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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. (NCT01979393)

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1 Abstract

This is a randomized phase II double blinded trial aiming to evaluate the role of maintenance therapy with cabozantinib in High Grade Uterine Sarcomas (HGUtS) after stabilization or response to chemotherapy following surgery or in metastatic first line treatment. 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) adenosarcomas the efficacy (progression-free survival (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). A cabozantinib/placebo dose of 60 mg daily is selected based upon results from preclinical and clinical studies. 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. A total of 54 patients randomized (1:1) to receive either cabozantinib monotherapy (experimental arm) or placebo (control arm) are needed to detect an increase from 50% to 80% PFS rate at 4 months. Recruitment started in February 2015, the trial has currently randomized 35 patients out of 83 registered.

2 Introduction

2.1 Background

Uterine sarcomas are rare tumors that account for approximately 1% of female genital tract malignancies and 8% of uterine cancers, with an incidence of approximately 0.4 per 100,000 women (Ref. 40). Although the aggressive behavior of most cases is well recognized, their rarity and histopathological diversity has contributed to the lack of consensus on risk factors and optimal treatment and the outcome remains poor (Ref. 2). According to 2012 systematic review of data from 1970 to 2011, leiomyosarcomas (LMS) is the most common subtype (63%), followed by endometrial stromal sarcoma (ESS) (21%) and less common subtypes as undifferentiated uterine sarcoma (Ref. 41). This study addresses high-grade entities that based on histopathology, clinical behavior and patient outcomes present similar high risk of recurrence and poor prognosis.

On the basis of previous published data, it seems that undifferentiated sarcomas are positive for Platelet Derived Growth Factor Receptor (PDGFR)-a (Ref. 6), androgen receptor (AR) (Ref. 7), and WT1 (Ref. 8). HGUS and high grade endometrial sarcoma (HGES) have very poor prognosis and most patients die of recurrent disease within two years of diagnosis. In a recent study (Ref. 10), the presence of vascular invasion was the only statistically significant prognostic factor, with a 5-year crude survival of 83% and 17% when vascular invasion was absent or present, respectively (P=0.02). Local recurrences and distant metastases are associated with a high mortality. *YWHAE-FAM22* ESS represent a clinically aggressive subtype of ESS classified as HGESS, and its distinction from the usual low-grade ESS with *JAZF1* rearrangement and from HGUtS with no identifiable molecular aberration. In general, standard guidelines and decision-making protocols include adjuvant chemotherapy with anthracyclines +/- ifosfamide at adequate doses in patients with good performance status and poorly differentiated sarcoma with stage I and II or in patients with advanced disease (stage III/IV) (Ref. 11). In general, the median survival for metastatic HGUtS is less than 1 year. Typically, management of metastatic uterine sarcoma conforms to treatment practice for other metastatic soft tissue sarcomas (STS). The principles of management include surgical resection of isolated metastases, radiation to sites of local recurrence for disease control, and palliative systemic chemotherapy for advanced disease. No curative therapeutic option is currently available, with the possible exception of surgery for metastases isolated to the lung (Ref. 12). Systemic treatment for HGUS paralleled that for adult-type STSs, using doxorubicin +/- ifosfamide as single agents or in combination (Ref. 13).

LMSs are the most common subtype of uterine sarcoma; most are high-grade malignancies with a high risk for recurrence and progression. Overall survival (OS) is dependent on stage, with 5-year survival estimates for stage I, 76%; stage II, 60%; stage III, 45%; and stage IV disease, 29% (Ref. 49). Uterine LMSs are staged using the International Federation of Gynecology and Obstetrics 2009 uterine sarcoma staging system, although anatomic staging systems perform poorly in survival prognostication (Ref. 50). Objective response rates can be achieved with systemic treatment for metastatic uterine LMS; in patients with symptomatic disease, chemotherapy may provide palliation of symptoms. There is no established superior first line chemotherapy regimen. Reasonable regimens to consider for first-line therapy include doxorubicin, doxorubicin plus ifosfamide, gemcitabine, gemcitabine plus docetaxel with objective response observed between 17 and 36% of patients (Ref. 51, Ref. 52, Ref. 53, Ref. 54). Pazopanib 800 mg oral daily achieved objective response in about 6% of patients with metastatic STS in a phase III trial. The PFS was 20 weeks with pazopanib versus 7 weeks with placebo. There was no difference in OS (Ref. 55). This is currently the most frequently second line therapy for metastatic LMS after failure to CT including trabectedine.

Adenosarcomas of the female genital tract are rare malignancies, originally described in the uterus, the most common site of origin, but they may also arise in extra uterine locations. Uterine

adenosarcomas make up 5% of uterine sarcomas and tend to occur in postmenopausal women. Tumors that exhibit a high-grade sarcomatous overgrowth have a worse outcome. Extra uterine adenosarcomas also have a higher risk for recurrence. In view of their rarity, there have not been any clinical trials in adenosarcomas and relatively little research (Ref. 56). The management of patients with high grade metastatic adenosarcomas is similar to the management of patients with metastatic high grade sarcomas. It seems unlikely that there is an intrinsic difference between high grade sarcomas arising in adenosarcomas and their histological counterparts that arise de novo and a similar approach to management as in other sarcomas is reasonable.

2.2 Rationale

Due to the absence of effective treatments for HGUtS and the poor prognosis, new agents need to be investigated in these rare diseases.

The vast majority of patients with metastatic soft-tissue and bone sarcomas have rapid disease progression and poor OS despite currently available palliative chemotherapy even with the best multimodality treatment. Although patients achieving clinical benefit with initial therapy may continue to receive chemotherapy until disease progression or unacceptable toxicity, chemotherapy can also be stopped after maximal benefit has been obtained with ongoing surveillance of metastatic disease until eventual disease progression. The benefits of continuing chemotherapy have never been proven to be greater than stopping therapy once benefit has been obtained, and there are known risks from cumulative drug-associated toxicities, such as cardiac toxicity associated with doxorubicin.

