PROTOCOL TITLE The efficacy of **Cabo**zantinib in **A**dvanced **SA**livary gland cancer **P**atients, a phase II clinical trial' (Cabo ASAP)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ACC	Adenoid cystic carcinoma
ADT	Androgen deprivation therapy
AE	Adverse Event
AR	Adverse Reaction
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
ctDNA	Circulating tumor DNA
CV	Curriculum Vitae
DoR	Duration of response
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
QoL	Quality of life
SDC	Salivary duct carcinoma
(S)AE	(Serious) Adverse Event
SGC	Salivary gland cancer
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Salivary gland cancer (SGC) is a rare cancer with 24 histological subtypes. Treatment options for locally advanced and/or metastatic SGC are limited. The tyrosine kinase inhibitor cabozantinib suppresses tumor growth, angiogenesis, and metastasis, and has been approved for renal cell carcinoma and thyroid cancer. Cabozantinib may also be of value in advanced SGC because c-MET, one of the targets of cabozantinib, is frequently overexpressed in SGC.
Objectives: To assess the objective response rate (ORR), progression free survival (PFS), overall survival (OS), duration of response (DoR), toxicity, and quality of life (QoL) of patients with advanced SGC treated with cabozantinib in 3 cohorts: salivary duct carcinoma (SDC), adenoid cystic carcinoma (ACC), other SGC's.
Study design: Single arm, single center, phase II clinical trial
Study population: Patient with c-MET positive, locally advanced, recurrent, and/or metastatic SGC.
Intervention: Cabozantinib tablets 60 mg once daily until progressive disease, intolerable toxicity, or investigator and/or patient decision to withdraw for a maximum duration of 2 years.
Main study parameters/endpoints: study endpoints are in line with the objectives.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Burden and risks: Patients will use the study medication for a maximum duration of 2 years. During these 2 years, patients will make 17 study related visits. 12 CT scans will be made and patients will be asked to fill in questionnaires 7 times. The safety of Cabometyx is well known because of studies in renal cell carcinoma.
Benefit: Because Cabometyx has not been tested in SGC patients before, the chance of responding to treatment is unknown. The Simon 2-stage design will be used to prevent exposure of too many patients to ineffective treatment without discarding a potential effective treatment because of treatment failure in some patients.
Group relatedness: The study does not involve minors and/or incapacitated subjects.

1. INTRODUCTION AND RATIONALE

SGC is a rare cancer. The annual incidence rate ranges from 0.4-2.6 cases per 100,000 people. Besides, SGC's are histological diverse. Twenty-four histological types can be distinguished.[1] Primary treatment consists of resection of the affected salivary gland and a neck dissection, mostly followed by postoperative radiotherapy. Treatment options for patients with locally recurrent and/or metastatic disease (later: advanced disease) systemic treatment options are limited to androgen deprivation therapy (ADT) and HER2-targeted therapies in selected cases. Chemotherapy may be used for palliation, but the effect is limited. Therefore, new treatment options for advanced SGC are urgently warranted.

Cabozantinib is an oral, small-molecule inhibitor of tyrosine kinases, including c-MET, VEGFR, and AXL. In preclinical models, cabozantinib has been shown to suppress tumor growth, angiogenesis, and metastasis.[2] In clinical practice, it has been approved for treatment of advanced renal cell carcinoma in patients who received prior anti-angiogenic therapy (cabometyx® tablets),[3] and treatment of progressive, metastatic medullary thyroid cancer (Cometriq® capsules).[4] Next to this, it has shown promising results in bone metastases of castration-resistant prostate cancer.[5]

Cabozantinib may also be of value in the treatment of advanced SGC because c-MET, one of the targets of cabozantinib, is frequently overexpressed in SGC. In ACC, c-MET overexpression has been shown in 53.2% of patients.[6] In SDC, c-MET overexpression has been shown in 39.7% of patients.[7]

No data are available on the efficacy of cabozantinib in SGC. We will conduct a phase II, single arm clinical trial to investigate the efficacy of cabozantinib in c-MET positive SGC. Three patient groups will be included: (1) advanced SDC, (2) advanced ACC, and (3) advanced SGC of other subtypes. As ACC can originate in the salivary glands, but also in other parts of the body, such as lung, trachea, breast and cervix, these patients can also be included in the study and will be analyzed in the cohort with advanced ACC patients.

