5:

Table 5 Date of Progression or Censoring for TTP

Situation	Date of progression or censoring	Outcome
Death before or after first planned disease assessment	Date of death	Censored
Disease progression between planned disease assessments	Date of first disease assessment showing disease progression	Event
No baseline disease assessment or no evaluable post-baseline disease assessments	Date of first dose of ^{177}Lu-OPS201	Censored
Surgical resection or subsequent anticancer treatment started before disease progression (without disease progression beforehand)	Date of last disease assessment prior to surgery or start of subsequent anticancer treatment	Censored
Disease progression after missing two or more consecutively scheduled disease assessments	Date of last disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last disease assessment	Censored

DOR will be calculated as follows for subjects who have a BOR of CR or PR:

DOR (months) = (Event/Censoring Date – Response Start Date + 1) / 30.4375

Subjects who meet one or more of the following conditions will be right-censored for DOR:

- amputation or surgical resection of tumour in the absence of documented disease progression.
- subsequent anticancer therapy in the absence of documented disease progression
- died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
- alive and without documented disease progression on or before the data cut-off date

If a subject meets more than one of these conditions, then the scenario that occurs first will be used for the analysis. The progression or censoring date will be determined based on the conventions listed in Table 6.

Table 6 Date of Progression or Censoring for DOR

Situation	Date of progression or censoring	Outcome
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Surgical resection or subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last disease assessment prior to surgery or start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last disease assessment	Censored

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration (each cycle) compared to baseline, as assessed by volumetric CT/MRI.
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause. Subjects who were lost to follow-up or who were still alive at the time of analysis will be censored at the last day the subject was known to be alive or data cut-off date, whichever occurs first. OS will be calculated as follows:
- OS (months) = (Death or Censoring Date – First Dose Date + 1)/30.4375
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Change in ^{68}Ga-OPS202 uptake on PET scan after the second ^{177}Lu-OPS201 administration (second cycle) as assessed by SUV_{max} and SUV_{mean} in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR.
- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT.
- Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by the identification of avid lesions in subjects screened for ^{177}Lu-OPS201 treatment at baseline.
- Diagnostic sensitivity of 68Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ^{177}Lu-OPS201 SPECT/CT.

Subject Reported Outcomes

Changes in health-related quality of life scores from baseline to EOCT measured by EQ-5D-5L and EORTC QLQ-C30.

3.1.3 Safety endpoints

Safety and tolerability measured by the type, nature, severity, expectedness and frequency of AEs overall and per grade according to the current version of the NC-CTCAE (version 5.0) and significant laboratory abnormalities.

Pharmacokinetics, biodistribution and dosimetry endpoints and measurement timepoints for phase II will be defined according to the phase I results.

3.1.4 Exploratory endpoints

Phase I/II

Biomarkers

- Association between the uptake on ^{68}Ga-OPS202 PET/CT with sstr2 expression on tumours as determined by IHC.
- Change in renal safety biomarkers compared to baseline.
- Change from baseline in tumour microenvironment, transcriptomics, DNA repair, gene mutations and other disease markers of interest.
- Change from baseline in DNA repair capacity in blood.

Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of additional biomarkers from the biobank samples will be performed outside the scope of the main study and reported separately.

Serum and whole blood ribonucleic acid (RNA) samples will be collected during

screening, on Day 1 of Cycle 2 and at EOCT visit.

Instructions for collection, processing, handling and shipment of the banking samples will be outlined in the laboratory manual.

3.1.5 Multiplicity

No multiple testing will be performed in this study.

Therefore, type I error will not be adjusted.

3.1.6 Significance testing and estimation

As this is a descriptive safety and tolerability study, no formal statistical testing of safety will be carried out.

3.2 Analysis methods

3.2.1 Efficacy

3.2.1.1 Therapeutic Efficacy of ^{177}Lu-OPS201

Tumour response will be evaluated by the ICL. Phase I analyses on tumour responses will be using the MTCA evaluable population. Phase II analyses on tumour responses will be using the ITT population and the PP population.

Phase I

- The summaries of BOR will include number and percentage of subjects in each of these categories (CR, PR, SD, PD, NE, NA). BOR will be assessed based on RECIST v1.1

(Eisenhauer EA, 2009). BOR by ^{68}Ga-OPS202 PET mGa-RECIST, will also be analysed similarly. BOR by ^{18}F-FDG-PET PERCIST v1.0 and by mGa-PERCIST will be analysed similarly as BOR by RECIST 1.1 using each of these categories (CMR, PMR, SMD, PMD, NE, NA).

- ORR over the two treatment cycles of the core study measured by the ICL. Objective response is defined as the percentage of subjects with BOR as PR and CR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. The point estimates of the ORR will be calculated and accompanied by a 95% exact binomial confidence interval (CI) using the Clopper-Pearson method. ORR by ^{68}Ga-OPS202 PET, mGa-RECIST will also be analysed similarly. ORR of CMR and PMR by PERCIST 1.0 and by mGa-PERCIST will be analysed similarly as ORR by RECIST 1.1.
- DCR by RECIST v1.1 defined as the percentage of subjects who have achieved a response of CR, PR or stable disease, will be analysed and summarised in the same manner as ORR.
- PFS by RECIST v1.1 will be summarised descriptively using the Kaplan-Meier method. The Kaplan-Meier estimates of the median PFS, and the corresponding 2-sided 95% confidence intervals calculated using Greenwood's formula will be presented.
- OS is defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of death due to any cause. Subjects who have not died will be censored at the date of last contact which may be identified from a visit date or any study assessment (physical examination, vital signs, ECOG performance status, ECG, study drug record, radiological evaluation, laboratory sampling, concomitant or follow-up procedures), AE, medication, or disposition information. OS will be calculated using the Kaplan-Meier method. One-year and two-year survival are defined as the subject survival probability at 1 year and 2 years, respectively, after the date of first dose of ^{177}Lu-OPS201. One-year and two-year survival probability along with the associated 2-sided 95% confidence intervals, will be provided. If there are a sufficient number of OS events (i.e., deaths), median OS time, first and third quartiles and associated 95% 2-sided confidence intervals, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). Kaplan-Meier OS curves also will be provided.
- Change (%) in tumour volume from volumetric CT (or MRI) and sum of the diameters of the target lesion per RECIST version 1.1 from Screening to 6 weeks after each ^{177}Lu-OPS201 administration (each cycle) will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their best change (%) or largest reduction (%) from Screening in the sum of the diameters in target lesions. Spider and swimmer plots will be used to display the change in tumour burden over time for individual subjects and the occurrence of clinical outcomes of interest (e.g., tumour response, disease progression, treatment discontinuation, death).
- Quantitative changes (%) (SUV normalised by lean body mass (SUL)max and SULmean) in tumour-to-background 18F-FDG-PET uptake from Screening and 6 weeks after second 177Lu-OPS201 administration from the second cycle will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their best change (%) or largest reduction (%) from Screening in SULmax and SULmean in target lesions. Spider and swimmer plots will be used to display the change in tumour burden over time for individual subjects and the occurrence of clinical outcomes of

interest (e.g., tumour response, disease progression, treatment discontinuation, death). Numbers and percentages of CMR (complete metabolic response), PMR (partial metabolic response), SMD (stable metabolic disease), and PMD (progressive metabolic disease) using PERCIST v1.0 criteria will be summarised.

