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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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Abstract

Background: Uterine sarcomas are a group of rare tumors that includes different subtypes. Patients with histopathological high-grade diseases are at high-risk of recurrence or progression, and have poor prognosis. We aim to explore the most appropriate management in patients with uterine high-grade sarcomas.

Primary Objective: To assess the efficacy of maintenance treatment with cabozantinib in patients with high-grade uterine sarcomas who achieved clinical benefit after standard chemotherapy.

Study Hypothesis: Maintenance treatment with cabozantinib after standard chemotherapy given as an adjuvant treatment after curative surgery, or in locally advanced or metastatic disease, increases progression-free survival compared to placebo

Trial Design: This randomized double blinded phase II trial.

Major Exclusion/Inclusion Criteria: Adult patients with high-grade undifferentiated uterine sarcomas, high-grade endometrial stromal sarcomas, high-grade leiomyosarcoma, and high-grade adenosarcoma, FIGO (Federation International gynecologue Obstétricien) stage II/III to IV in stable disease or who achieved complete or partial response with doxorubicin +/- ifosfamide, and assigned them 1:1 to 60 mg daily cabozantinib (experimental arm) or placebo (control arm), as maintenance therapy. Exclusion criteria included low-grade sarcoma.

Primary endpoint: Progression-free survival at 4 months (4m-PFS).

Sample Size: The study planned to enroll 90 patients to allow the randomization of 54 patients to detect an improvement in 4m-PFS from 50% to 80% with 15% significance level and 85% power.

Estimated Dates for Accrual Completion: Recruitment started in February 2015, the trial has currently enrolled 83 patients, among whom 35 patients have been randomized. The end of recruitment is anticipated for December 2020.

Trial Registration: ClinicalTrials.gov, number NCT01979393.

1 Introduction

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 (1). Uterine sarcomas belong to a heterogeneous group of tumors including leiomyosarcomas as the most common subtype (63%), endometrial stromal sarcoma (21%), and less common subtypes gathered as undifferentiated uterine sarcoma (2). The 5-year survival estimates for stage I is 76%, for stage II, 60%, for stage III, 45%, and for stage IV disease, 29% (3). Histopathology characteristics define patients with high-grade diseases at high risk of recurrence, progression, and poor prognosis. High Grade Undifferentiated Uterine Sarcoma (HGUtS) and High Grade Endometrial Stromal Sarcoma (HGESS) have a very poor prognosis; most patients die from recurrent disease within two years of diagnosis. Endometrial stromal sarcomas with *YWHAE-FAM22* fusions represent a clinically aggressive subtype of endometrial stromal sarcoma classified as high-grade endometrial stromal sarcoma, and are distinct from the usual low-grade endometrial stromal sarcoma with *JAZF1* rearrangement and from high-grade undifferentiated uterine sarcomas with no identifiable molecular aberration. Undifferentiated sarcomas have been shown to express Platelet Derived Growth Factor Receptor-a (PDGFR-a) (4), androgen receptor (AR) (5), and Wilm's Tumor1 (WT1) (6). The management of patients with high-grade metastatic adenosarcomas is similar to the management of patients with metastatic high-grade sarcomas (7).

For localized disease, standard guidelines include adjuvant chemotherapy with anthracyclines +/- ifosfamide in patients with good performance status and poorly differentiated stage I and II sarcoma, or in patients with advanced disease (stage III/IV) (8). Typically, management of metastatic uterine sarcoma conforms to treatment practice for other metastatic soft tissue sarcomas. Systemic treatment for HGUtS paralleled that for adult-type soft tissue sarcomas, using doxorubicin +/- ifosfamide as single agents or in combination (9). No consensus for first line chemotherapy regimen has been established yet. First-line therapy currently includes doxorubicin, doxorubicin plus ifosfamide, gemcitabine, gemcitabine plus docetaxel, with objective response ranging from 17 to 36% (10-13).