Before and during treatment we will collect blood samples for future analysis of circulating tumor DNA (ctDNA). ctDNA is cell-free DNA in the blood circulation which originates from the tumor. Analysis of ctDNA may be of value for early response prediction. In colorectal cancer, treatment response and failure can be predicted by a decrease and increase of ctDNA.[8] In this study, we will draw blood for ctDNA analysis using Roche cell-free DNA tubes before start of treatment, after 2 weeks, after 4 weeks, and before every evaluation CT-scan. Samples will be analyzed for ctDNA levels to evaluate whether treatment response and failure can be predicted.

2. OBJECTIVES

Objectives will be analyzed separately in all 3 cohorts of c-MET positive, advanced SGC: (1) SDC, (2) ACC originated in the salivary glands or other sites of the body, (3) other SGC's

Primary Objective

- Assess the ORR. ORR is defined as the sum of the complete remissions plus partial responses.[9] The best response will be used in each patient.

Secondary Objectives

- Assess the PFS. PFS will be defined as time from study enrollment until disease progression or death.
- Assess the OS. OS will be defined as time from study enrollment until date of death of any cause.
- Asses the DoR. DoR is defined as time from study enrollment until date of documented tumor progression or death
- Assess the toxicity of cabozantinib. Toxicity will be scored according to NCI CTC common criteria v 4.0.[10]
- Assess the QoL of patients treated with cabozantinib using EORTC questionnaires.
- Assess the response rate by using continuous tumor shrinkage end-points, as was advocated by Billingham et al[11] and Wason et al.[12]
- ctDNA will be assessed to evaluate whether response and disease progression can be predicted.

More details about the definitions and analysis of primary and secondary outcomes are described in chapter 8.1.

3. STUDY DESIGN

Design: single arm, single center, phase II clinical trial

Duration: inclusion is expected to take aproximately two years

Setting: single center study (Radboud University Medical Center, Nijmegen, the Netherlands)

Assessments

During the study patients will be seen every 2 weeks for the first 8 weeks, then every 4 weeks for the first 6 months, then every 8 weeks in the first year, and every 12 weeks in the second year. The following assessments will be done:

	History / physical exam	Blood analysis	CtDNA	Urine	ECG	Imaging	Questionarres	Toxicity	Any other
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week 0	X	X	X	X	X	X	X		X
Week 2	X	X	X	X	X			X	X
Week 4	X	X	X					X	X
Week 6	X	X						X	X
Week 8	X	X	X			X	X	X	X
Week 12	X	X						X	X
Week 16	X	X	X			X	X	X	X
Week 20	X	X						X	X
Week 24	X	X	X			X	X	X	X
Week 32	X	X	X			X		X	X
Week 40	X	X	X			X	X	X	X
Week 48	X	X	X			X		X	X
Week 56	X	X	X			X	X	X	X
Week 68	X	X	X			X		X	X
Week 80	X	X	X			X		X	X
Week 92	X	X	X			X		X	X
Week 104	X	X	X			X		X	X
At PD	X	X	X			X	X	X	X

1. History / physical exam
    - Standard history and physical examination
2. Blood analysis
    - Hematology: haemoglobin, blood cell count (RBC, WBC count and differential, platelets)
    - Biochemistry: AST, ALT, AP, GGT, LD, bilirubin, creatinine, urea, Na, K, Ca, P, Mg, albumin, . TSH and free T4 in week 0.
3. ctDNA
    - blood sample for ctDNA analysis
4. Urine
    - protein/creatinine ratio

5. ECG
    - Standard ECG
6. Imaging
    - CT- or MR-scanning of primary tumor area and regional lymph nodes
    - Chest plus abdominal CT
        - *An independent endpoint review committee will be installed to verify responses according to RECIST version 1.1.*[13]
7. Questionnaires:
    - EORTC QLQ-C30
    - EORTC QLQ-H&N35
    - PSSHN
    - VAS
8. Toxicity
    - Toxicity profile according to NCI CTC common criteria v 4.0
9. Any other
    - Any other diagnostic procedure that the investigator deems necessary

4. STUDY POPULATION

4.1 Population (base)

Study population:

Patients with c-MET positive, advanced SGC

- c-MET positivity
  - Immunohistochemistry
    - c-MET expression will be evaluated by immunohistochemical staining on a biopsy of the primary tumor (in case of locally advanced or locally recurrent disease) or a biopsy of metastasis (in case of metastatic disease). The D1C2 antibody (Cell Signaling®) will be used.
    - The staining pattern will be scored as cytoplasmic and membranous staining using a semiquantitive scoring system (negative / weak / moderate / strong). Weak, moderate and strong cytoplasmic and/or membranous staining will be regarded as c-MET positive disease.
  - NGS
    - C-MET mutations and amplifications will be assessed using Next-Generation Sequencing (NGS) of Formalin-Fixed, Paraffin-Embedded (FFPE) tissue using Single Molecule Molecular Inversion Probes (smMIP's).[14]
    - MET (NCBI Reference Sequence NM_001127500.2) will be sequenced in the following regions: codon 168, 375, 982-1027, 1230-1284, 1304.
- Advanced SGC
  - Advanced SGC is defined as either/or
    - Locally advanced SGC
    - Locally recurrent SGC
    - Metastatic SGC
- Patients will be analyzed in 3 cohorts (see statistical plan for more information)
  - SDC: n=9/17 patients
  - ACC: n=9/17 patients
    - In this cohort, patients with advanced ACC originating from the salivary glands and ACC originating from other body parts will be included.
  - Other SGC's: n=9 patients

Source population:

Study participants will be drawn from the following source population:

- Patients with SGC who are treated at the Department of Medical Oncology of the Radboudumc.
- Patients with SGC who are reffered to the Department of Medical Oncology of the Radboudumc in order to evaluatie eligability to particpate in this study.
- Patients with SGC who heard or read about this study and contact the investigators to ask whether they can take part in the study. Potential participants will not be actively recruited. However, there will be a message on the website of Dutch Salivary Gland Cancer Patient Platform: http://speekselklierkanker.org/. This message is added to this submission (see 'E3 Wervingsmateriaal').

4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Disease specific
  - locally advanced, recurrent, and/or metastatic SGC (excluding sarcomas and mesenchymal tumors)
  - c-MET positive disease (see paragraph 4.1)
  - Measurable disease per RECIST version 1.1
  - Cohort-specific criteria
    - SDC cohort:
      - Direct inclusion (no objective tumor growth prior to inclusion needed)
    - ACC cohort:
      - Inclusion after objective growth in the last three months or complaints due to the disease
    - Other SGC's
      - Inclusion after objective growth in the last three months or complaints due to the disease
- General conditions
  - Age ≥18 years
  - Eastern Cooperative Oncology Group performance status of 0 or 1.
  - Normal number of neutrophils and thrombocytes
  - Liver function:
    - ALT and AST < 2.5 x upper limit of normal (ULN)
    - Total bilirubin ≤ 1.5 x ULN (except for Gilbert's syndrome)
    - Serum albumin ≥28 g/L
  - Renal function:
    - Creatinine < 1.5 x ULN or calculated creatinine clearance ≥ 40 ml/min
    - Urine protein/creatinine ratio ≤113.1 mg/mmol (≤1 mg/mg) or 24-hour urine protein <1 g
  - Hemoglobin A1c (HbA1c) ≤ 8% or a fasting serum glucose ≤ 9 mmol/l

4.3 Exclusion criteria

- General conditions
    - A known allergy for cabozantinib or its components
    - Long QT-syndrome
    - Pregnancy or lactation
    - Patients (M/F) with reproductive potential not implementing adequate contraceptives measures
    - Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before inclusion
    - Major surgery within 3 months before randomization. Complete wound healing from major surgery must have occurred 1 month before inclusion and from minor surgery at least 10 days before inclusion
    - Uncontrolled illness including, but not limited to
        - Cardiovascular disorders including symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
        - Uncontrolled hypertension defined as sustained systolic BP > 150 mm Hg, or diastolic BP > 100 mm Hg
        - Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before inclusion
        - Serious active infections
- Concomitant treatments
    - Concomitant (or within 4 weeks before inclusion) administration of any other experimental drug under investigation.
    - Concurrent treatment with any other anti-cancer therapy.
    - Concomitant anticoagulation.
        - Low dose aspirin for cardioprotection and low dose LMWH are permitted.
    - Radiation therapy within the last 4 weeks before inclusion

4.4 Sample size calculation

The Simon two-stage design[15] will be used, with a null hypothesis of at most 5% response rate (not warranting further investigation) and an alternative hypothesis of at least 25% response rate (leading to further investigation). The statistical error rates of the design are $\alpha = 0.05$ and $\beta = 0.80$. The first stage consists of 9 patients per cohort ((1) SDC, (2) ACC) evaluable for response. If 0 responses out of the first 9 evaluable patients are observed, the study will be stopped with the conclusion that the drug should not be further investigated. In any other situation, the study will be continued until 17 patients are evaluable for response per cohort. If ≤2 responses out of these 17 patients are observed the study will accept the null hypothesis, with the conclusion that the drug should not be investigated further. If >2 responses out of 17 patients are observed, the null hypothesis will be rejected with the conclusion that the drug should be further investigated. In the third cohort (other SGC) 9 patients will be included to evaluate the efficacy of cabozantinib in other subtypes of c-MET positive SGC. Because different subtypes are included in this cohort, these results are hypothesis forming but will not be used for statistical analysis. Therefore, this study cohort will be closed after the first stage with 9 patients.