An effective and convenient therapy that could be used to maintain benefits from prior cytotoxic chemotherapy, such as prolonged disease stability, might offer a useful addition to the pharmacologic management of sarcoma patients with metastatic disease. Angiogenesis plays an important role in the growth and dissemination of HGUtS and other STSs. High VEGF expression is an independent, poor prognostic factor for increased risk of metastases and decreased OS. (Ref. 15, Ref. 16, Ref. 17)

2.2.1 Anti-angiogenic therapeutics activity in STS

Pazopanib (Votrient [GW786034]; GlaxoSmithKline) is an orally bioavailable, adenosine triphosphate-competitive tyrosine kinase inhibitor of vascular endothelial growth-factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth-factor receptor (PDGFR)-α and –β, and v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog (c-kit) that has activity in multiple cancers, including renal cell cancer, sarcomas, cervical and ovarian cancer. It is FDA-approved for the treatment of advanced renal-cell carcinoma and was approved for the treatment of patients with advanced STS who have received prior chemotherapy, excluding GIST and adipocytic STS (Ref. 19).

Maki and his colleagues conducted a phase II multi arm study with single-agent sorafenib at a dose of 400 mg twice daily in patients with advanced STS (Ref. 22). Although the response rates were lower with sorafenib in this study than standard cytotoxic agents, PFS for leiomyosarcoma and angiosarcoma patients was comparable, supporting the activity of sorafenib in these diagnoses. In comparison, imatinib was inactive in 16 angiosarcoma patients as part of a phase II study, supporting VEGF receptor blockade as the key mechanism of action of sorafenib in these histologies.

Regorafenib, a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and tumor cell signaling kinases (RET, KIT, PDGFR, and Raf), was assessed in a randomized phase II in patients with metastatic STSs previously treated with anthracycline. Regorafenib is active in non-adipocytic soft tissue sarcomas. In the leiomyosarcoma cohort, progression-free survival was 3·7 months (95% CI 2·5-5·0) with regorafenib versus 1·8 (1·0-2·8) months with placebo (HR 0·46 [95% CI 0·46-0·80] p=0·0045). In the other sarcoma cohort (i.e. non-liposarcoma, leiomyosarcoma or synovial sarcoma), progression-free

survival was 2·9 months (95% CI 1·0-7·8) with regorafenib versus 1·0 (0·9-1·9) with placebo (HR 0·46 [95% CI 0·25-0·81] p=0·0061) (Ref. 60, Ref. 61).

2.2.2 Cabozantinib and its potential role

VEGFR2 (vascular endothelial growth factor receptor 2), MET (hepatocyte growth factor [HGF] receptor), and RET (rearranged during transfection) all play important roles in cancer biology. Up regulation of MET is found in a wide range of malignancies—including thyroid, prostate, ovarian, lung, and breast cancers—and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo*. MET-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway or by androgen deprivation in the treatment of prostate cancer. Cabozantinib (XL184) inhibits the receptor tyrosine kinases VEGFR2, MET, AXL and RET. *In vivo* pharmacodynamic activity of cabozantinib against VEGFR2, MET, AXL and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib inhibited tumor angiogenesis, tumor invasiveness and metastasis, and the progression of tumors in bone compared to sunitinib. This activity on VEGFR2 and MET make a good rational to evaluate cabozantinib in cancer, as angiogenesis pathways are one of the drivers of tumor progression.

Cabozantinib is supplied as both capsules and tablets, but the two formulations are not interchangeable. Cabozantinib capsules (140 mg) were approved by the FDA on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). On 21 March 2014, cabozantinib capsules (140 mg) were approved by the European Commission for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC (EXAM study). On 25 April 2016, cabozantinib tablets (60 mg) were approved by FDA in patients with advanced RCC who have received prior anti-angiogenic therapy. Cabozantinib is commercially available as both capsules and tablets in the United States and is currently available only as capsules in the European Union. It is currently undergoing clinical trials in the following indications: STS, prostate cancer, ovarian cancer, glioblastoma, melanoma, breast cancer, non-small cell lung cancer, and hepatocellular cancer.

Given the activity of cabozantinib in several malignancies and the activity of VEGF-targeting agents, such as pazopanib, sorafenib and sunitinib in STS, agents from the similar class could be explored in the management of patients in maintenance treatment after chemotherapy in HGUS, HGESS, HGLMS and HG adenosarcoma. In this context, and due to the anti-tumor activity, spectrum of action, cabozantinib is proposed as the novel therapy in this trial. The aims are to evaluate the therapeutic benefit of maintenance treatment with cabozantinib for patients with HGUS, HGESS, HGLMS and HG adenosarcoma who have achieved response (RECIST 1.1 CR or PR) or stable disease (RECIST 1.1 SD) to chemotherapy in first line treatment or at first metastatic relapse.

2.3 International Rare Cancers Initiative

The International Rare Cancers Initiative (IRCI) is a strategic collaboration between Cancer Research UK, the UK National Institute for Health Research Cancer Research Network (NCRN), the US National Cancer Institute (NCI), the European Organisation for Research and Treatment of Cancer (EORTC) and the French National Institute of Cancer (INCa). IRCI's aim is to facilitate the development of clinical trials for patients with rare cancers in order to improve outcomes. This trial was initiated by the EORTC internally as a collaboration between the EORTC Soft Tissue Bone Sarcoma Group (STBSG) and the EORTC Gynecological Cancer Group (GCG). Although the protocol was developed through the IRCI platform with input from all parties, ultimately only the NCRN group was able to join recruitment.