Faced with the lack of effective treatments and the poor prognosis in patients with high-grade undifferentiated uterine sarcomas, new agents need to be investigated. Indeed, chemotherapy is currently mainly use as palliative treatment and the best multimodality treatment did not allow sustainable results. The benefits of continuous scheme of chemotherapy administration have never been demonstrated superior to therapy disruption after first response observed, and related risks from cumulative drug-associated toxicities, such as cardiac toxicity associated with doxorubicin may be avoided.

A therapy allowing to stabilize disease or to delay progression after prior cytotoxic chemotherapy might help the management of sarcoma patients with advanced/metastatic disease. Angiogenesis plays an important role in the growth and dissemination of high-grade undifferentiated uterine sarcomas and other soft tissue sarcomas. High VEGF (Vascular endothelial growth factor) expression has been identified as an independent prognostic factor, increasing risk of metastases and decreasing overall survival (14-16). Pazopanib has been approved by the FDA (Food and Drug Administration) for patients with advanced soft tissue sarcomas who have received prior chemotherapy (17). A randomized phase II investigated regorafenib, a multikinase inhibitor of VEGFR1, VEGFR2, VEGFR3, (vascular endothelial growth factor receptor) and tumor cell signaling kinases (RET, KIT, PDGFR, and Raf) in patients with metastatic soft tissue sarcomas previously treated with anthracycline. 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 soft tissue sarcomas groups, 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) (18,19).

Cabozantinib (XL184) inhibits the receptor tyrosine kinases VEGFR2, MET, AXL, and RET. Preclinical *in vivo* studies showed pharmacodynamic inhibition of VEGFR2, MET, AXL and RET with cabozantinib, associated with tumor growth inhibition and even tumor shrinkage. Cabozantinib capsules (140 mg) were approved by the FDA and EMEA (European Medecine Agency) for the treatment of patients with progressive, metastatic medullary thyroid cancer and also approved by the FDA in patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. Based on the activity of cabozantinib observed in several malignancies and the activity of pazopanib and regorafenib as VEGF-targeting agents in soft tissue sarcomas, maintenance treatment after chemotherapy in patients with high-grade uterine sarcomas warrant further exploration.

2. Methods

a) Trial Design

This randomized double blinded phase II trial aims to evaluate cabozantinib as maintenance therapy in women with high-grade uterine sarcomas after stabilized disease or response achieved with chemotherapy following surgery or in advanced first line treatment. This trial planned that 54 patients will be randomized (1:1) to receive either cabozantinib as monotherapy (experimental arm) or placebo (control arm). The efficacy of maintenance treatment will be assessed by formal comparison between these two arms of the primary endpoint: by progression-free survival at 4 months (4m-PFS). At progression, cross-over to cabozantinib is permitted. Key secondary endpoints include overall survival and toxicity. Study design is reported figure 1.

Patient are registered in a period ranging from 4 weeks before the initiation and no later than 12 weeks after the first dose administration of 1st line treatment. This screening step allows timely central histological review. Randomization is performed after pathological confirmation by a central review board and should occur no later than 12 weeks after last administration of 1st line treatment.

Eligible patients are randomized to receive either cabozantinib monotherapy or placebo. Cabozatinib should 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 given for 2 years or prematurely discontinued for disease progression, diagnosis of a second malignancy, patient refusal, 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 another cancer treatment, unless ethically impossible. After documented disease progression according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) (20), unblinding of treatment allocation is allowed. Subjects receiving cabozantinib shall be treated at investigator discretion. Subjects receiving placebo shall be offered the option of receiving cabozantinib. This cross-over is not mandatory and left at the investigator decision.