- Change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202 PET/CT from Screening and 6 weeks after second 177Lu-OPS201 administration (second cycle) will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their change (%) from Screening in tumour uptake to 6 weeks after second 177Lu-OPS201 administration (second cycle).
- Change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202-PET/CT from Screening to 6 weeks after second 177Lu-OPS201 administration (second cycle) will be summarised descriptively by BOR tumour response according to RECIST v1.1.
- Correlation between change (%) in tumour uptake on 68Ga-OPS202 (assessed based on SUVmax and SUVmean) PET/CT at baseline with tumour response to 177Lu-OPS201 therapy using ceCT/MRI RECIST v1.1 will be assessed. Spearman correlation coefficient and its p-value will be reported for change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202-PET/CT from Screening and tumor response 6 weeks after second 177Lu-OPS201 administration (second cycle)
- Correlation between the number of lesion counts from 68Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images at screening and the number of lesion counts from 177Lu-OPS201 SPECT/CT at 24 hours after the first 177Lu-OPS201 administration (Cycle 1) will be assessed by Pearson correlation coefficient and its p-value.

Phase II

- ORR over the two treatment cycles of the core study measured by the ICL. Objective response is defined as the sum of PR and CR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. The point estimates of the ORR will be calculated and accompanied by a 95% exact binomial confidence interval (CI) using the Clopper-Pearson method. ORR by ^{68}Ga-OPS202 PET mGa-RECIST, will also be analysed similarly. ORR of CMR and PMR by PERCIST 1.0 and by mGa-PERCIST will be analysed similarly as ORR by RECIST 1.1.
- The summaries of BOR will include number and percentage of subjects in each of these categories (CR, PR, SD, PD, NE, NA). BOR will be assessed based on RECIST v1.1 (Eisenhauer EA, 2009). BOR by ^{68}Ga-OPS202 mGa-RECIST will also be analysed similarly. BOR by ^{18}F-FDG-PET PERCIST v1.0 and by mGa-PERCIST will be analysed similarly as BOR by RECIST 1.1 using each of these categories (CMR, PMR, SMD, PMD, NE, NA).
- DRR by RECIST v1.1 defined as the percentage of subjects who have achieved a response of CR, PR or stable disease, will be analysed and summarised in the same manner as ORR.
- PFS by RECIST v1.1 will be summarised descriptively using the Kaplan-Meier method. The Kaplan-Meier estimates of the median PFS, and the corresponding 2-sided 95% confidence intervals calculated using Greenwood's formula will be presented.

- OS is defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of death due to any cause. Subjects who have not died will be censored at the date of last contact which may be identified from a visit date or any study assessment (physical examination, vital signs, ECOG performance status, ECG, study drug record, radiological evaluation, laboratory sampling, concomitant or follow-up procedures), AE, medication, or disposition information. OS will be calculated using the Kaplan-Meier method. One-year and two-year survival are defined as the subject survival probability at 1 year and 2 years, respectively, after the date of first dose of ^{177}Lu-OPS201. One-year and two-year survival probability along with the associated 2-sided 95% confidence intervals, will be provided. If there are a sufficient number of OS events (i.e., deaths), median OS time, first and third quartiles and associated 95% 2-sided confidence intervals, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). Kaplan-Meier OS curves also will be provided.
- DCR by RECIST v1.1, defined as the percentage of subjects who have achieved a response of CR, PR or stable disease, will be analysed and summarised in the same manner as ORR.
- TTP by RECIST v1.1, defined as the time from date of first dose of ^{177}Lu-OPS201 to the date of first documentation disease progression as determined by the investigator, will be analysed and summarised in the same manner as PFS.
- TTR by RECIST v1.1, defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of the first documentation of a response (CR or PR whichever occurs first) in a subject who responded, will be analysed and summarised in the same manner as PFS.
- DoR by RECIST v1.1, defined as the time from date of first documentation of response (CR or PR whichever occurs first) to the date of disease progression or to death due to any cause, whichever occurs first, will be analysed and summarised in the same manner as PFS.
- Change (%) in tumour volume from volumetric CT (or MRI) and sum of the diameters of the target lesion per RECIST version 1.1 from Screening to 6 weeks after each ^{177}Lu-OPS201 administration (each cycle) will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their best change (%) or largest reduction (%) from Screening in the sum of the diameters in target lesions. Spider and swimmer plots will be used to display the change in tumour burden over time for individual subjects and the occurrence of clinical outcomes of interest (e.g., tumour response, disease progression, treatment discontinuation, death).
- Quantitative changes (%) (SUV normalised by lean body mass (SUL)max and SULmean) in tumour-to-background 18F-FDG-PET uptake from Screening and 6 weeks after second 177Lu-OPS201 administration from the second cycle will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their best change (%) or largest reduction (%) from Screening in SULmax and SULmean in target lesions. Spider and swimmer plots will be used to display the change in tumour burden over time for individual subjects and the occurrence of clinical outcomes of interest (e.g., tumour response, disease progression, treatment discontinuation, death). Numbers and percentages of CMR (complete metabolic response), PMR (partial metabolic response), SMD (stable metabolic disease), and PMD (progressive metabolic disease) using PERCIST v1.0 criteria will be summarised.
- Change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202 PET/CT from Screening and 6 weeks after second 177Lu-OPS201

administration (second cycle) will be summarised descriptively. Waterfall plots will be used to depict graphically for individual subjects of their change (%) from Screening in tumour uptake to 6 weeks after second 177Lu-OPS201 administration (second cycle).

- Change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202-PET/CT from Screening to 6 weeks after second 177Lu-OPS201 administration (second cycle) will be summarised descriptively by ORR tumour response according to RECIST v1.1.
- Correlation between change (%) in tumour uptake on 68Ga-OPS202 (assessed based on SUVmax and SUVmean) PET/CT at baseline with tumour response to 177Lu-OPS201 therapy using ceCT/MRI RECIST v1.1 will be assessed. Spearman correlation coefficient and its p-value will be reported for change (%) in tumour uptake (assessed based on SUVmax and SUVmean) on 68Ga-OPS202-PET/CT from Screening and tumor response 6 weeks after second 177Lu-OPS201 administration (second cycle)
- Correlation between the number of lesion counts from ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images at screening and the number of lesion counts from ^{177}Lu-OPS201 SPECT/CT at 24 hours after the first ^{177}Lu-OPS201 administration (Cycle 1) will be assessed by Pearson correlation coefficient and its p-value.
- Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by the identification of avid lesions in subjects screened for ^{177}Lu-OPS201 treatment at baseline will be summarised and analysed in the same manner as ORR.
- Changes in health-related quality of life scores from baseline to EOCT measured by EQ-5D-5L will be summarised descriptively. Frequency tables will be used to display the number and percentage of subjects of reported problems for each level and each dimension of the EQ-5D-5L by scheduled time point. Shift tables presenting the 2-way frequency tabulation from baseline to the worst post-baseline values will be presented for each dimension of the EQ-5D-5L.
- Changes in health-related quality of life scores (global health status/QoL and each functional scale) from baseline to EOCT measured by EORTC QLQ-C30 will be summarised descriptively.