Feasibility analysis:

The Radboud university medical center is a tertiary referral center for head and neck cancer and SGC in particular, receiving referrals from all other academic medical centers and the Dutch Cancer Institute in the Netherlands. In 2016 and 2017 approximately 80-90 new locally recurrent or metastatic SGC patients (40% SDC, 40% ACC, 20% other SGC's) visited our outpatient department. Next to this, we closely collaborate with the SGC patient network in the Netherlands. Therefore we believe it is feasible to enroll 17 SDC patients, 17 ACC patients and 9 other SGC patients in two years.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will use cabozantinib tablets (Cabometyx®) once daily until progressive disease, intolerable toxicity, or investigator and/or patient decision to withdraw for a maximum duration of 2 years.

- Starting dose
  - 60 mg once daily
  - Liver function disorder: 40 mg once daily
  - Renal impairment: Cabozantinib should be used with caution in patients with mild or moderate renal impairment, but no dose reduction is necessary
- Dose reductions
  - Grade 3 or greater toxicities or intolerable grade 2 toxicities: temporary interrupt treatment untill side effects recovered to grade 1 toxicity or less. Resume therapy at 40 mg once daily if necessary and at 20 mg once daily at a subsequent episode
  - Dose reductions are recommended for events that, if persistent, could become serious or intolerable.
- Missed dose
  - If there are still 12 hours or more before the next dose is due, then the missed dose should be taken as soon as possible. The next dose should be taken at the normal time.
  - If the next dose is due in less than 12 hours, then the missed dose should not be taken. The next dose should be taken at the normal time.
- Method of administration
  - Cabometyx is for oral use. The tablets should be swallowed whole and not crushed.
  - Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking Cabometyx.\

5.2 Use of co-intervention (if applicable)

- No co-intervention is allowed during the study period.
- Concomitant medicinal products that are strong inhibitors of CYP3A4 (i.e. azoles, erytromycine, antiretroviral drugs, grapefruit juice) should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 (rifampicine, certain anti-epileptics, st. John’s wort) should be avoided.

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Cabometyx 20/40/60 mg film-coated tablets. See chapter 1, 2 and 3 of the Summary of product characteristics for more information.

6.2 Summary of findings from non-clinical studies

In nonclinical toxicology studies of cabozantinib in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues, and secondary changes were observed in bone and pancreas. Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, produced fetal external malformations in rats, and decreased fertility in male and female rats. The metabolite present at highest concentrations in humans administered cabozantinib, EXEL-1644, was negative in an in vitro bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats. In a 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes. No clinical cases of pheochromocytoma have occurred to date. No carcinogenic signal was observed in a rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks. See chapter 4 of the IB and paragraph 5.3 in the Summary of product characteristics for more information.

6.3 Summary of findings from clinical studies

17 clinical studies of cabozantinib for oncology indications including four Phase 1 studies, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 studies (a placebo-controlled study in subjects with medullary thyroid cancer, two active-controlled studies in subjects with CRPC, one ongoing open-label, active-controlled study in subjects with renal cell carcinoma, and one ongoing and enrolling double-blinded placebo-controlled study in subjects with hepatocellular carcinoma, one ongoing and enrolling Phase 4 study in medullary thyroid cancer, one ongoing maintenance “roll-over” study, and one expanded access study (Table 5-1 in the IB) are done. In addition, there are eleven clinical pharmacology studies (Table 5-2 in the IB); nine were conducted in healthy subjects alone, one study was conducted that included healthy subjects and subjects with renal impairment, and one study was conducted that included healthy subjects and subjects with hepatic impairment. In addition to these company-sponsored clinical studies, twenty-nine externally-sponsored studies and seventeen National Cancer Institute -Cancer Therapy Evaluation Program (CTEP) trials have enrolled subjects in oncology indications. Study results are summarized in paragraph 5.5 of the IB and paragraph 5.1 of the Summary of product characteristics.