The study was approved by the appropriate Institutional Review Board (IRB), and patients provided written informed consent for trial-specific procedures. The trial is registered with ClinicalTrials.gov, number NCT01979393.This study is funded from donations from the family de Spoelbergh and by La Ligue Nationale contre le Cancer from France. In addition, Exelixis, Inc. is providing Cabozantinib for this study. Study sites are members of the International Rare Cancer Initiative (IRCI). 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 aims to facilitate the development of clinical trials in patients with rare cancers. EORTC initiated this trial through a collaboration between the EORTC Soft Tissue Bone Sarcoma Group (STBSG) and the EORTC Gynecological Cancer Group (GCG). The protocol was developed through the IRCI network with input from all parties, but only the NCRN group was involved in the recruitment.

b) Participants

Adult patients with high-grade undifferentiated uterine sarcomas, high-grade endometrial stromal sarcomas, high-grade leiomyosarcoma, and high-grade adenosarcoma, FIGO stage II and III (adjuvant chemotherapy proposed), or FIGO stage IV (first line chemotherapy proposed) are eligible

for treatment with doxorubicin +/- ifosfamide. Patients should have WHO/ECOG performance status 0-2 and should be able to swallow and retain oral tablets.

Exclusion criteria included low-grade endometrial stromal sarcoma, leiomyosarcoma (low or intermediate grade), carcinosarcoma, low-grade adenosarcoma, rhabdomyosarcoma (alveolar or embryonal), and soft tissue PNET (Primitive Neuro- Ectodermal Tumor) of uterus/cervix. Randomised patients should have histological evidence of high-grade undifferentiated uterine sarcomas, high-grade endometrial stromal sarcomas, high-grade leiomyosarcoma, and high-grade adenosarcoma centrally confirmed. They should be non-progressive (CR (complete response), PR (partial response), SD (stable disease)) after first-line treatment (4 to 6 cycles of doxorubicin alone or in combination with ifosfamide) and at time of randomization.

c) Outcomes

The primary objective is to assess the efficacy of maintenance treatment with cabozantinib in patients who achieved clinical benefit (CR, PR, or SD) after standard chemotherapy as measured by 4m-PFS. Secondary efficacy endpoints evaluate PFS, OS, response rate , and duration of response. We report safety profile of cabozantinib in patients with high-grade uterine sarcoma (Common Terminology Criteria for Adverse Events (CTCAE) v4.0). 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.

d) Sample size

Using a 1-sided Fisher exact test, stratified on adjuvant versus metastatic disease, and response at end of chemotherapy, 54 patients are needed to detect an increase from 50% to 80%, with 85% power and a 15% significance level. Using such design characteristics, but assuming progression-free survival 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 should be registered. A total of 35 progression-free survival events at the time of final analysis is expected. This would allow to show a HR=0.49 with a 1-sided test at 15% significance level with 85% power.

e) Randomization and blinding

A minimization technique is used to randomize the patients between the two treatment arms, stratified on collaborative group (EORTC *versus* NCRN), disease (adjuvant *versus* metastatic),

response after first line chemotherapy (CR, PR *versus* SD) and operability (operable *versus* inoperable). The method used for treatment allocation is a modified version of the dynamic allocation method (21-23) and assigns a treatment arm to each patient at the moment it is entered into the clinical trial by choosing among the available treatment arms in such a way that the stratification factors are balanced over all the treatment arms within preset constraints.

i- This triple-blind randomized placebo-controlled phase II trial aims to randomize (1:1) 54 patients to receive either cabozantinib monotherapy (experimental arm) or placebo (control arm). Due to the rarity of uterine sarcomas, the few data mainly based on small retrospective series (24) were used for hypotheses assumptions. We used survival data in endometrial and uterine sarcomas from previous EORTC studies to define 4 month-PFS (4m-PFS). We therefore determine a 4m-PFS rate of 50-60% for the control arm. A comparative phase II design as proposed by Korn et al (25) is preferred over a non-comparative design, in established reference outcomes due to the uncertainty inherent to these rare cancer populations. The result is a comparative phase III trial design with increased error rates. (See sample size)

ii. The treatment arm allocation procedure is triple-blinded: the patient, the local treatment staff, and the trial management are not aware of the treatment. Unblinding of treatment allocation may occur after progression. In case of a safety concern affecting a patient, the investigator site can request to unblind the patient.

f) 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 4m-PFS using a 1-sided stratified Fisher exact test (26) at the 15% significance level. The estimate of the 85% one-sided confidence interval (CI) for the proportion of interest will be derived from the exact binomial distribution. 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.