3.2.1.2 Diagnostic Sensitivity of ^{68}Ga-OPS202 (For Phase 1 and Phase 2):

a) Diagnostic sensitivity of ^{68}Ga-OPS202 imaging at baseline using RECIST as the SOT by subject-based analysis. The SOT is the results on RECIST from the contrast enhanced CT (or contrast enhanced MRI) scan images performed 6 weeks after second ^{177}Lu-OPS201 administration (second cycle). Complete response (CR), partial response (PR) and stable disease (SD) will be considered as positive response, while progressive disease (PD) will be considered as negative response.

Diagnostic sensitivity between ^{68}Ga-OPS202 at baseline and SOT will be assessed using performance specified in Table 7.

Table 7 Diagnostic performance of 68Ga-OPS202 PET/CT compared to RECIST as the SOT

^{68}Ga-OPS202 PET/CT scan results	**SOT results (using RECIST)**	
	Positive (CR + PR + SD) 6 weeks post 2nd ^{177}Lu OPS201	**Negative (PD) 6 weeks post 2nd ^{177}Lu OPS201**
Subjects with lesions detected by Ga-OPS202 at baseline	Positive Response	Negative Response

The sensitivity corresponds to the probability of positive response from ^{177}Lu-OPS201 based on lesions identified with ceCT (or ceMRI). Sensitivity will be computed using following formula, for overall subjects (subject-based approach):

$$Sensitivity = \frac{Positive\ Response}{Positive\ Response + Negative\ Response}$$

For Phase 1 subjects only, the above analysis will be repeated using volumetric RECIST as SOT.

b) Diagnostic sensitivity of ^{68}Ga-OPS202 imaging at baseline using mGa-RECIST as the SOT by subject-based analysis. The SOT is the results from mGa-RECIST from the contrast enhanced CT (or contrast enhanced MRI) scan images performed 6 weeks after second ^{177}Lu-OPS201 administration (second cycle). Complete response (CR), partial response (PR) and stable disease (SD) will be considered as positive response, while progressive disease (PD) will be considered as negative response.

Diagnostic sensitivity between ^{68}Ga-OPS202 at baseline and SOT will be assessed using performance specified in Table 8.

Table 8 Diagnostic performance of 68Ga-OPS202 PET/CT compared to mGa-RECIST* as the SOT

^{68}Ga-OPS202 PET/CT scan results	**SOT results (using mGa-RECIST)**	
	Positive (CR + PR + SD) 6 weeks post 2nd ^{177}Lu OPS201	**Negative (PD) 6 weeks post 2nd ^{177}Lu OPS201**
Subjects with lesions detected by ^{68}Ga-OPS202 PET/CT at baseline	Positive Response	Negative Response

*modified Ga-RECIST using RECIST criteria on only those lesions which are ^{68}Ga-OPS202 avid at baseline

The sensitivity corresponds to the probability of positive response from ^{177}Lu-OPS201 based on lesions identified with ^{68}Ga-OPS202-PET/ceCT (or ceMRI). Sensitivity will be computed using following formula, for overall subjects (subject-based approach):

$$Sensitivity = \frac{Positive\ Response}{Positive\ Response + Negative\ Response}$$

For Phase 1 subjects only, the above analysis will be repeated using volumetric mGa-RECIST as SOT.

c) Diagnostic sensitivity of ^{68}Ga-OPS202 imaging at baseline by subject-based, organ-based and lesion-based analysis compared to standard-of-truth (SOT). The SOT is the contrast enhanced CT (or contrast enhanced MRI) scan images acquired at baseline.

Diagnostic sensitivity between ^{68}Ga-OPS202 at baseline and SOT at baseline will be assessed using performance specified in Table 9.

Table 9 Diagnostic performance of 68Ga-OPS202 PET/CT compared to SOT of ceCT (or ceMRI)

^{68}Ga-OPS202 PET/CT scan results	**SOT results (ceCT/ceMRI)**	
	Lesions detected at baseline	**Lesions not detected at baseline**
Lesions detected at baseline	True Positive (TP)	False Positive (FP)
Lesions not detected at baseline	False Negative (FN)	True Negative (TN)* [will remain unknown]

*True negative will remain unknown at the lesion level

The sensitivity corresponds to the probability that the ^{68}Ga-OPS202 scan at baseline detects the lesions, given that the lesions are detected (positive) by SOT at baseline. This measurement refers to the ability of the test to correctly identify those lesions with the outcome of interest. Sensitivity is defined as the proportion of lesions with a positive 'standard' test response who also have a positive 'experimental' test response.

For each assessment, the sensitivity will be computed using following formula, for each subject, for each organ and overall lesions:

$$Sensitivity = \frac{TP}{TP + FN}$$

d) Diagnostic sensitivity of ^{68}Ga-OPS202 imaging at baseline by both organ-based and lesion-based analysis compared to the SOT of ^{177}Lu-OPS201 SPECT/CT after first administration. The contrast enhanced CT (or contrast enhanced MRI) scan images acquired at baseline will be used for anatomical location and lesion mapping between the two imaging techniques.

Diagnostic sensitivity between ^{68}Ga-OPS202 at baseline and ^{177}Lu-OPS201 SPECT/CT as SOT will be assessed using performance specified in Table 10.

Table 10 Diagnostic performance of 68Ga-OPS202 compared to SOT of 177Lu-OPS201 SPECT/CT

^{68}Ga-OPS202 scan results	**SOT results (^{177}Lu-OPS201 SPECT/CT)**	
	Lesions detected after first administration of ^{177}Lu-OPS201	**Lesions not detected after first administration of ^{177}Lu-OPS201**
Lesions detected at baseline	True Positive (TP)	False Positive (FP)
Lesions not detected at baseline	False Negative (FN)	True Negative (TN) [will remain unknown]*

*True negative will remain unknown at the lesion level

The sensitivity corresponds to the probability that the ^{68}Ga-OPS202 detects the lesion identified on the ^{177}Lu-OPS201 SPECT/CT scan after first administration. This measurement refers to the ability of the test to correctly identify those lesions with the outcome of interest. Sensitivity is defined as the proportion of lesions with a positive 'standard' test response who also have a positive 'experimental' test response.