6.4 Summary of known and potential risks and benefits

Cabozantinib has a well known safety profile, with 2467 patients treated within a clinical trial. Adverse event experienced by ≥20% of these patients are listed in table 1-1 of the

IB. Serious adverse events experienced by ≥1% of these patients are listed in table 1-2 of the IB. Benefits of cabozantinib in other cancers are described in paragraph 5.5 of the IB.

6.5 Description and justification of route of administration and dosage

Cabozantinib tablets are meant to be taken orally only and not to be crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity. Cabozantinib is meant to be taken without food (subjects should not eat for at least 2 hour before and at least 1 hour after taking cabozantinib) with a full glass (at least 240 ml) of water. If a dose is missed, the missed dose should not be taken less than 12 h before the next dose. Dosage is described in paragraph 5.1 of this protocol and table 1 in the Summary of product characteristics (page 4).

6.6 Dosages, dosage modifications and method of administration

Starting dose of cabometyx is 60 mg once daily (40 mg once daily in case of liver function disorders). Recommended dose modifications are described in paragraph 5.1 of this protocol and table 1 in the Summary of product characteristics (page 4). The trial medication will be stored at the trial pharmacy and can be ordered by filling in an AKF-form. Subsequently, the research nurse of the medical oncology department will hand the medication over to the patient on the outpatient department.

6.7 Preparation and labelling of Investigational Medicinal Product

Preparation and labeling of the commercially available medicinal product will be performed by the pharmacy department according to in-house SOP and IB.

6.8 Drug accountability

Drug accountability will be registered per patient and overall. For ‘per patient drug accountability’ a drug dispensing log will be used (see the attachment). In this log, drug dispension and returned drugs will be registered. A drug accountability log will be used for an overview of all dispensed and returned drugs (see the attachment).

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- Assess the ORR
    - Response will be measured according to RECIST version 1.1.[13]
    - ORR is defined as the sum of the complete remissions plus partial responses.[9]
    - The best response will be used in each patient.
    - An independent endpoint review committee will be installed to verify responses.

8.2 Secondary study parameters/endpoints (if applicable)

- Assess the PFS
    - PFS is defined as time from study enrollment until disease progression or death.
    - Outcome will be scored as ‘progressed’ or ‘censored’ according to the FDA guidance for industry of clinical trial endpoints.[9]
- Assess the OS
    - OS is defined as time from study enrollment until date of death of any cause.
    - Analysis of OS will be done at the end of the study (study related follow-up will be until 3 years after start of treatment)
- Asses the DoR
    - DoR is defined as time from study enrollment until date of documented tumor progression or death
    - Only patients with a CR or PR will be included in the assessment of DoR.
- Assess the toxicity of cabozantinib in SGC patients
    - Toxicity will be scored according to NCI CTC common criteria v 4.0.
- Assess the QoL of SGC patients treated with cabozantinib
    - QoL will be assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, PSSHN and VAS questionnaires.
- Assess the response rate of patients with advanced SGC treated with cabozantinib by using continuous tumor shrinkage end-points, as was advocated by Billingham et al[11] and Wason et al.[12]
- ctDNA will be assessed to evaluate whether treatment response and disease progression can be predicted.

8.2.1 Other study parameters (if applicable)

- History
    - Birth date
    - Gender
    - General medical history
    - Medication use
    - Allergies
    - SGC history: diagnosis date, location primary tumor, TNM stage at diagnosis, ex-PA?, AR-status, HER2-status, type of surgery, date of surgery, postoperative radiotherapy, date of radiotherapy, adjuvant systemic therapy, location of recurrence, date of recurrence, palliative treatments
- Clinical examination:
    - Vital signs
    - Body weight
- Laboratory tests: Hematology, biochemistry, urine (see assessments)
- ECG: QT time, abnormalities

8.3 Randomisation, blinding and treatment allocation

This is a single arm study, so randomisation, blinding and treatment allocation are not applicable.

8.4 Study procedures

In chapter 3 (study design) we describe which assessments will be done and when. Below we describe what this means for a patient who decides to participate: how many study related visits will be made, how much blood will be drawn, how much radiation will be used etcetera.