For the secondary endpoints, no formal comparisons between arms will be performed. For time-to-event endpoints (PFS, OS and response duration), curves will be estimated using the Kaplan-Meier technique (27) 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 v4.0 will be displayed by treatment arm.

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 approximately 80% power to detect a HR=0.5 in either progression-free survival or overall survival assuming a two-sided significance test at 10% and a 50%-50% split between groups of interest.

3. Discussion

As of February 25th 2020, 11 out of 11 EORTC sites in 6 countries and 7 out of 11 UK sites have been activated for patient recruitment. A total of 82 patients have been registered, representing 91% of our target (90 patients), including 35 randomized patients, out of 54 (64%) patients expected. Recruitment is scheduled to end in 2020. Figure 2 shows the accrual of registered and randomized patients. The screening failure rate is higher than anticipated. 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 and progression during 1st line, accounting together for two thirds of the screening failures. This highlights the importance of central review in rare cancers as the histological diagnosis was changed in 1 in 3 cases.

We can also note 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. Success can nevertheless not be guaranteed as recently demonstrated by the premature discontinuation of the randomized phase III trial GOG (Gynecologic Oncologic Group)-0277/IRCI 001 investigating gemcitabine plus docetaxel followed by doxorubicin versus observation in patients with uterus-limited, high-grade uterine leiomyosarcomas (EudraCT 2012-002852-17; NCT01533207)(28).

