# A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in High Grade Uterine Sarcoma (HGUtS) after stabilization or response to doxorubicin +/- ifosfamide following surgery or in metastatic first line treatment

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Primary objectiveThe main objective of the trial is to assess in High Grade Undifferentiated Uterine Sarcoma (HGUS), High Grade Endometrial Stromal Sarcoma (HGESS), High Grade Leiomyosarcomas (HGLMS) and High Grade (HG) adenosarcoma , the efficacy (...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Reproductive neoplasms female malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53073

**Source**
ToetsingOnline

**Brief title**
Cabozantinib maintenance in HGUtS

### Condition

- Reproductive neoplasms female malignant and unspecified

**Synonym**
high grade uterine sarcoma (HGUtS), uterine sarcoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** European Organisation for Research in Treatment of Cancer (EORTC)
**Source(s) of monetary or material Support:** EORTC

## Intervention

**Keyword:** cabozantinib, HGUtS, maintenance treatment

## Outcome measures

### Primary outcome

The primary endpoint is the progression free survival rate at 4 months after

randomization to cabozantinib or placebo.

### Secondary outcome

* Progression free survival (RECIST 1.1)

* Overall survival

* Response rate and duration of response to cabozantinib (RECIST 1.1)

* Response rate to doxorubicin-based chemotherapy after registration on trial

for the patients with measurable disease

* Health-related Quality of life (QLQ-C30 + QLQ-EN24)

* Safety of Cabozantinib in HGUS according to the "Common Terminology Criteria

for Adverse events" version 4.0 (CTCAE 4.0)

# Study description

### Background summary

High grade uterine sarcoma (HGUtS) is a rare and aggressive type of endometrial cancer. The chemotherapy response is generally poor, as is the prognosis. In

this rare subgroup of tumors, hardly any specific trials have been done previously. Angioinvasion in the primary tumor seems to be the most relevant prognostic biological factor. Cabozantinib is an oral angiogenesis inhibitor, with activity against the receptor tyrosine kinases VEGFR2, MET, and RET.

## Study objective

Primary objective

The main objective of the trial is to assess in High Grade Undifferentiated Uterine Sarcoma (HGUS), High Grade Endometrial Stromal Sarcoma (HGESS), High Grade Leiomyosarcomas (HGLMS) and High Grade (HG) adenosarcoma , the efficacy (PFS at 4 months) of maintenance treatment with cabozantinib when compared with placebo after clinical benefit (CR, PR and SD) to standard chemotherapy (doxorubicin +/- ifosfamide) (given as an adjuvant treatment after curative surgery, or for locally advanced or metastatic disease).

Secondary objectives

* To assess the efficacy of maintenance treatment with cabozantinib when compared with placebo, via progression-free survival (PFS) and overall survival (OS) and, among patients with measurable disease, via response rate (RR) and duration of response.
* To describe the safety profile of cabozantinib in patients with High Grade Uterine Sarcoma
* To explore the response rate to chemotherapy in first line treatment for patients with measurable disease

Exploratory objectives
* To evaluate HRQoL for each arm

## Study design

This is a randomized phase II double blinded trial aiming to evaluate the role of maintenance therapy with cabozantinib in High Grade Undifferentiated Sarcoma (HGUtS) after stabilization or response to chemotherapy following surgery or in metastatic first line treatment.

In this trial, 54 patients will be randomized (1:1) at the EORTC Headquarters to receive either cabozantinib monotherapy (experimental arm) or placebo (control arm).
The activity of cabozantinib maintenance will be assessed by formal comparison of the progression-free survival at 4 months to that of the control arm (placebo).

## Intervention

Non-progressive patients (CR, PR, SD) at the end of the first line treatment will be randomized to receive as protocol treatment either cabozantinib 60 mg monotherapy once daily or placebo.

Protocol treatment is continued until completion (2 years) or occurrence of a withdrawal criterion.
Patients randomized to the control arm can receive cabozantinib at the time of relapse, after unblinding of the study arm.

**Study burden and risks**

After standard 1st line chemotherapy, participants will be randomized to maintenance therapy with placebo or cabozantinib for a maximum of 2 years. During this period they have to come to hospital regularly, with blood tests and imaging that are not part of standard protocol outside the framework of a clinical trial. Participants randomized to cabozantinib may experience side effects.

# Contacts

**Public**
European Organisation for Research in Treatment of Cancer (EORTC)

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1) At registration, - Patients who are suitable for treatment with doxorubicin +/- ifosfamide and fall within one of the following patient populations:
* HGUS, HGESS, HGLMS and HG adenosarcoma:
* FIGO stage II and stage III : if adjuvant chemotherapy is proposed
* FIGO stage IV: if first line chemotherapy is proposed, -Patients can be registered no earlier than 4 weeks prior to start of the 1st line treatment and no later than 4 weeks after last administration of 1st line treatment., - 1 formalin fixed paraffin embedded (FFPE) block of tumor tissue (if not available, at least 1 H/E (haematoxylin/eosin) and 15 unstained slides) is sent after registration of a patient. Histological central review is mandatory to confirm histology and grade. , - Patients must be at least 18 years old, - Before patient registration, written informed consent for central collection of tissue block or slides and any other trial-specific procedures must be obtained from the patient according to ICH/GCP, and national/local regulations, allowing for collection, storage and analysis of tissue and screening procedures., 2) At Randomization, - Patients can be randomized within 12 weeks after last administration of 1st line treatment, before the start of protocol treatment, - Central pathological confirmation: Histological evidence of HGUS, HGESS, HGLMS and HG adenosarcoma Non-progressive patients (CR, PR, SD) at the end of the first line standard chemotherapy (4 to 6 cycles of doxorubicin alone or in combination with ifosfamide)., - Non-progressive patients (CR, PR, SD) at the end of the first line standard chemotherapy (4 to 6 cycles of doxorubicin alone or in combination with ifosfamide)., - Patients able to swallow and retain oral tablets., - WHO/ECOG performance status 0-2 , - Recovery to baseline or <= Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy, - The subject has organ and marrow function and laboratory values as follows before randomization, * Absolute neutrophil count (ANC) >= 1500/mm3 without colony stimulating factor support for 7 days
* Platelets >= 100,000/mm3
* Hemoglobin >= 9 g/dL
* Bilirubin <= 1.5 * the upper limit of normal (ULN). For subjects with known Gilbert*s disease, bilirubin <= 3.0 mg/dL
* Serum albumin >= 2.8 g/dl
* Serum creatinine <= 1.5 * ULN or creatinine clearance (CrCl) >= 50 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:

CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72) × 0.85
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3.0 * ULN or <= 5.0 x ULN if liver metastases
* Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis
* Urine Dipstick: If Urine Dipstick >= 2+, determine Urine Protein to Creatinine Ratio (UPCR) by quantitative analysis; if UPCR * 1, then a 24-hour urine protein must be assessed. Any patient with protein > 150 mg over 24 hours would not be eligible.
* Serum phosphorus, calcium, magnesium and potassium >= LLN
* Prothrombin time (PT) or international normalized ratio (INR) * 1.2 X upper limit of normal (ULN), - Clinically normal cardiac function based on the institutional lower limit of normal (LVEF assessed by MUGA or ECHO), normal 12 lead ECG (no prolongation of corrected QT interval (QTc) > 500 msecs according to Fridericia's formula) and no history of any one or more of the following cardiovascular conditions within the past 6 months:, * Cardiac angioplasty or stenting
* Clinically-significant cardiac arrhythmias
* Myocardial infarction
* Unstable angina
* Coronary artery bypass graft surgery
* Symptomatic peripheral vascular disease
* Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
* No history of congenital long QT syndrome, - Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment is permitted., - Women of child bearing potential (WOCBP) must have a negative serum/urine pregnancy test within 72 hours prior to the first dose of study treatment. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons., - Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 4 months after the last study treatment., - Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 8 weeks after the last study treatment., - Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

## Exclusion criteria

At randomization, - The following tumor types are NOT eligible: low-grade ESS, leiomyosarcoma (low or intermediate), carcinosarcoma, low-grade adenosarcoma, rhabdomyosarcoma (alveolar or embryonal) and soft tissue PNET of uterus/cervix., - No contraindications to cabozantinib (e.g. no known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to cabozantinib), - No planned use of chemotherapy, radiation therapy, radionuclide treatment, small molecule TKI or hormonal therapy, and any other investigational agent during the treatment period., - No prior treatment with cabozantinib, - No concurrent severe, clinically relevant hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment, - No patient with concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;, - No concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel); , - No patients who have suffered a cerebrovascular accident at any time in the past, patients who have suffered a transient ischemic attack in the past 6 months, patients who have suffered a deep venous thrombosis (DVT) or a pulmonary embolism in the past 6 months , - No Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:"known" intra-abdominal tumor/metastases invading GI mucosa: , * active peptic ulcer disease,
* inflammatory bowel disease (including ulcerative colitis and Crohn*s disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
* malabsorption syndrome
* Ongoing visceral complications from prior therapy
* Prior gastrointestinal surgery (particularly when associated with delayed or incomplete healing)
Any of the following within 6 months before the first dose of study treatment:
* abdominal or vaginal fistula
* gastrointestinal perforation
* bowel obstruction or gastric outlet obstruction
* intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with Cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment., - No clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment, - No patients with evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of study treatment (Cabozantinib/placebo)., - No patients with radiographic evidence of cavitating pulmonary lesion(s)., - No patients with tumor in contact with, invading or encasing any major blood vessels., - No

evidence of active bleeding or bleeding diathesis.

- No hemoptysis >= 2.5ml of red blood within 3 months before the first dose of study treatment., - No signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment, - No major surgery or trauma within 12 weeks prior to first dose of study drug and/or presence of any non-healing wound, fracture or ulcer. Complete wound healing from major surgery must have occurred one month before the first dose of study treatment., - Patients with clinically relevant ongoing complications from prior surgery are not eligible, - No poor oral hygiene or invasive dental or orofacial procedures within 28 days before the first dose of study treatment., - Prior radiation therapy:, * No radiation therapy for bone metastasis within 2 weeks, or any other external radiation therapy within 2 weeks before the first dose of study treatment. Patient must have fully healed and there are no ongoing sequelae from the previous radiation therapy before the first dose of study treatment.
* No systemic treatment with radionuclides within 6 weeks before the first dose of study treatment.
* Patients with clinically relevant ongoing complications from prior radiation therapy are not eligible., - No concurrent or planned treatment with strong inhibitors or inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) , - No other malignancies within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death, treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ treated surgically with curative intent, and non-muscle invasive urothelial cell carcinoma).

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 06-10-2015 |
| Enrollment: | 6 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | cometriq |
| Generic name: | cabozantinib |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 22-04-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-07-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-01-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

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| Approved WMO Date: | 09-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-06-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-12-2022 |
| Application type: | Amendment |
| Review commission: | MEC Academisch Medisch Centrum (Amsterdam)<br><br>Kamer G4-214<br><br>Postbus 22660<br><br>1100 DD Amsterdam<br><br>020 566 7389<br><br>mecamc@amsterdamumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-000762-11-NL |

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT01979393 |
| CCMO | NL51944.018.15 |