- Treatment
  - A patient will use Cabometyx tablets once daily for a maximum of 2 years
- OPD visits
  - A patient will visit the OPD at week 0 (baseline), 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 56, 68, 80, 92, 104 if he/she is on treatment for the maximum duration of 2 years. This means 17 planned study related visits in 2 years.
- Laboratory tests
  - Blood will be drawn by venapuncture at every visit.
  - At every visit, the following blood will be drawn:
    - First tube is always discarded→ 3 ml tube
    - Hematology → 3 ml EDTA tube
    - Biochemistry → 3 ml lithium-heparin tube
    - ctDNA → 3x 8.5 ml Roche cell free DNA tubes
    - total: 34.5 ml of blood per visit
- Urine analysis
  - A urine portion will be analyzed for protein/creatinine ratio before start of treatment, after 2 weeks, and when clinically indicated.
- ECG
  - An ECG will be made before start of treatment, after 2 weeks, and when clinically indicated.
- Imaging
  - A neck-, chest-, and abdominal CT scan will be made in week 0, 8, 16, 24, 32, 40, 48, 56, 68, 80, 92 and week 104 if a patient stay on treatment during the maximum of 2 years. So 12 CT-scans of approximately 15 mSv will be made, resulting in a yearly exposure of 90 mSv. Taking the terminal disease into account, this corresponds to a effective dose in healthy adults of 9 mSv, which is a moderate risk. In our opinion, this exposure is justified concerning the relevance of the study. See the radiation ethic form for further details.
- Questionnaires
  - Questionairres will be taken 7 times (at baseline, week 8, week 16, week 24, week 40, week 56 and at PD)
  - The follow questionnaires will be taken:
    - EORTC QLQ-C30: 30 questions
    - EORTC QLQ-H&N35: 35 questions
    - PSSHN[16]: 3 questions
    - VAS: 1 question
    - Total: 30+35+3+1=69 questions

8.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.6 Replacement of individual subjects after withdrawal

If a participant decides to withdraw before start of treatment with Cabometyx, another patient will be recruited to replace this participant. If a participant withdraws after start of treatment, this patient will be regarded as ‘lost to follow-up’ and won’t be replaced.

8.7 Follow-up of subjects withdrawn from treatment

All participants who received at least one dose of Cabometyx, will have study related follow-up for 3 years after the start of the study in order to establish PFS en OS. If a participant withdraws before start of Cabometyx, there will be no study related follow-up. Once study related follow-up is finished, patients will get follow-up as standard medical care.

8.8 Premature termination of the study

The Simon 2-stage design of this study prevents unnecessary exposure of an ineffective treatment. After the first stage (9 patients in each cohort) an interim analysis will be done to see whether continuation of the trial is indicated. See the sample size calculation for more details.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);

2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Investigator's Brochure.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

MonitoringCabometyx is registered in advanced renal cell carcinoma. Additional toxicity is not expected in SGC. Therefore a DSMB deemed unnecessary.The study will be monitored according to the NFU guideline ‘Kwaliteitsborging mensgebonden onderzoek 2.0’. For this study with a moderate risk, moderate intensive monitoring will be applied (see page 18 of the NFU guideline).

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Following Simon's design (as described in section 4.4) for RECIST v1.1, the null hypothesis will be rejected if more than 2 responses out of 17 patients are observed; in that case the conclusion is that the drug should be further investigated. This design yields a type I error rate of 0.047 and power 0.81 when the true response rate is 0.25. A 95% CI for the overall response rate per RECIST v1.1 will be calculated using the binomial distribution. Next to this, responses (CR, PR, SD and PD) will be described using simple descriptive statistics.

10.2 Secondary study parameter(s)

- Assess the PFS
    - PFS will be estimated by a Kaplan-Meier curve
        - In SDC patients, PFS will be compared to PFS in AR-positive SDC patients which received ADT[17,18] and HER2-positive SDC patients which received docetaxel plus trastuzumab.[19]
        - In ACC patients, PFS will be compared to PFS in ACC patients which received mitoxantrone monotherapy,[20,21] vinorelbine monotherapy,[22] epirubicin monotherapy,[23] or cisplatin plus anthracycline combination therapies[24]
        - In other SGC patients, PFS will be described per individual case.
- Assess the OS
    - OS will be estimated by a Kaplan-Meier curve
        - In SDC patients, OS will be compared to a historical cohort of patients receiving best supportive care and a cohort receiving ADT.[18]
        - In ACC patients, median OS after disease recurrence is 6.4 years, and median OS after metastasis is 3.7 years.[25] OS of our study patients will be compared to these data and to OS data of phase II studies in ACC mentioned above (assess the PFS).
        - In other SGC patients, survival will be described per individual case
- Toxicity and QoL questionnaires will be described using simple descriptive statistics.
- Assess the response rate of patients with advanced SGC treated with cabozantinib by using continuous tumor shrinkage end-points, as was advocated by Billingham et al[11] and Wason et al.[12]
- Tumor shrinkage will be shown in a waterfall plot.