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5. FIGURES

Figure 1. Study design

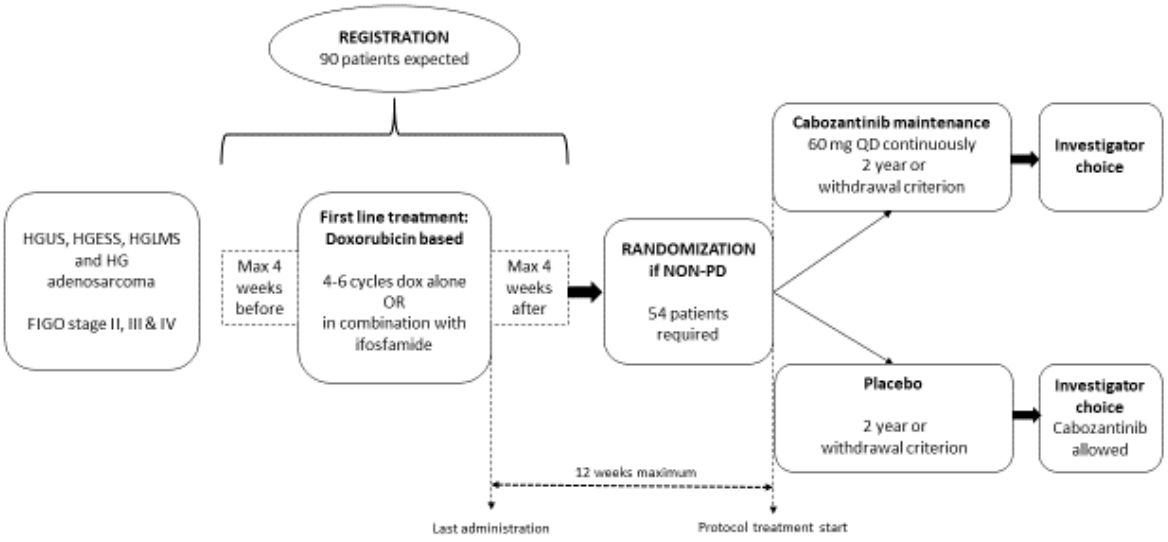
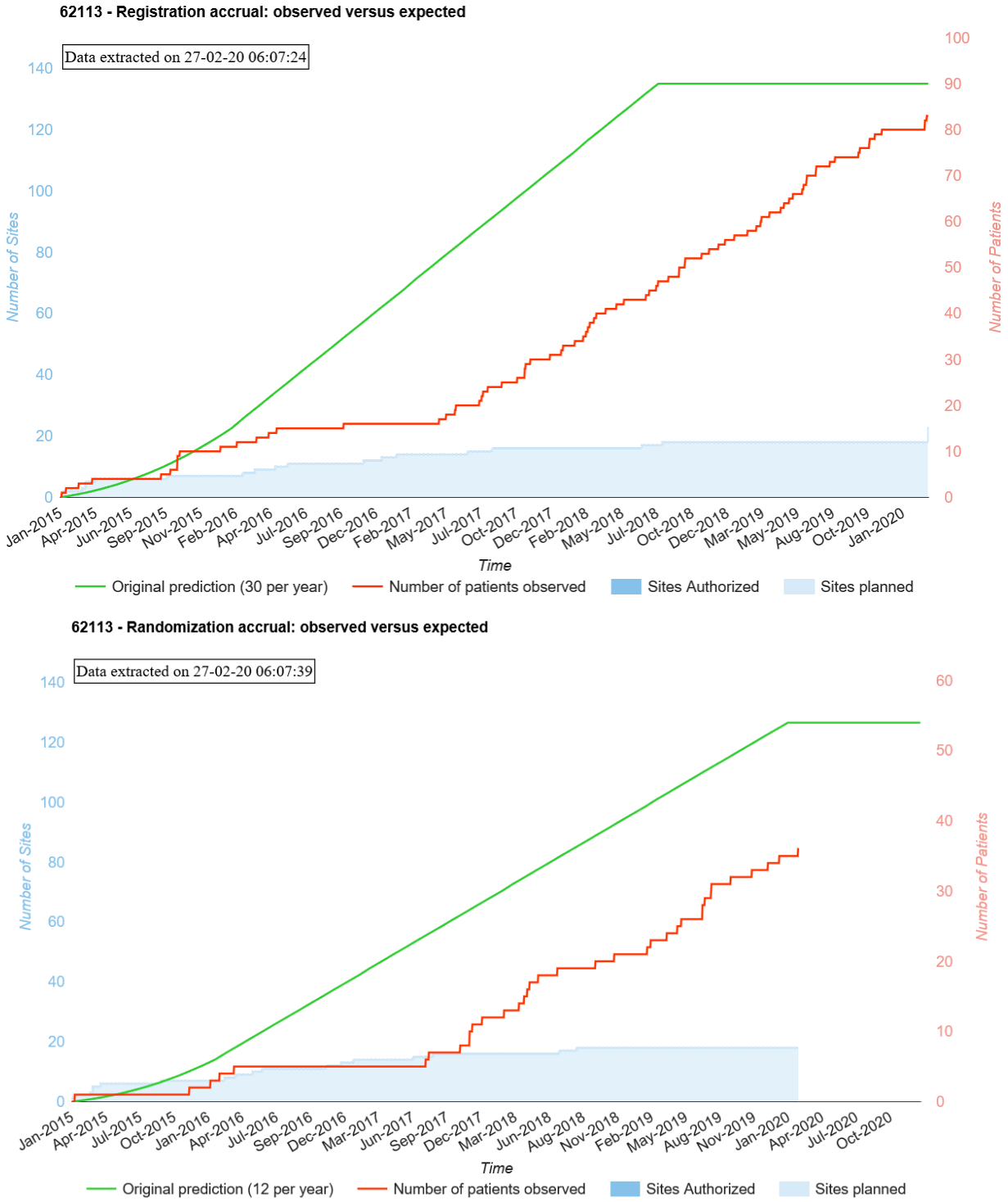


Figure 2. Recruitment rate



5. 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
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.