3 Trial Design

This is a randomized phase II double blinded trial aiming to evaluate the role of maintenance therapy with cabozantinib in HGUS, HGESS, HGLMS and HG adenosarcoma after stabilization or response to chemotherapy following surgery or in advanced first line treatment. In this trial, 54 patients will be randomized (1:1) to receive either cabozantinib monotherapy (experimental arm) or placebo (control arm).The activity of cabozantinib maintenance will be assessed by formal comparison of PFS at 4 months to that of the control arm (placebo). To make the trial more attractive to patients and investigators, in the placebo arm cross-over to cabozantinib at progression is permitted. Due to this cross-over, the selected primary endpoint is PFS as it is unaffected by the potential cross-over effect. Overall survival and toxicity remain key secondary endpoints.

The enrollment process is composed of two steps. Patient registration must take place between 4 weeks before the start and no later than 4 weeks after the administration of the first dose of 1st line treatment. Written informed consent for collection of tissue blocks or slides and any other trial-specific procedures are obtained from the patient. This screening step is needed to allow for timely central histological review. Randomization is only allowed after pathological confirmation by central review and should occur no later than 12 weeks after last administration of 1st line treatment.

Eligible patients will be randomized to receive either cabozantinib monotherapy or placebo. Cabozatinib will start between three and twelve weeks after the end of the doxorubicin based regimen (see Appendix A for allowed regimens and doses of doxorubicin +/- ifosfamide). Protocol treatment is continued until completion (2 years) or occurrence of a withdrawal criterion. These criteria are the occurrence of any of the following: disease progression, diagnosis of a second malignancy, patient refusal, excessive toxicity (impeding further protocol therapy), unblinding of the study treatment, pregnancy or failure to use adequate contraception.

Patients discontinuing therapy in the absence of progression should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient. After documented disease progression (according to RECIST 1.1; Ref 62), the treatment will be unblinded. Subjects receiving cabozantinib shall be treated at the investigator discretion. Subjects receiving placebo shall be offered the option of receiving cabozantinib up to further progression. This cross-over is not mandatory and at the investigator decision.

4 Patient selection criteria

The following eligibility criteria are mandatory and will be verified at the registration and randomization step respectively.

4.1 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

The following tumor types are NOT eligible: low-grade ESS, leiomyosarcoma (low or intermediate grade), carcinosarcoma, low-grade adenosarcoma, rhabdomyosarcoma (alveolar or embryonal) and soft tissue PNET of uterus/cervix.

See appendix B for FIGO staging of uterine sarcomas.

- 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 blocks 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.

4.2 At Randomization

- Central pathological confirmation: Histological evidence of HGUS, HGESS, HGLMS and HG adenosarcoma.
- Non-progressive patients (CR, PR, SD) after first line treatment (standard chemotherapy consisting of 4 to 6 cycles of doxorubicin alone or in combination with ifosfamide) and at time of randomization.
- No contraindications to cabozantinib (e.g. no known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to cabozantinib)
- Patients able to swallow and retain oral tablets.
- No planned use of chemotherapy, radiation therapy, radionuclide treatment, small molecule TKI or hormonal therapy, and any other investigational agent (Cabozantinib/placebo) during the treatment period.
- No prior treatment with cabozantinib
- 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 non-significant and/or stable on supportive therapy
- The subject has organ and marrow function and normal laboratory values before randomization
- Clinically normal cardiac function based on the institutional LLN (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 specific cardiovascular conditions within the past 6 months
- No history of congenital long QT syndrome: For QTc interval > 500 msec within 1 month before the first dose of study treatment: three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the patient meets eligibility in this regard.
- 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 (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., 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.
- 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 ≥ 0.5 teaspoon (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.
- 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).
- Women of child bearing potential (WOCBP) must have a negative serum/urine pregnancy test within 3 days prior to the first dose of study treatment. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., 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

5 Objectives of the trial

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

Secondary objectives include the efficacy of maintenance treatment with cabozantinib when compared with placebo using alternative endpoints namely: progression-free survival (PFS), overall survival (OS), response rate (RR), and duration of response among patients with measurable disease. Another secondary objective is to describe the safety profile of cabozantinib in patients with HGUS, HGESS, HGLMS and HG adenosarcoma (CTCAE 4.0). Exploratory objectives are to evaluate the response rate to doxorubicin-based chemotherapy for patients with measurable disease and to evaluate Health-Related Quality of Life (HRQoL) in each arm.

6 Statistical considerations

6.1 Statistical design

This is a randomized phase II blinded trial aiming to randomize 54 patients equally over two arms to receive cabozantinib monotherapy (experimental arm) or placebo (control arm).

The primary objective of the trial is to detect a difference of 30% in the primary endpoint, PFS rate at 4 months, in favor of the experimental treatment arm. Due to the rarity of uterine sarcomas there are few randomized data to provide reliable outcome estimates. The evidence is mostly based on retrospective (small) series (Ref. 1). A review of survival data for endometrial and uterine sarcomas extracted from previous EORTC studies, revealed a median PFS of 4 months. As high grade ESS may be underrepresented in this dataset, we assume a PFS rate at 4 months for the control arm of 50-60%. A comparative phase II design as proposed by Korn et al (Ref. 32) is preferred over a non-comparative design due to the uncertainty in established reference outcomes inherent to rare cancer populations. The result is a comparative phase III trial design with increased error rates. Using a 1-sided Fisher exact test, stratified by adjuvant versus metastatic disease and response at end of chemotherapy, at a level of significance of 15% (alpha), a total of 54 patients are needed to detect an increase from 50% to 80% with 85% power. With these design characteristics, but assuming PFS rate at 4 months for the control arm of 60%, an improvement of 28% (i.e. from 60% to 88%) could be detected. In order to randomize the required 54 patients, a total of 90 patients are expected to be registered. This sample of 54 randomized patients should yield an expected total of 35 PFS events at the time of final analysis. This would allow to detect a HR=0.49 with a 1-sided test at 15% significance level with 85% power.