10.3 Other study parameters

Background variable will be described using simple desricptive statistics and will be presented in a table.

10.4 Interim analysis

- According to the Simon 2-stage design, interim analysis of treatment efficacy will be done after 9 patients in each cohort. Treatment efficacy will be established by the response rate, in which a treatment response is defined as a complete remission or partial response, based on RECIST version 1.1 criteria. In case of 0 response, this

cohort will be terminated. In case of ≥1 response(s), 8 additional patients will be included in stage 2. This interim analysis will be performed by the researcher. The monitor will check the responses, in order to establish whether patients can be included in stage 2.

- For OS, a planned interim analysis will be done after a median follow-up of 3 years. The monitor will analyze interim safety and efficacy data in according to the NFU guideline 'Kwaliteitsborging mensgebonden onderzoek 2.0', for moderate risk studies. Next to this, the monitor will check if the study can proceed to stage 2, based on treatment efficacy in stage 1, as described at the first bullet of this paragraph.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 8, 19 October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the personal data protection act (Wet Bescherming Persoonsgegevens), and the Medical Treatment Agreement Act (WGBO).

11.2 Recruitment and consent

Patients will be informed about the study by their treating physician during normal patient care. Detailed information about the study can be offered by the investigators during normal patient care or by phone call. If a patient decides to participate, the baseline study visit will be planned, which starts with reviewing inclusion and exclusion criteria and signing the IC.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Benefits: because cabometyx has not been tested in SGC patients before, the chance of responding to treatment is unknown. The Simon 2-stage design will be used in order to prevent exposure of too many patients to ineffective treatment without discarding a potential effective treatment because of treatment failure in some patients.
Risk assessment: Safety of Cabometyx is well known because of studies in renal cell carcinoma.[3] The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%), and nausea (2%). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar-plantar erythrodysaesthesia syndrome (PPES) (42%), hypertension (37%), vomiting (32%), weight decreased (31%), and constipation (25%).[26]
Group relatedness: the study does not involve minors and/or incapacitated subjects

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Travel expenses and parking costs will be paid.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Patient identification

During registration an unique patient record ID will be allocated to the patients. This record ID will be used for identification of the patients and should be reported on all case record forms (CRFs). Data and patient material will be handled confidentially and if possible anonymously. When it is necessary to trace data or material to an individual subject, we will use a subject identification number list to link the data to the subject. This list will be safeguarded by the Principle Investigator. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP).

Data management

Data will be collected on *electronic* Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. The e-CRF will be completed on site by the local investigator or an authorized staff member. All CRF entries must be based on source documents. Guidelines for completing the CRF will be provided by the Trial office Hematology-Oncology, Nijmegen. Access to the e-CRF will be provided by the Trial office Hematology-Oncology, Nijmegen only to authorized site staff members. Training materials will be provided by the Trial office Hematology-Oncology, Nijmegen.

12.2 Monitoring and Quality Assurance

Source data verification of the CRFs and check of the Investigator Study File documents will be performed by the clinical research monitor of the Radboudumc, according to the procedures The NFU guideline “Kwaliteitsborging mensgebonden onderzoek 2.0’’ for studies with a moderate risk.

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the

first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

Prior to initiation, the study will be submitted to clinicaltrials.gov. All the results will officially be published. Ipsen will provided with a copy of any manuscript, paper or poster not less than thirty (30) days prior to their submission to a scientific journal or presentation at scientific meetings and a reasonably detailed summary or abstract of any other oral or written publication not less than thirty (30) days prior to their submission or presentation. In case the investigator receives no response within thirty (30) days the investigator will be free to publish. Upon request by Ipsen, presentation, submission for publication or other disclosure, will be withhold for an additional ninety (90) days to allow Ipsen to seek patent protection.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases. The targets of cabozantinib include several tyrosine kinases known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET (hepatocyte growth factor [HGF] receptor), vascular endothelial growth factor receptor 2 (VEGFR2, also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely-related tyrosine kinases KIT and FLT-3. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis. Next to this, MET expression has been shown in 53.2% of ACC patients[6] and 39.7% SDC patients.[7]

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Cabozantinib has been studied in humans in different cancers (see chapter 5 of the IB) and has been approved for metastatic medullary thyroid cancer and advanced renal cell carcinoma. The safety profile of cabozantinib and the efficacy in other cancers is therefore well known. Cabozantinib has not been studied in SGC before. We will use a 2-stage design in order to minimize sample size in case of low-activity.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Anti-tumor activity is shown in other cancers in humans (paragraph 5.5 of the IB). Currently, no SGC cell cultures or organoid cultures are available to test cabozantinib efficacy in SGC in vitro.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Cabozantinib is a multikinase receptor tyrosine kinase. These targets (see 13.1a) inhibit different factors in cancer progression, such as cell proliferation and tumor neovascularisation. However, these targets are not tumor-specific and therefore induce certain side effects. These side effects are extensively studied in human beings in previous studies in other cancers. Anticipated adverse events and management of adverse events are described in paragraph 6.2 of the IB

e. Analysis of potential effect

Because cabozantinib has not been studied in SGC before, potential efficacy can't be predicted. The Simon 2-stage design will be used to minimize exposure of patients to this treatment in case of low-acitivity.

f. Pharmacokinetic considerations

Following oral administration of cabozantinib capsules or tablets, T_{max} ranged from 2 to 5 hour post-dose. The terminal half-life (for predicting drug washout) is approximately 120

hour. Repeat daily dosing of cabozantinib capsules at 140 mg for 19 days resulted in a 4- to 5-fold higher mean cabozantinib accumulation (based on AUC) compared with a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

A PopPK analysis of cabozantinib was performed using data collected from 289 cabozantinib-treated subjects with solid tumors following oral administration of 140-mg capsule daily doses. The predicted effective half-life for that formulation at that dose was approximately 55 h, V/F is approximately 349 L, and CL/F at steady-state was estimated to be 4.4 L/h. This PopPK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).

More information about the pharmacokinetics can be found in paragraph 5.2 of the IB.

g. Study population

The study population are patients with locally advanced and/or metastatic SGC. This is a life-treatening condition and at the moment of inclusion the condition is unstable, because SDC is an aggressive tumor and for the others types of SGC objective growth is needed prior to inclusion. Next to this, treatment options are very limited in this situation (see introduction). Women with child bearing potential could be included in the study, but have to take contraceptive measures in order to participate.

h. Interaction with other products

In summary, currently available data suggest that cabozantinib: (1) is not anticipated to markedly induce or inhibit CYP enzymes at clinically-relevant plasma concentrations; (2) is a substrate for CYP3A4; (3) may have the potential to inhibit the P-gp transport activity but is not a substrate of P-gp; and (4) is a substrate of drug-transporter MRP2. More information can be found in paragraph 6.4 of the IB.

i. Predictability of effect

Treatment effect will be measured with CT-scans every 8 weeks using RECIST criteria. It is not possible to predict treatment effect reliable before the first evaluation CT scan. In this study, we will collect blood samples for ctDNA analysis. The ctDNA samples will be analyzed in order to establish whether disease response can be predicted before the first evaluation CT-scan using ctDNA.

j. Can effects be managed?

In general side effects can be managed by either supportive treatment and/or dose reductions. Specific management of side effects is described in paragraph 6.2 of the IB. If side effect occur, the Radboudumc has 24-hour facilities including a level 3 intensive care to manage side effects.

13.2 Synthesis

To sum up, SGC is a rare cancer with few treatment options in case of disease recurrence or distant metastases. New treatment options are therefore urgently

warranted. Because c-MET overexpression is established in ACC and SDC, treatment with the tyrosine kinase inhibitor cabozantinib (which targets MET, among others) could be a new treatment option.

In order to minimize risk of this experimental treatment, we took certain measures. First of all, only patients with a reasonable health (see inclusion criteria) can be included. Second, we use the Simon 2-stage design in order to minimize exposure of patients in case of minimal efficacy. Third, we took standard precautions such as a moderate monitoring according to NFU guidelines. And Finally, we will only include c-MET positive tumors in order to increase the chance of treatment efficacy. In case of treatment efficacy in c-MET positive salivary gland tumors, a future study may investigate the efficacy of cabozantinib in all salivary gland tumors, as cabozantinib has more targets then only c-MET.

In our opinion, the remaining risks of this therapy are acceptable for patients participating in the study, taking the lack of other treatment options, well-known safety profile of cabozantinib, and safety measures into account. According to the NFU risk classification, this study has a moderate risk (moderate chance of moderate damage).

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