For each assessment, the sensitivity will be computed using following formula, for each organ and overall lesions:

$$Sensitivity = \frac{TP}{TP + FN}$$

3.2.2 Safety

All safety data will be included in the data listings and summary tables will be based on the safety population.

For phase I study, continued monitoring of DLTs and toxicities will be performed. At the time of each data review board (DRB), the available safety data, including DLTs, toxicities, physiological parameters, ECG, laboratory test results and selected organ absorbed radiation doses (kidney and BM) will be tabulated to guide the radioactivity selection during the dose escalation.

For the overall study, descriptive statistics will be calculated for the safety parameters. No formal statistical analyses of safety data are planned.

Summaries will be prepared by cohort and, as needed, by timepoint.

The NCI-CTCAE version 5.0 classification will be used to classify all TEAEs and laboratory abnormalities.

3.2.2.1 Adverse events

Adverse events will be coded initially using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 and updated regularly.

Listings will be presented and sorted by cohort and within cohort sorted by cancer type for phase I and by cancer type for phase II, with subject id, start time of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study. Listings sorted by primary system organ class, preferred term, verbatim, subject id, start time of AEs may be also required.

Listings of serious adverse events (SAE), adverse events leading to discontinuation of study treatment and listings of deaths will also be presented.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- It was not present prior to receiving the first administration of ^{177}Lu-OPS201; or
- It was present prior to receiving the first administration of ^{177}Lu-OPS201 but the intensity increased during the active phase of the study; or
- It was present prior to receiving the first administration of ^{177}Lu-OPS201, the intensity is the same but the drug relationship became related during the active phase of the study.

A ^{68}Ga-OPS202 TEAE is defined as any AE that occurs if:

- It was not present prior to receiving the administration of ^{68}Ga-OPS202; or
- It was present prior to receiving the administration of ^{68}Ga-OPS202 but the intensity increased after the administration of ^{68}Ga-OPS202; or
- It was present prior to receiving the administration of ^{68}Ga-OPS202, the intensity is the same but the drug relationship became related after the administration of ^{68}Ga-OPS202.

TEAE period for ^{68}Ga-OPS202 will be from the administration of ^{68}Ga-OPS202 to one day after the administration. All ^{68}Ga-OPS202 TEAE will be summarized together.

An overall summary table of all adverse events will be presented, which will summarise the following information:

- Any TEAEs,
  - ^{177}Lu-OPS201-related TEAEs,

- ^{68}Ga-OPS202-related TEAEs,
- OPS301-related TEAEs,

• NCI CTCAE grade 3/4/5 TEAEs,
  - ^{177}Lu-OPS201-related NCI CTCAE grade 3/4/5 TEAEs,
  - ^{68}Ga-OPS202-related NCI CTCAE grade 3/4/5 TEAEs,
  - OPS301-related NCI CTCAE grade 3/4/5 TEAEs,
• DLT TEAEs,
• Deaths due to TEAEs,
• Treatment-emergent SAEs,
  - ^{177}Lu-OPS201-related treatment-emergent SAEs,
  - ^{68}Ga-OPS202-related treatment-emergent SAEs,
  - OPS301-related treatment-emergent SAEs,
• Discontinuation of study treatment due to TEAEs,
  - Discontinuation of study treatment due to ^{177}Lu-OPS201-related TEAEs,
  - Discontinuation of study treatment due to ^{68}Ga-OPS202-related TEAEs,
  - Discontinuation of study treatment due to OPS301-related TEAEs,
• Dose reduction due to TEAEs,
  - Dose reduction due to ^{177}Lu-OPS201-related TEAEs,
  - Dose reduction due to ^{68}Ga-OPS202-related TEAEs,
  - Dose reduction due to OPS301-related TEAEs,
• Dose interruption due to TEAEs, and
  - Dose interruption due to ^{177}Lu-OPS201-related TEAEs,
  - Dose interruption due to ^{68}Ga-OPS202-related TEAEs,
  - Dose interruption due to OPS301-related TEAEs,
• Dose increased due to TEAEs, and
  - Dose increased due to ^{177}Lu-OPS201-related TEAEs,
  - Dose increased due to ^{68}Ga-OPS202-related TEAEs,
  - Dose increased due to OPS301-related TEAEs

Summary tables of adverse events will be provided with the number and percentage of subjects with adverse events classified by primary system organ class, preferred term (ordered alphabetically) and associated NCI/CTC worst grade. In the event of multiple occurrences of the same adverse events being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related) will be chosen. Maximum grade or severity will be tabulated by subject for each MedDRA SOC and PT. Analyses of AEs and SAEs may be performed: regardless of the relationship to the IIP/IRPP and related to the IIP/IRPP. Moreover, all AEs including SAEs and SAEs only will be tabulated.

^{68}Ga-OPS202 TEAEs occurred during TEAE period for ^{68}Ga-OPS202 will be summarized following the same manners and flagged in all adverse events data listings.

3.2.2.2 Laboratory data

Laboratory data must be listed in Standard International (SI) units and also be listed in local units.

A separate listing of normal ranges for SI units will be provided by gender and age where relevant.

Laboratory data will be listed in SI units and abnormal values will be flagged (High, [H], Low [L], clinically significant [C], NCI-CTC grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.

A listing will be presented of all values for a subject with at least a clinically significant abnormal value.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria, version 5.0. The NCI CTC grade (0 to 4) of haematology and biochemistry by cycle and by subject and will be listed in the Section 16.2.8. Listings of the laboratory parameters in section 14.3.4 & 14.3.5 will include listings of NCI-CTC Grade 3 and 4 haematological toxicities, listings of NCI-CTC Grade 3 and 4 biochemical toxicities and listings of out of range biochemistry parameters that could not be graded using NCI-CTC grade (below LLN – normal – above ULN).

For white blood cells (WBC), neutrophils, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir will be calculated (refer to Appendix 1, Derived data).

For categorical urinalysis data (normal/abnormal) frequency tables, by cohort and/or cancer type will be presented at each scheduled assessment as well as the change from baseline with the following categories: improved, stable, worsened and abnormal worsening. Shift tables may be presented for the number and percentage of subjects with [normal, abnormal].

For continuous urinalysis data, summary statistics, by -cohort and/or cancer type, will be presented at each scheduled assessment for actual values and changes from baseline.

3.2.2.3 Maximum Tolerated Single and Cumulative Activity

Individual listings and treatment summaries of DLTs with CTCAE code and grade will be presented. The incidence of subjects with DLTs during Cycles 1 or 2 of the radioactivity escalation will be summarised by cohort and/or cancer type and, if possible, modelled as a function of the cumulative radioactivity for Cycles 1 and 2 using Bayesian logistic regression.

Details for the Bayesian logistic regression is described in a separate analysis plan and protocol Appendix 1.

3.2.2.4 Vital signs

Vital signs will be listed at each assessment by cohort and/or cancer type and subject. Any unscheduled vital signs will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug.

Summary statistics by cohort and/or cancer type will be presented at each scheduled assessment for actual values and changes from baseline.

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by cohort and/or cancer type, at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable).

3.2.2.5 ECG

ECG results will be listed at each assessment by cohort and/or cancer type and subject. Any unscheduled ECG will be flagged [U] in the listings.

Baseline will be defined as the last ECG measurement collected prior to the first dose of study drug.

For continuous ECG parameters, summary statistics, by cohort and/or cancer type, will be presented at each scheduled assessment for actual values and changes from baseline.

For sinus rhythm, a frequency table by cohort and/or cancer type, will be presented at each scheduled assessment.

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by cohort and/or cancer type, at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable).

3.2.2.6 Physical examination

For physical exam assessments (abnormal, not clinically significant / abnormal, clinically significant /normal), a frequency table will be presented, by cohort and/or cancer type, at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > normal > not evaluable).

3.2.3 Exploratory biomarkers

- The association between the uptake on ^{68}Ga-OPS202 PET/CT with sstr2 expression on tumours as determined by IHC will be explored.
- Immunohistochemistry staining of sstr2 of the primary tumour is defined by three parameters:
  - % of positive tumour cells (at the membrane compartment) ranging from 0% to 100%
  - Intensity of staining with score of 0, 1, 2 or 3
  - H score=% of positive cells ×Intensity of staining. H score ranges from 0 to 300.

^{68}Ga-OPS202 PET/CT uptake will be measured by SUV_{mean} at screening.

Pearson's correlation coefficient will be used to estimate the correlation between SUV_{mean} and % of positive cells.

The correlations between SUV_{mean} and the intensity of staining as well as between SUV_{mean} and H score will be examined using Spearman's correlation coefficient.

Additionally, H score will be split into two categories as follows: negative if H score < 50 or positive if H score ≥ 50. As for SUV_{mean}, a sample will be considered positive if SUV_{mean} is > 0 and negative is SUV_{mean} is 0.

H score (positive/negative) and SUV_{mean} (positive/negative) will be described in a 2x2 table using descriptive statistics (frequencies and percentage).

Individual values of H score (positive/negative) and SUV_{mean} (positive/negative) will be listed by subject.

- Change in renal biomarkers compared to baseline (Day 1) will be summarised descriptively.
- Change in pancreatic function biomarkers compared to baseline (Day 1) will be summarised descriptively.
- Change in testicular function biomarkers compared to baseline (Day 1) will be summarised descriptively.

- Change from baseline (Cycle 1 Day 1 before infusion) in DNA-DSB in peripheral lymphocytes, and DNA repair in blood and in tumour tissue will be summarised descriptively.
- Change from screening in tumour microenvironment, transcriptomics, and other disease markers of interest will be summarised descriptively.
- Germinal mutations in blood measured before infusion will be summarised descriptively.

3.2.4 Missing data and outliers

3.2.4.1 Missing data

Missing data will not be imputed. Only observed data will be used in the summaries and analyses.

3.2.4.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly, a medication with partial start and stop dates could be considered as prior and concomitant treatment).

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

3.2.4.3 Outliers

Any outlier identified prior to database lock, which is impossible/implausible will be excluded from the analysis. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

If any outliers are identified after database lock, the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.

A search of outliers by CCI should be performed before database lock and actions with the sponsor should be defined.

3.2.5 Subject disposition and withdrawals

A listing of dates of assessments (relative day) and number of cycles will be presented by subject for each cohort and cancer type.

The numbers and percentages of subjects enrolled and included in each of the ITT, PP and safety populations will be tabulated. The reasons for subject exclusions from each of the populations will be listed and tabulated. In addition, the numbers of subjects who received study

treatment, discontinued and completed at each of the study periods (e.g. active follow-up period, survival follow-up period) will be tabulated. Primary reasons for discontinuation of study treatment will be listed and tabulated.

3.2.6 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed for the total study population and by cohort, cancer type and subject.

Summary statistics will be provided for demographic and baseline characteristics for the total study population and by cohort.

Demographic characteristics will include

- age (years),
- sex (male, female),
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported),
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other),
- country,
- weight (kg),
- height (cm), and
- body mass index (BMI) in kg/m^2,
- body surface area (m^2)
- ECOG Performance Status (0, 1, 2, 3, 4)

Baseline disease characteristics will include

- cancer type (breast cancer, small cell lung cancer)
- time from initial diagnosis of primary disease until the informed consent date (months)
- time from first relapse after last treatment until the informed consent date (months)
- TNM Classification of Malignant Tumours (TNM) Staging for tumour, node, metastasis
- breast cancer history
  - primary tumour site (left, right)
  - primary tumour histopathological type (invasive carcinoma, carcinoma in situ)
    - Invasive carcinoma (ductal, lobular, not otherwise specified, other)
    - Carcinoma in situ (ductal, not otherwise specified)
  - Scarff-Bloom-Richardson histological grade (SBR I, SBR II, SBR III)
  - Estrogen receptor status (positive, negative, not done)
  - Progesterone receptor status (positive, negative, not done)
  - HER2 receptor status(positive, borderline, negative, not done)
  - BRCA 1 or 2 mutation (positive, negative, not done)
- small cell lung cancer history
  - anatomical stage - limited disease (0, IA1, IA2, IA3, IB, IIA, IIB, IIIA, IIIB, IIIC)
  - anatomical stage - extensive disease (IVA, IVB)
  - primary tumour site (upper right lobe, middle right lobe, lower right lobe, upper left lobe, lower left lobe, hilar lymph nodes, right bronchus, left bronchus)
- prior chemotherapy for cancer (yes, no)

- prior hormonal therapy for cancer (yes, no)
- prior immunotherapy for cancer (yes, no)
- prior CDK4/6 inhibitors for breast cancer (yes, no)
- prior targeted agents for cancer (yes, no)
- prior radiotherapy for cancer (yes, no)
- prophylactic cranial irradiation for cancer (yes, no)
- prior surgical procedures for cancer (yes, no)
- Best response from prior chemotherapy, hormonal, immunotherapy, CDK4/6 inhibitors, targeted agents (CR, PR, stable disease (SD), progressive disease (PD), inevaluable (NE), not available (NA))

3.2.7 Medical and surgical history

Medical and surgical history will be coded initially using MedDRA Version 21.0 and updated regularly.

Listings will present the preferred term and verbatim text. The listings will be sorted by cohort, cancer type, subject, primary system organ class, preferred term and verbatim text.

A frequency table of the number and percentage of subjects will be provided for medical and surgical history by primary system organ class and preferred term for each cohort and cancer type.

3.2.8 Subject compliance

Number of treatment cycles completed by each subject will also be summarised by cohort and cancer type. Planned ^{177}Lu-OPS201 dose and planned peptide mass dose will be summarised descriptively by cycle, and by cohort and cancer type and in total.