A minimization technique is used to randomize the patients between the two treatment arms, stratifying for collaborative group (EORTC vs NCRN), disease (adjuvant versus metastatic), response at end of first line chemotherapy (CR, PR vs SD) and operability (operable vs inoperable). Statistical analysis plan

6.1.1 Statistical methods

The primary analysis will be performed according to the intent to treat principle: all randomized patients will be analyzed in the arm they were allocated by randomization. The superiority of the experimental arm against the control arm will be tested for PFS rate at 4 months using a 1-sided stratified Fisher exact test (Ref. 33) at the 15% significance level. The estimate of the 85% one-sided CI for the proportion of interest will be computed on the basis of the exact binomial distribution. The estimate of the difference between the binary proportions of the two treatment arms and the associated CI will be computed as well.

Compliance tables to follow-up visits and to follow-up CT scans for assessment of progression (as PFS rate is the primary endpoint) will be produced. Compliance will be compared between arms using Fisher exact tests at each time point of assessment. High and similar compliance in both arms is required to avoid potential bias in the primary comparison. If a significant difference is found in the overall population, a preplanned subgroup analysis will be made in the adjuvant and metastatic subgroups respectively (closed testing procedure). The test in each subgroup will be performed on the primary endpoint as a Fisher exact test at 15% significance level. The type I error is not adjusted for multiple testing as this is an exploratory subgroup analysis. The homogeneity of the results in the two subgroups will not be formally tested.

For the secondary endpoints (progression free survival, overall survival and response rate), no formal comparisons between arms will be performed. For time to event endpoints (PFS, OS and RR duration), curves will be estimated using the Kaplan-Meier technique (Ref. 34) by treatment arm. Hazard ratios and medians will be displayed with their 95% confidence interval. Response rates as per RECIST (version 1.1) will be displayed by treatment arm in each subgroup together with their 95% exact confidence interval.

Safety data will be displayed by treatment arm in each subgroup for those patients who received at least one dose of the protocol treatment. The worst toxicity grade over all cycles according to the CTCAE criteria version 4.0 will be displayed by treatment arm.

6.1.2 Pre-planned sensitivity or exploratory analyses

In case of high rate of drop-out, non-compliance with the tumor assessment schedule or non-assessable progression status, a sensitivity analysis for the primary endpoint will be performed. The analysis will consider different methods for those patients with inadequate disease assessment at 4 months. The PFS rate at 4 months will be estimated via Kaplan-Meier or interval censoring methodology.

A preplanned subgroup analysis will be made in each of the histology subgroups (HGUS, HGESS, HGLMS and HG adenosarcoma).

In order to assess the treatment effect of ifosfamide addition to doxorubicin during the screening phase, a preplanned comparative analysis is foreseen. Due to the lack of randomization, the ifosfamide addition is left to the discretion of the treating physician and will be influenced by subject and disease characteristics. As a result, baseline characteristics of treated subjects can differ systematically from those of subjects treated with monotherapy. In order to overcome such systematic differences when estimating the effect of ifosfamide on clinical outcomes, the subjects will be balanced via a propensity score, i.e. the probability of treatment assignment conditional on observed baseline characteristics. Conditional on an adequate propensity score, the distribution of observed baseline covariates will be similar between the two treatment groups: doxorubicin +/- ifosfamide treated patients. The outcomes of interest are response rate at end of the doxorubicin+/- ifosfamide treatment, progression-free survival and overall survival. All registered patients who received at least one cycle of doxorubicin+/- ifosfamide therapy will be included in this analysis. Assessment of the response rate will be limited to those patients with measurable disease.

The available power to assess the response rate, progression-free survival and overall survival is difficult to estimate as the available sample size will depend on the number of patients registered in order to reach the 54 randomizations. Assuming 75 available patients and a response rate of 40%, the 95% CI width for the response rate would be 2x6%. A total of 50 events would yield approx. 80% power to detect a HR=0.5 in either PFS or OS assuming a two-sided significance test at 10% and a 50%-50% split between groups of interest.

6.2 Interim analyses

No formal interim analysis for the activity endpoints is planned for this study. There was a formal evaluation of the adherence to the initial dose of 60 mg of cabozantinib. In the case of an unacceptable high proportion of dose reductions or termination, the initial dose would be set at 40 mg (with the possibility to re-escalate) for the remaining patients. A 30% or less rate of patients needing dose modification during the first two cycles will be considered acceptable; while a rate of 50% or more is considered as unacceptable.

7 Discussion

As of February 25th 2020, 11 out of 11 EORTC sites in 6 countries (BE, FR, DE, IT, NL, ES) and 7 out of 11 UK sites have been activated for patient recruitment. A total of 82 patients have so far been registered, which is 91% of our target (90 patients). Of those, 35 patients were randomized out of a targeted total of 54 patients (64%).
Recruitment is scheduled to end in 2020. Figure 2 shows the accrual registered and randomized patients: observed versus expected

The screening failure rate is higher than anticipated. The assumption during the trial design was that only 40% of registered patient would not be eligible for randomization. In practice, this rate is closer to 55% (35 out of 79). The major reasons for non-randomization were a change in histological diagnosis by central review (15/44=34%) and progression during 1st line (14/44=32%) accounting for two thirds of the screening failures. Other reasons included patient decision, inadequate organ or marrow function or randomization > 12 weeks after 1st line. This highlights the importance of central review in rare cancers as 1 in 3 cases the histological diagnosis was changed. Unfortunately, the poor prognosis of these tumours adds substantial drop-out during the screening process. As planned per protocol, an evaluation of the adherence to the initial dose of 60 mg of cabozantinib was done to verify the feasibility of this starting dose. Based on two consecutive evaluations (June and October 2018), no concerns for pursuing the recruitment at the 60 mg dose were found and the trial continues with this initial dose as planned.

We can also remark on the complexity of conducting clinical randomized trials in the field of rare cancers. This needs to be a priority not only for industry sponsored trials but also for academic groups

The original concept of this trial was much more ambitious, enrolling HGUtS patients in the first line setting with subsequent follow-up for a maintenance study in patients who responded, and a randomization for patients who progressed during chemotherapy into a salvage treatment. This original trial design combined three objectives: improving response to 1st line chemotherapy, maintenance with anti-angiogenics and survival using a new compound at relapse. Such a platform trial would reduce time and costs compared to three separate studies. However, only industry support could only be provided for maintenance therapy; the other settings attracted no support. Randomization between two common regimens (doxorubicin alone versus doxorubicin + ifosfamide) was considered for the 1st line setting to add extra value to the overall trial but no consensus could be reached and this randomization was dropped to simplify the trial and increase potential recruitment. Institutions will use their local standard (limited to doxorubicin ± ifosfamide) and a retrospective propensity-based comparison on the ifosfamide addition is planned.

Conducting clinical trials in rare cancers remains difficult. In addition to severe design restrictions due to the need to keep sample sizes low, successful collaboration among various parties is required and often compromises due to practical limitations or lack of funding are common place. Success is rarely guaranteed as demonstrated by the prematurely closure of the GOG-0277/IRCI 001 trial (A phase III randomised trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high-grade uterine leiomyosarcoma; EudraCT 2012-002852-17; NCT01533207; Ref 63).

8 References

Ref. 1 Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. Lancet Oncol 2009;10:1188–1198

Ref. 2 D'Angelo E and Prat J. Uterine sarcomas: A review. Gynecol. Oncol. 2010;116(1):131-139

Ref. 3 Gadducci A, Cosio S, Romanini A, Genazzani AR. The management of patients with uterine sarcoma: a debated clinical challenge. Crit Rev Oncol Hematol. 2008;65(2):129-142

Ref. 4 de Saint Haubain Somerhausen and Dal Cin. 1 ed. WHO press. 2011:109-125

Ref. 5 Leea C-H, Oua W-B et al. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. PNAS. 2012; 109(3):929–934

Ref. 6 Caudell JJ, Deavers MT, Slomovitz BM, Lu KH, Broaddus RR, Gershenson DM, Ramondetta LM. Appl. Immunohistochem. Mol. Morphol. 13.2 (2005): 167-70 Imatinib mesylate (gleevec)--targeted kinases are expressed in uterine sarcomas. Appl Immunohistochem Mol Morphol. 2005;13(2):167-170

Ref. 7 Moinfar F, Regitnig P, Tabrizi AD, Denk H, Tavassoli FA. Expression of androgen receptors in benign and malignant endometrial stromal neoplasms Virchows Arch. 2004;444(5):410-414

Ref. 8 Coosemans A, Amini Nik S, Caluwaerts S, Lambin S, Verbist G, Van Bree R, et al. Upregulation of Wilms' tumour gene 1 (WT1) in uterine sarcomas Eur. J. Cancer. 2007;43(10):1630-1637

Ref. 9 Amant F, Vloeberghs V, Woestenborghs H, Debiec-Rychter M, Verbist L, Moerman P, Vergote I. ERBB-2 gene overexpression and amplification in uterine sarcomas. Gynecol Oncol. 2004;95(3):583-587

Ref. 10 Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. 2009;54(3):355-364

Ref. 11 Sutton G, Blessing JA, Park R, DiSaia PJ, Rosenshein N. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. Obstet. Gynecol. 1996;87(5 Pt 1):747-750

Ref. 12 Anderson TM, McMahon JJ, Nwogu CE, Pombo MW, Urschel JD, Driscoll DL, et al. Pulmonary resection in Metastatic Uterine and Cervical Malignancies Gynecol Oncol 2001;83(3):472–476

Ref. 13 S. Kanjeekala S, Chambersb A, et al. Systemic therapy for advanced uterine sarcoma: A systematic review of the literature. Gynecol Oncol. 2005;97:624–637

Ref. 14 Investigator's brochure version 10.0 (02 July 2014)

Ref. 15 Heymach JV. Angiogenesis and antiangiogenic approaches to sarcomas. Curr Opin Oncol. 2001;13(4):261–269.

Ref. 16 Yoon SS, Segal NH, Olshen AB, Brennan MF, Singer S. Circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma. Ann Oncol. 2004;15(8): 1261–1266.

Ref. 17 Rutkowski P, Kaminska J, Kowalska M, Ruka W, Steffen J. Cytokine serum levels in soft tissue sarcoma patients: correlations with clinico-pathological features and prognosis. Int J Cancer. 2002 Aug 1;100(4):463-71.

Ref. 18 Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, Collin F, Pandite L, Marreaud S, De Brauwer A, van Glabbeke M, Verweij J, Blay JY. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19):3126-3132

Ref. 19 van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P; EORTC

Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-1886

Ref. 20 Weiner TM, Liu ET, Craven RJ, Cance WG. Expression of growth factor receptors, the focal adhesion kinase, and other tyrosine kinases in human soft tissue tumors. Ann Surg Oncol. 1994;1(1):18–27.