A listing will be presented for ^{177}Lu-OPS201 infusion administration (site, side, planned and actual ^{177}Lu-OPS201 dose, planned and actual peptide mass dose, radioactivity measurement before and after injection, start/end date and time) by subject for each cohort and cancer type. Deviations from planned and actual dose will be presented.

A listing will be presented for ^{68}Ga-OPS202 administration (actual radioactivity dose, radioactivity dose and volume before and after administration, and date and time) by subject for each cohort and cancer type.

Other information collected on eCRF for ^{177}Lu-OPS201 and ^{68}Ga-OPS202 administration will also be listed.

All the protocol deviations identified prior to database lock will be also listed by subject for each cohort and cancer type.

The impact of major protocol deviation on the phase II primary efficacy analysis and phase I and phase II dosimetry analysis will be investigated by comparing the results of the ITT and PP population analyses.

3.2.9 Prior and concomitant therapies

Prior and concomitant therapies will be coded initially using WHO-Drug Dictionary Version Mar 2018 B3 and updated regularly. The therapeutic class will correspond to the second level of ATC code, which is, corresponding to the first 3 figures of ATC code.

Listings will be presented for the therapeutic class, preferred term and verbatim text. The listings will be sorted by cohort and cancer type, subject, chronological start date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant therapies by therapeutic class and preferred name for each cohort and cancer type.

Prior, concomitant, and post-treatment medications will be summarised separately. Categorization will be defined as follows:

- Prior medications will include medications which started prior to the start date and time of the first ^{177}Lu-OPS201 administration.
- Concomitant medications will include medications taken any time from the start date and time of the first ^{177}Lu-OPS201 administration through 30 days following end date and time of the last ^{177}Lu-OPS201administration or until the start of a subsequent anticancer therapy, whichever is earlier. Medications that started prior to the first dose of study drug but continued into treatment are considered concomitant.
- Post-treatment medications will include medications taken any time after from the start date and time of the first ^{177}Lu-OPS201 administration through 30 days following end of study drug administration or until the start of a subsequent anticancer therapy, whichever is earlier.

Anticancer Treatment received during follow-up period be summarised separately.

3.2.10 Pharmacokinetics

The PK analysis of OPS201 will be performed under the responsibility of the sponsor's Clinical PK department.

Analysis of PK data by a noncompartmental approach will be documented in a separate SAP.

Individual plasma and urine concentrations of OPS201 will be listed and summarised by time points using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean and geometric coefficient of variation assuming lognormally distributed data). Linear and semi-logarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

Any suspicious concentration will be investigated and kept in the PK analysis if possible. All excluded concentrations will be justified in the report.

If OPS201 levels are measurable in plasma and urine, PK parameters of OPS201 (including, but not limited to, C_{max}, AUC, $t_{1/2}$, Cl, V_d, A_e, renal clearance) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of OPS201 and on the individual urine concentrations.

An attempt to build an integrated model taking into account PK, dosimetry as well as efficacy and safety data will be made if warranted by the data. The exploratory analysis will be captured in a separate data analysis plan and reported in a standalone report.

3.2.11 Radiation Dosimetry of ^{177}Lu-OPS201

The radiation dosimetry analysis of the radiopharmaceutical ^{177}Lu-OPS201 will be performed under the responsibility of the sponsor's Clinical PK department.

Further details on dosimetry assessments and on dosimetry parameters will be provided in a separate data analysis plan.

The dosimetry assessments will be performed and reported according to the criteria set by the EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting (Lassmann 2011).

Calculations will be conducted on the following parameters (only, but not limited to, in organs showing uptake):

- Maximal uptake (%)
- Organs receiving the highest absorbed dose
- Specific absorbed dose to the target lesion (Gy/GBq)
- Specific absorbed dose per organ (Gy/GBq)
- Cumulative absorbed organ doses (Gy)

Cumulative absorbed organ doses (Gy)/Organs of highest radioactivity uptake will be identified visually. Regions of interest (ROI) will be placed over these organs to determine the relative radioactivity in the respective organs. TACs (time radioactivity curves), describing % IA/ROI of the radioactivity amount injected versus time, considering renal excretion radioactivity) will be derived. The absorbed organ doses of the dose-limiting organs (kidney, BM and liver) will be evaluated and reported to the investigator before the next administration of ^{177}Lu-OPS201 can be initiated to enable radioactivity adaptations in the event the next dose may exceed the organ limits

for the kidney (23 Gy) and for the BM (1.5 Gy or up to 2 Gy during core trial and additional cycles, respectively). Of note, imaged-based dosimetry results associated to overlying tumors/lesions resulting in absorbed dose overestimation will not be used for dose radioactivity adaptation. In this case, the dose radioactive adaptation will rely on an overall benefice/risk dosimetry evaluation.

A Bayesian power model will be considered to relate the cumulative ^{177}Lu-OPS201 radioactivity during Cycles 1 and 2 of the dose escalation to the cumulative absorbed dose in the BM and kidney. Vague priors will be used. The posterior predictive distribution of the exposure will be summarised by radioactivity level. Detailed Bayesian power model for phase I dose escalation is documented in a separate analysis plan.

The maximum cumulative absorbed dose where the posterior predictive probability of remaining below the target organ limits (1.5 Gy for BM and 23 Gy for kidney) will be estimated from that model, as the radiation-safety component of the MTCA.

The dosimetry for all organs other than BM and kidney will be assessed and finalised for the final clinical study report, whereas dosimetry data for BM and kidney must be available for the DRB meetings. These data can be reviewed at any time if a major safety issue occurs.

3.2.12 Derived data

The derived data are variables which are calculated from the raw data in the CRF and not included in the database.

3.2.13 Visit windows

No study visit windows will be used for analyses. Within CRFs each unscheduled visit will be linked to a scheduled visit which will be used to identify visits.

3.2.14 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented n, number of missing values, arithmetic mean, standard deviation, median and the range (minimum, maximum).

Mean, median, standard deviation and standard errors of the mean (SE) values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary.

Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).

Percentiles (e.g., 25% or first quartile, 75% third quartile) should be presented to one decimal place more than the raw/derived data.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

All text fields must be left justified and numeric or numeric with some text specification must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.15 Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.16 Interim/futility analysis

Phase I

Safety and radiation exposure data will be reviewed on an ongoing basis during the radioactivity escalation.

Proceeding to the Next Cohort

The DRB meeting for radioactivity and peptide mass escalation will take place after three subjects of the radioactivity escalation cohort have completed two cycles of ^{177}Lu-OPS201. The DRB will review all available safety and dosimetry data from the study to decide if the escalation can proceed as planned If DLTs are reported, a statistical Bayesian modelling approach will be implemented to produce more precise radioactivity-DLT and organ absorbed doses curves to guide the radioactivity selection and predict a radioactivity not exceeding the predicted MTCA/MTSA that could be tested in the next cohort of radioactivity escalation.