Ref. 21 Franklin WA, Christison WH, Colley M, Montag AG, Stephens JK, Hart CE. In situ distribution of the beta-subunit of platelet-derived growth factor receptor in non-neoplastic tissue and in soft tissue tumors. Cancer Res. 1990;50(19):6344–6348

Ref. 22 Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol. 2005;23(5):965–972

Ref. 23 Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009; 27(19):3133–3140

Ref. 24 von Mehren M, Rankin C, Goldblum JR, et al. Phase 2 Southwest Oncology Group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. Cancer. 2012;118(3):770–776)

Ref. 25 Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II trial from the French Sarcoma Group (GSF/GETO). Oncologist. 2012;17(2):260–266

Ref. 26 George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer. 2009;45(11):1959–1968.

Ref. 27 Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). Ann Oncol. Epub June 17, 2012.

Ref. 28 Hensley ML, Sill MW, Scribner DR Jr, et al. Sunitinib malate in the treatment of recurrent or persistent uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol. 2009;115(3): 460–465.

Ref. 29 Gordon MS, Vogelzang NJ, Schoffski P, et al. Activity of Cabozantinib (XL184) in soft tissue and bone: Results of a phase II randomized discontinuation trial (RDT) in patients (pts) with advanced solid tumors.J Clin Oncol 29: 2011 (suppl; abstr 3010)

Ref. 30 Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, Dunning MJ, Gale D, Forshew T, Mahler-Araujo B, Rajan S, Humphray S, Becq J, Halsall D, Wallis M, Bentley D, Caldas C, Rosenfeld N. Analysis of circulating tumor DNA to monitor metastatic breast cancer. NEJM 2013 Mar 28;368(13):1199-209.

Ref. 31 Eisenhauer E, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version1.1). Eur J Cancer. 2009;45(2):228-247

Ref. 32 E. L. Korn, S. G. Arbuck, J. M. Pluda, R. Simon, R. S. Kaplan, M. C. Christian: Clinical Trial Designs for Cytostatic Agents: Are New Approaches Needed? Journal of Clinical Oncology, J Clin Oncol 19(1), 2001, 265-271

Ref. 33 Fisher, R. A. (1954) Statistical Methods for research workers. Oliver and Boyd. Edinburgh.

Ref. 34 Kaplan, E.L. & Meier, P.: Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 53, 1958, 457–481.

Ref. 35 Aaronson NK, Ahmedzai S, Bergman B, et al., for the European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI 85: 365-376, 1993)

Ref. 36 Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, Galalae R, Schmalz C, Barlow E, Jensen PT, Waldenström AC, Bergmark K, Chie WC, Kuljanic K, Costantini A, Singer S, Koensgen D, Menon U, Daghofer F. EORTC Quality of Life Group. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24) Eur J Cancer. 2011 Jan;47(2):183-90.)

Ref. 37 Fairclough D. Patient reported outcomes as endpoints in medical research.Statistical Methods in Medical Research 2004; 13: 115-138). Average, highest and lowest change from baseline will be considered

Ref. 38 Benson et al. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. JCO Jul 15, 2004:2918-2926

Ref. 39 Wright JR, Ung Y, Julian J, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007;25:1027-32.

Ref. 40 Koivisto-Korander R, Martinsen JI, Weiderpass E, et al. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. Maturitas. 2012;72:56-60

Ref. 41 Acta Oncol. 2012 Jul;51(6):694-705. doi: 10.3109/0284186X.2012.689111. Diagnosis and treatment of sarcoma of the uterus. A review. Tropé CG1, Abeler VM, Kristensen GB.

Ref. 42 Lancet Oncol. 2009 Dec;10(12):1188-98. doi: 10.1016/S1470-2045(09)70226-8. Clinical management of uterine sarcomas. Amant F1, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I.

Ref. 43 J Natl Compr Canc Netw. 2009 May;7(5):550-6; quiz 557. Carcinosarcomas (malignant mixed Müllerian tumor) of the uterus: advances in elucidation of biologic and clinical characteristics. Kernochan LE1, Garcia RL.

Ref. 44 Malouf GG, Lhomme´ C, Duvillard P, et al. Prognostic factors and outcome of undifferentiated endometrial sarcoma treated by multimodal therapy. Int J Gynaecol Obstet. 2013;122:57-61.

Ref. 45 Amant F, Floquet A, Friedlander M, Kristensen G, Mahner S et al. Gynecologic Cancer InterGroup (GCIG) Consensus Review for Endometrial Stromal Sarcoma Inter J Gyne.Volume 2014; 24: S67-S72.

Ref. 46 Omura GA, Major FJ, Blessing JA, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomes. Cancer. 1983;22:626-632.

Ref. 47 Piver MS, Rutledge FN, Copeland L, et al. Uterine endolymphatic stromal myosis: a collaborative study. Obstet Gynecol. 1984;64:173-178.

Ref. 48 Cheng X, Yang G, Schmeler KM, et al. Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy. Gynecol Oncol. 2001;121:121-327.

Ref. 49 Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008;112:820.

Ref. 50 Zivanovic O, Leitao MM, Iasonos A, et al. Stage specific outcomes of patients with uterine leiomyosarcoma: a comparison of the FIGO and AJCC staging systems. J Clin Oncol. 2009;27:2066-2072.

Ref. 51 Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). Cancer. 1985;55:1648.;

Ref. 52 Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 1996;62:226.;

Ref. 53 Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. Gynecol Oncol. 2004;92:644.;

Ref. 54 Hensley ML, Blessing JA, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol.2008;109:3029

Ref. 55 Sutton GP, Blessing JA, Barrett RJ, et al. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: A Gynecologic Oncology Group study. Am J Obstet Gynecol. 1992;166:556.

Ref. 56 Friedlander ML, Covens A, Glasspool RM, et al. Gynecologic Cancer InterGroup (GCIG) Consensus Review for Mullerian Adenosarcoma of the Female Genital Tract Int J Gynecol Cancer 2014;24: S78-S82

Ref. 57 Schroeder BA, Rodler ET, Loggers ET, et al. Clinical benefit of trabectedin in uterine adenosarcoma. Med Oncol. 2013;30:501;

Ref. 58 Maeda M, Mabuchi S, Matsumoto Y, et al. Activity of pegylated liposomal doxorubicin for extragenital mullerian adenosarcoma with sarcomatous overgrowth: a case report and a review of the literature. Eur J Gynaecol Oncol. 2011;32:542-546)

Ref. 59 Tanner EJ, Toussaint T, Leitao MM, et al. Management of uterine adenosarcomas with and without sarcomatous overgrowth. Gynecol Oncol. 2013;129:140-144

Ref. 60 Mir O, Brodowicz T, Italiano A, Wallet J, Blay JY, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016;17(12):1732-42;

Ref. 61 Brodowicz T, Liegl-Atzwager B, Tresch E, Taieb S, Kramar A, Gruenwald V, et al. Study protocol of REGOSARC trial: activity and safety of regorafenib in advanced soft tissue sarcoma: a multinational, randomized, placebo-controlled, phase II trial. BMC Cancer. 2015 Mar 14;15:127

Ref. 62 Schwartz LH, Litiere S, de VE, Ford R, Gwyther S, Mandrekar S et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016 July;62:132-7.

Ref. 63 Hensley ML, Enserro D, Hatcher H, Ottevanger PB, Krarup-Hansen A, Blay JY et al. Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study. J Clin Oncol 2018 October 5; JCO1800454.