If the starting cumulative radioactivity of 9 GBq is not well tolerated, another cohort with a decreased cumulative radioactivity will start. In this case, the cumulative radioactivity could be determined using the statistical Bayesian approach, for example, 7.5 GBq (one administration of 4.5 GBq followed by an administration of 3 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered)).

Stopping Rules for Dose Escalation

The radioactivity escalation will be stopped as soon as:

- the MTCA and/or MTSA have been defined with good precision; or
- the maximum planned radioactivity of 12.9 GBq, fractionated into two administrations separated by 6 weeks, is administered without safety concerns and is thus defined as the MACA.

Once the radioactivity escalation has been completed, the MTCA level may be repeated based on the results of the Bayesian model in a last cohort of three to five subjects with the same peptide mass dose to confirm the safety profile. If the MTCA is not reached and if limiting organ absorbed doses are not exceeded at the highest planned radioactivity (12.9 GBq) and if no individual withdrawal criteria are met, the inclusion of an additional cohort with a higher cumulative radioactivity will be evaluated.

Peptide Mass Dose Evaluation

In parallel with the radioactivity escalation phase, once the first cycle of a radioactivity level is considered acceptably tolerated by the DRB, the radioactivity level will be repeated with a higher peptide mass dose (700 µg (±15%)). Three additional cohorts of three to five subjects will thus be enrolled in the peptide mass dose evaluation.

The DRB for peptide mass dose escalation will meet after the third subject of each cohort has received the first cycle of ^{177}Lu-OPS201 with DLT assessments performed.

The DRB will review all safety and dosimetry data and allow the peptide mass dose escalation. The cohort with the high peptide mass dose (700 µg) will thus only start when the first cycle of the corresponding radioactivity level tested with 300 µg peptide mass dose has been evaluated by the DRB and has been considered acceptably tolerated.

Moreover, the administration of the second cycle of the peptide mass dose evaluation cohorts can only proceed once the second cycle of the corresponding radioactivity level has been considered acceptably tolerated. The same subject cannot participate in the radioactivity escalation cohort and the peptide mass dose cohort.

At the time of DRB meeting, all cumulative available information will be reviewed.

Phase II

An interim analysis will be performed for futility based on the first stage of Simon's optimal two-stage design within each cohort.

For the SCLC cohort, the first stage consists of 29 subjects. An analysis will be conducted after approximately 29 subjects have been assessed on the ORR. The ORR assessment cut-point for the 29th subject is 6 weeks after Cycle 2 dose. The probability of early termination (PET) after the first stage is 0.6555. If seven responses or less are seen in the first 29 subjects then the trial is stopped. Otherwise accrual continues to a total of 69 response evaluable subjects.

For the BC cohort, the first stage consists of 33 subjects. An analysis will be conducted after approximately 33 subjects have been assessed on the ORR. The ORR assessment cut-point for the 33rd subject is 6 weeks after Cycle 2 dose. The probability of early termination (PET) after the first stage is 0.6374. If four responses or less are seen in the first 33 subjects then the trial is stopped. Otherwise accrual continues to a total of 87 response evaluable subjects.

3.2.17 Role of data review board (DRB)

The data review board (DRB) for radioactivity escalation, consisting of a team of "permanent" decision makers (the core team), including selected principal investigators and Ipsen personnel, will review the safety and dosimetry data and jointly decide with the sponsor whether to proceed with the enrolment of the next cohort. Details of roles and responsibilities of DRB are described in the DRB charter.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.3 or higher. All outputs will be in Microsoft Word Format.

4.2 Validation programs

Programs will be validated according to CCI [redacted]

4.3 Restitution of the programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

Due to Premature Closure of this study, the analysis for the Clinical Study Report was revised. Following data listings outputs are selected.

Discontinued subjects

- Subject Disposition (Eligibility Screened Population)
- Inclusion Criteria Description
- Exclusion Criteria Description
- Screening Failures (Eligibility Screened Population)

Protocol deviations –

- Protocol Deviations (Eligibility Screened Population)

Demographic data

- Demographics (Eligibility Screened Population)
- Tumour Characteristics (Eligibility Screened Population)
- Significant Medical and Surgical History (Eligibility Screened Population)

Compliance and/or drug concentration data

- IIP Preparation (Eligibility Screened Population)
- IIP Administration and Extent of Subject Exposure (Eligibility Screened Population)

Adverse event listings (each subject)

- All Adverse Events (Eligibility Screened Population)
- Serious Adverse Events (Eligibility Screened Population)
- Adverse Events Leading to Deaths (Eligibility Screened Population)
- Adverse Events with NCI CTC Grade >=3 (Eligibility Screened Population)

6 REFERENCES

(1) Eisenhauera EA, Therasseb P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009; 45: 228 – 247.

(2) Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. 1982: 38: 29-41.

(3) Lassmann M, Hanscheid H, Chiesa C et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging. 2008;35: 1405-12.

7 APPENDICES

Appendix 1: Derived Data

The following derived data will be calculated and included in the listings:

(1) Age (specified DEMOG table)

Subject age (years) will be derived as (screening date – birth date)/365.25 and truncated to the largest integer that is less than or equal to the calculated result.

(2) BMI (specified VSIGN table)

BMI (kg/m^2) will be derived as Weight (kg)/[Height(cm)/100]^2 and rounded to the nearest decimal.

(3) Body Surface Area (specified VSIGN table)

Body Surface Area (m^2) will be derived as (Weight (kg)$^{0.425}$ × Height(cm)$^{0.725}$ × 71.84)/10000 and rounded to the nearest decimal.

(4) Changes from baseline

Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

(5) Percent change from baseline

Percent reduction from baseline will be calculated as a percentage of decrease from baseline (e.g. 100×(1-(assessment at the visit)/(assessment at baseline))).

If assessment at baseline is zero, percent change will not be calculated. Unless when both assessment at baseline and assessment at the visit are zero, percent change will not be set as zero.

(6) Adverse event duration

If the start date of the adverse event is identical to the date of last administration, then"<1" day will be presented, otherwise it will be calculated as (start date - last administration date)+1 and presented in days. If the start date and the associated information do not allow to state about the last dose received (partial start date or start at administration day without knowing if it started before or after the drug intake), all the possible time since last dose will be presented [i.e.: if a subject received a daily administration and reported an AE at second administration day but without indication about before or after the drug intake the time since last dose will be as "2 / <1"]. If the start date is partial, the time since last dose will be presented as an superior inequality (i.e.: for an AE started in FEB2004 after the only administration performed on 31JAN2004, the time since last dose will be as "≥2" days). If the start date is missing the time since last dose will not be presented although the AE will be assigned to each dose received before its end date.

(7) Concomitant therapy duration

If times are available, the duration of concomitant treatments/physiotherapy etc. will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) +1. If the recorded end date is CONT. (for continuing) then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e.: ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

(8) **Study day**

Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist).

(9) **Relative phase**

Relative phase variables describe the event date as pre, during and or post treatment relative to the first study medication intake date. There are two-phase variables:

1. VAR_SPH describes the start phase of an event relative to the first and the last date of study medication intake
2. VAR_EPH describes the end phase of an event relative to the first and the last date of study medication intake.

The phase code list consists of

0.5 = indeterminate

1 = pre

2 = during

3 = post

If the event start date is before the start date of study medication or before the start time of study medication, then

VAR_SPH = 1 (pre).

If the event start date is on or after the start date of study medication and on or before the end date of study medication, then VAR_SPH = 2 (during)

If the event start date is after the end date of study medication, then VAR_SPH = 3 (post)

If the event end date is before the start date of study medication, then VAR_EPH = 1 (pre)

If the event end date is on or after the start date of study medication and on or before the end date of study medication, then VAR_EPH = 2 (during)

If the event end date is after the end date of study medication, then VAR_EPH = 3 (post)

As a general rule, relative phase variables should be calculated for all date variables in a panel unless otherwise indicated (e.g.: AE, medical history, prior and concomitant medications, disease related histories, lab data). If dates are incomplete or completely missing, then information on cycle numbers should be used to complete the phases.

Relative phase variables should not be left indeterminate for adverse events, medical history and concomitant medications. It should be completed even in the case where dates are partial or completely missing by using worst-case scenario.

Worst Case Scenarios for Phase Variables

Item	Worst case scenario for the start phase _SPH	Worst case scenario for the end phase _EPH
Adverse events	During	During
Medical history	Pre	Pre
Concomitant medication	Pre	During

Phase variable should be left as Indeterminate.(0.5), only when no reasonable assumptions can be made due to missing or incomplete dates.

(10) **Relative days**

Relative days based on the very first study medication infusion/intake date (D1, Cycle 1) and the very last study medication infusion/intake date (D1, Cycle n) or first day of a given Cycle.

Four types of relative days (VAR_SrS, VAR_SrE, VAR_ErS and VAR_ErE) will be calculated for any event defined with start and stop dates (e.g.: AE, Prior and Concomitant medication, Medical history etc.) and three types of relative days (VAR_ArS, VAR_ArE and VAR_ArCxD1) will be calculated for assessments (e.g.: lab parameters, ECG, vitals etc.) unless otherwise specified.

For example: if VAR=AE then

AE_SrS: Relative days from start of the event to start of study drug administration.

AE_SrS will be calculated by using either of the following two formula:

- If AE onset was on or after initiation of study medication then
  AE_SrS = event start date – first study drug administration date + 1
- If AE onset was before initiation of study medication then
  AE_SrS = event start date – first study drug administration date

AE_ErS: Relative days from end of the event to start of study drug administration

AE_ErS will be calculated by using either of the following two formula:

- If AE end date was on or after initiation of study medication then AE_ErS = event end date – first study drug administration date + 1
- If AE end date was before initiation of study medication then AE_ErS = event end date – first study drug administration date

Relative assessment days based on the first drug administration will be calculated as following:

- If LAB sample date was on or after first drug administration then
- LAB_ArS = LAB sample date –first date of study drug administration + 1
- If LAB sample date was before first drug administration then
- LAB_ArS = LAB sample date –first date of study drug administration

Relative assessment days based on the last drug administration will be calculated in a similar fashion.

- If LAB sample date was on or after last drug administration then
  LAB_ArE = LAB sample date –last date of study drug administration + 1
- If LAB sample date was before last drug administration then
  LAB_ArE = LAB sample date –last date of study drug administration

Relative assessment cycle days based on the Day 1 of cycle X will be calculated in the similar fashion.

- LAB_ArCxD1: Relative assessment cycle days from lab sample date to D1 of cycle X (CxD1) will be calculated by using formula
- LAB_ ArCxD1 = lab sample date –CxD1 + 1

(Note : the relative assessment cycle days based on the day one of cycle one (C1D1) is the equal to relative assessment days based on first drug administration (i.e.: VAR_ArS).

(11) **AE duration**

AE duration will be set equal to the value recorded on the CRF if the duration is less than 24 hours. If the duration is not specified, then it will be calculated by using "AE_ErS - AE_SrS" recorded in days. If the end date is missing because the adverse event was ongoing then the duration will be listed as "ongoing".

(12) A **nadir** for a subject is defined as the lowest laboratory value or tumor evaluation (volume or longest diameter) during the whole treatment period (all cycles combined) among all infusions for that subject and a nadir for a cycle is defined as the lowest laboratory value or tumor evaluation (volume or longest diameter) in that cycle. The day to nadir in a cycle is the number of days between the nadir and the first date of study medication intake of that cycle.

(13) The **time to recovery** will be calculated for WBC, neutrophils, haemoglobin and platelets with toxicities grade 3 or 4. Recovery is defined as the return to grade 0, 1 or baseline level. The time to recovery is the number of days between the nadir and the date of first assessment of the recovery.

For the calculation of the nadir, day to nadir and time to recovery of haematological events, the cycles where G-CSF or red blood cell packs or platelets units have been given will be censored for the related parameter as following: WBC and neutrophils will be censored when G-CSF or total blood products are given, haemoglobin will be censored when red blood cell packs or total blood products or erythropoietin products are given and platelets when platelets units or total blood products are given. If the haematological supporting drugs were started before the nadir then any following assessment of this nadir such as day to nadir and time to recovery will be censored. If this therapy was initiated after the nadir is reached, only time to recovery will be censored. A listing detailing the censoring will be provided.

(14) **Neutrophils values**

In some cases, lab data may not be reported as they may be difficult to detect. When the White Blood Cells counts (WBC) are recorded, and if WBC $< 0.5*10^9$/L, then neutrophils value will be imputed as zero and thus will be considered to be in NCI grade 4.

(15) **Laboratory values grades**

Laboratory values grades will be assigned toxicity grades when available using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale (Version 5.0). Laboratory toxicity grades are "0", "1", "2", "3", "4". Some laboratory tests provide two sets of grades – one set for values that are too low and another set for values that are too high. For these parameters, both directions will be derived, i.e. one record with parameter decreased and one record with parameter increased. If more than one grade can be assigned, due to the high and low normal range values overlapping more than 1 grade, then the worst grade should be assigned.

(16) **Tumour assessments**

In case of missing tumour assessment at cycle n, it should be kept missing as long as the next evaluation at cycle n+1 is a Progressive Disease (PD). The best overall response in this case is 'not evaluable' if there are no previous assessments. Otherwise, the best overall response will be assessed by using tumour assessments up to cycle n-1.

On the other hand, if the assessment at cycle n+1 does not show any progression, this missing assessment (at cycle n) will be derived by using the assessment from previous cycle n-1 (last observation carried forward method). In this case the best overall response will be assessed as defined.