FIGURES

Figure 1 study Design

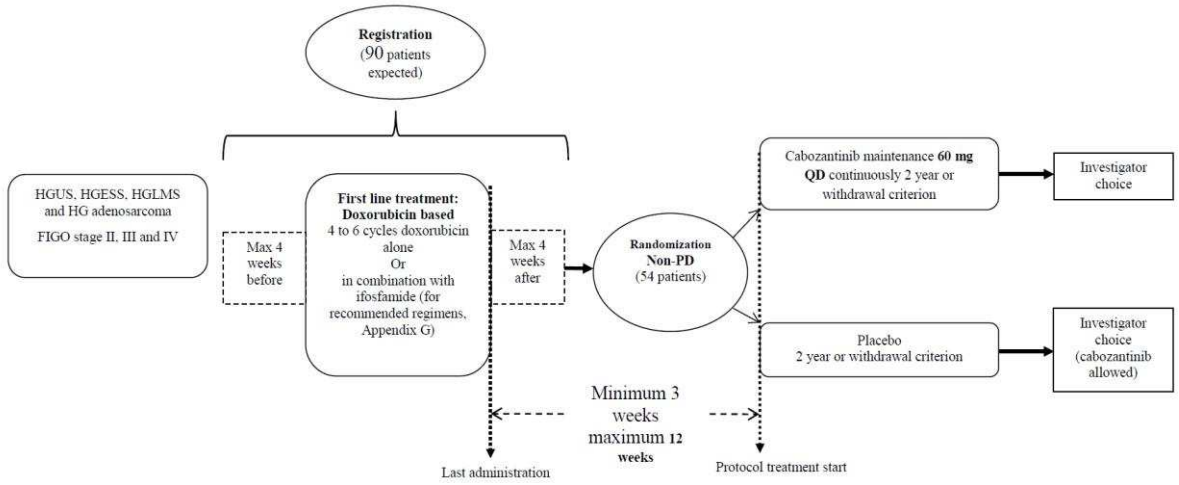
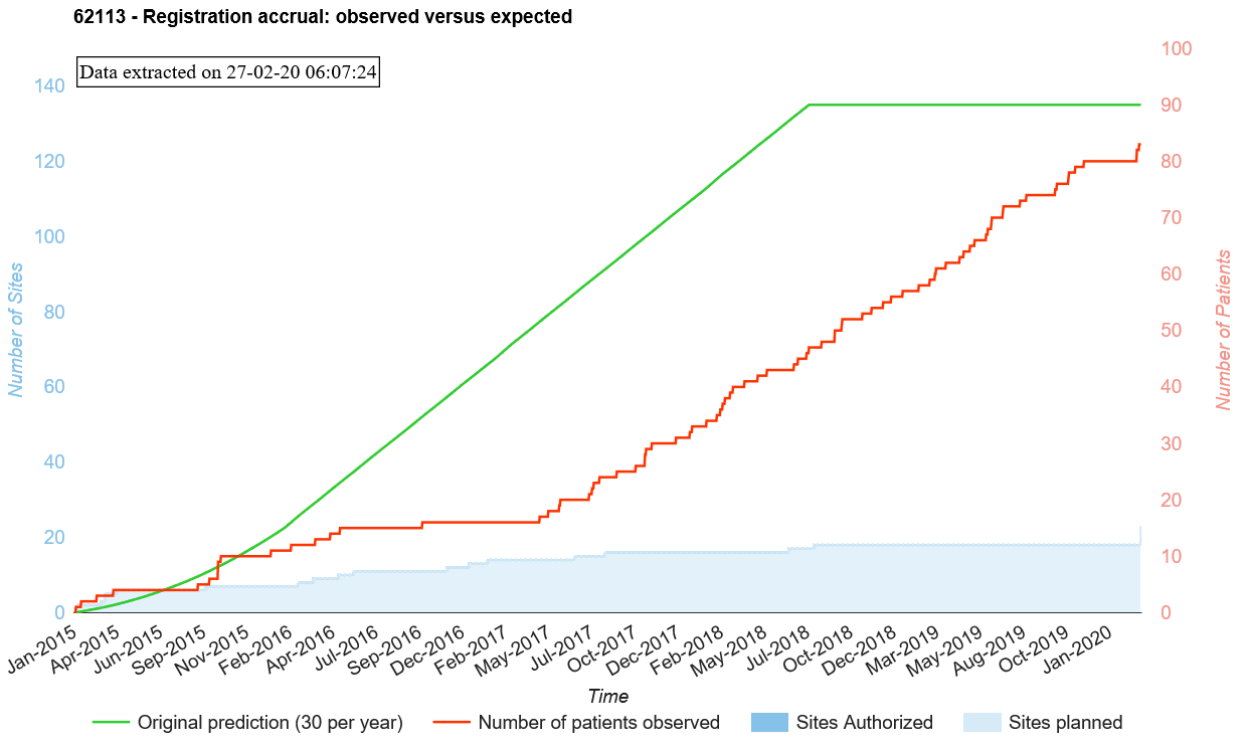
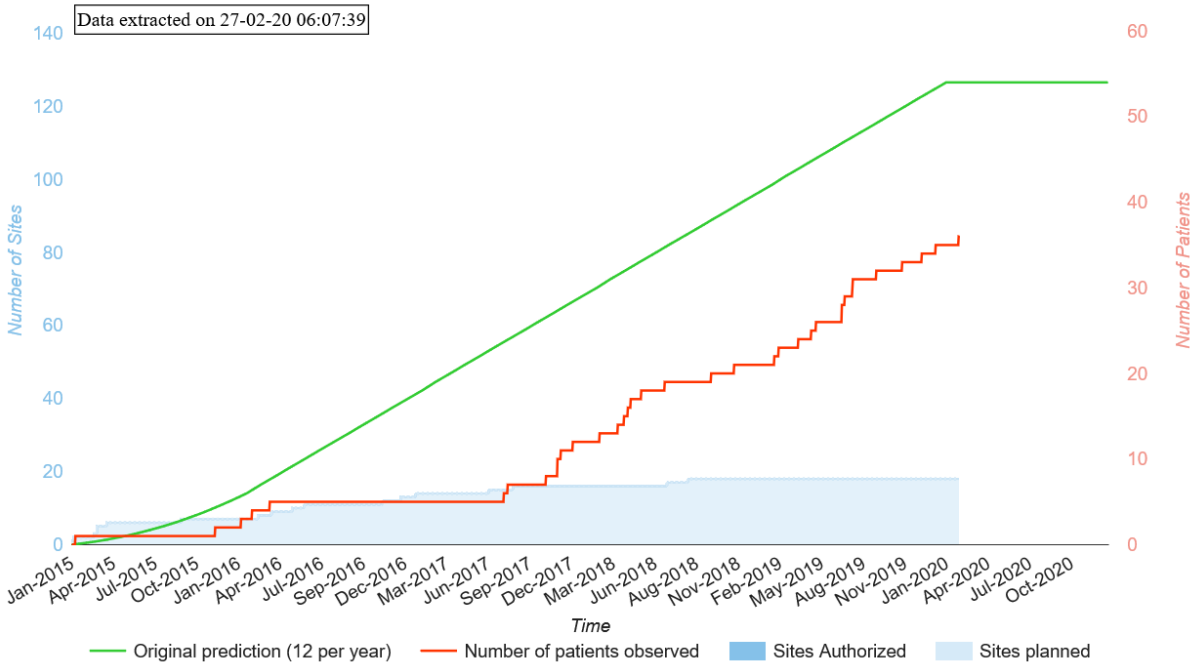


Figure 2. Recruitment and randomizations rate



62113 - Randomization accrual: observed versus expected



APPENDICES.

Appendix A: Regimens and doses for doxorubicin +/- ifosfamide

Single agent:

- *Doxorubicin*
- Doxorubicin (Adriamycin) 75 mg/m^2 iv bolus q3w

Santoro, A et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: A randomized study of the European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995; 13:1537

N.B.: Doxorubicin 50-60 mg/m^2 iv bolus q3w OR Doxorubicin 20-25 mg/m^2 iv bolus weekly x 3 for each cycle up to 6 cycles can be used alternatively, according to the discretion of the responsible clinician (Principal Investigator [PI]) at the site, depending on the individual patient.

Combination chemotherapy:

- *Regimen 1*
  Doxorubicin (Adriamycin) 50 mg/m^2 iv bolus d1 and Ifosfamide 5 g/m^2 iv , d1 with Mesna before, during and after in appropriate doses, q3 weeks. Growth factor support to be used at the discretion of the PI.

Le Cesne, A et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol 2000; 18:2676

- *Regimen 2*
  Doxorubicin (Adriamycin) 20 mg/m^2 x 3, d1-3 (total dose 60 mg/m^2), or by continuous IV infusion as per the original protocol and Ifosfamide 1.5 g/m^2/d iv x 4, d1-4 (total dose 6 g/m^2), with Mesna before, during and after in appropriate doses, q3 weeks. Growth factor support is advised, the type is at the discretion of the PI and institution.

Worden, FP et al. Randomized phase II evaluation of 6 g/m^2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m^2 of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. J Clin Oncol 2005; 23:105.

N.B.: Other G-CSF are also permitted according to local practice

Appendix B: FIGO staging for uterine sarcomas (2009)

Stage	Definition
Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm

Stage	Definition
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
Adenosarcomas	
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

[a] Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors