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EORTC Soft Tissue and Bone Sarcoma Group

Phase II trial of cabazitaxel in metastatic or inoperable locally advanced dedifferentiated liposarcoma

EORTC protocol 1202-STBSG

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Study Coordinator: Larry Hayward

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Protocol 1202

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Table of contents:

Table of appendices:

Protocol summary

Title of the Study	Phase II trial of cabazitaxel in metastatic or inoperable locally advanced dedifferentiated liposarcoma.
Objective(s)	The main objective is to determine whether cabazitaxel demonstrates sufficient antitumor activity (as measured by progression free survival at 12 weeks) in patients with metastatic or inoperable locally advanced dedifferentiated (DD) liposarcoma to justify further investigation of the efficacy of this treatment option in a phase III setting.
Methodology	This trial will be an international, multi-center, open label phase II trial where patients with metastatic or inoperable locally advanced DD liposarcoma will be treated with cabazitaxel
Number of patients Number planned (Statistical design) Number analyzed	The Simon two-stage design will be applied, 17 or 37 eligible and treated patients will be required, according to the number of responses observed in the first 17 evaluable patients. As patients will only be evaluable for the primary end-point 12 weeks after start of treatment, the accrual will be temporarily stopped after the inclusion of 19 patients, to allow for 10% of untreated or ineligible patients. Furthermore, to account for potential loss to follow-up and screening failure at central review, up to 50 patients will be enrolled if proceeding to stage 2.
Diagnosis and main criteria for inclusion	Patient enrollment will follow a two steps procedure as illustrated in chapter 4 and 12 (registration step 1: registration and central pathological review and registration step 2: eligibility confirmation). Patients must meet all of the criteria described in sections 3.1 and 3.2 in order to be eligible for treatment with cabazitaxel. 3.1 Registration step 1 ♦ Local diagnosis of DD liposarcoma ♦ Mandatory availability for shipment of formalin-fixed, paraffin-embedded, tumor-containing tissue blocks from primary tumor and/or metastatic site. Information on previous histopathology reports and previous molecular analysis will be entered in an electronic CRF, to accompany the tissue samples. ♦ If block cannot be provided , the following should be submitted: ♦ For cases that will be reviewed in UK (refer to chapter 15.3): 4 x 1 micron sections on coated slides, one thin H&E stained section and 20 unstained sections of usual thickness (2-4 micron) on coated slides. ♦ For cases that will be reviewed in France (refer to chapter 15.3): 3 x 4 micron sections on unstained (coated) slides for FISH and 15 unstained slides (4 micron) for immunohistochemistry. ♦ Before patient registration step 1, written informed consent for central collection of tissue block 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. 3.2 Registration step 2 ♦ Central pathology confirmation of DD liposarcoma within 3 weeks after registration step 1. ♦ Radiological or histological diagnosis of inoperable locally advanced or metastatic disease, with evidence of disease progression within the past 6 months prior to registration step 2. ♦ Clinically and/or radiographically documented measurable disease within 28 days prior to registration step 2. At least one site of disease must be unidimensionally measurable according to RECIST 1.1. ♦ Note: as DD liposarcoma commonly arises on a background of well differentiated liposarcoma, and as the latter well differentiated element can remain stable for prolonged periods without therapy, we recommend that when defining radiological measurable or target lesions per RECIST 1.1, especially in the region of the primary tumor mass if present, these should be chosen to include specifically the solid or higher density elements of the disease (which tend to correlate pathologically with the DD element), and not the low density fatty elements of the disease, which tend to correlate with the well differentiated element. ♦ One previous chemotherapy regimen for locally advanced or metastatic DD liposarcoma (this could include pre-operative chemotherapy for primary disease) ♦ Not more than 1 prior molecularly targeted therapy (e.g. CDK4 inhibitor). Any prior such therapy must be completed at least 2-4 weeks before registration step 2. ♦ Age 18-75 years old. ♦ WHO performance status 0-1. ♦ Adequate haematological, renal and hepatic function: ♦ Haematology: haemoglobin > 90 g/L or 5.6 mmol/L, absolute granulocytes > 1.5 x 10^9/L, platelets > 100 x 10^9/L. ♦ Renal: creatinine clearance (CrCl) * > 30 ml/min. ♦ Note: It is recommended that creatinine clearance is calculated using the estimated glomerular filtration rate (eGFR) methodology per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (21). If not supplied by the local laboratory, it can be calculated online using the link http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr. Direct measurement (e.g. EDTA) or other established methods of estimating creatinine clearance per local institution policies are acceptable. ♦ Hepatic: Bilirubin ≤ 1.0 times upper limit of normal (1.0xULN) of institutional limits, ALT and/or AST ≤ 1.5 x ULN. ♦ If isolated elevated bilirubin <2 x ULN and Gilberts syndrome

	suspected, suggest repeating bloods after food. If bilirubin improves to meet the criteria above this is acceptable. More severe persistent hepatic impairment of whatever cause would exclude the patient from treatment till resolved. ♦ Estimated life expectancy >3 months. ♦ No inflammation of the urinary bladder (cystitis). ♦ No symptomatic CNS metastases. If asymptomatic CNS metastases are present these should have been previously treated and stable for at least 3 months and patient should not require maintenance steroids. ♦ No other invasive malignancy within 5 years, with the exception of non-melanoma skin cancer, localized cervical cancer, localized and presumably cured prostate cancer or adequately treated basal or squamous cell skin carcinoma. ♦ No significant cardiac disease: i.e. active ischemic heart disease or cardiac failure (NYHA (Appendix D) > class 1). ♦ No uncontrolled severe illness or medical condition (including acute infection, uncontrolled diabetes), other than DD liposarcoma. ♦ All related adverse events from previous therapies must have recovered to ≤ Grade 1 (except alopecia). ♦ No concurrent or planned treatment with strong inhibitors or inducers of cytochrome P450 3A4/5 (listed in Appendix E). A one week wash-out period is necessary for patients who are already on these treatments. ♦ No known hypersensitivity to taxanes or their excipients (cabazitaxel, like docetaxel, is solubilized in polysorbate 80 and ethanol). ♦ Women of child bearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment. ♦ Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly. ♦ It is recommended that patients do not attempt to become pregnant or to breast feed after exposure to these chemotherapy agents, as there is no available data on safety. If despite this advice patients wish to do so, then it is recommended a minimum of 6 months should first be allowed to elapse from the last received dose. ♦ Men should use reliable contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of cabazitaxel. ♦ 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.

	Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.
Treatment Test product, dose and mode of administration	♦ Treatment: Cabazitaxel 25mg/m² IV infusion over 1 hour every 21 days.
Duration of treatment	Treatment should be continued until disease progression, unacceptable toxicity, >1 cabazitaxel dose level reduction, withdrawal of consent, physician's recommendation or occurrence of a second malignancy.
Criteria for evaluation	Progression free survival at 12 weeks (RECIST 1.1) For this purpose, the tumor size must be evaluated 12 weeks after start of treatment in all patients (even if protocol therapy has been discontinued, unless progression has previously been documented).
Efficacy	Time to progression Progression free survival Overall survival Objective tumor response (RECIST 1.1) Time to onset of response Duration of response
Safety	The safety will be assessed according to the CTCAE V. 4.0
Statistical methods	The Simon optimal two-stage design will be used, with the following hypotheses (based on the EORTC STBSG retrospective analysis): ♦ P0 will be taken as 20% (the threshold to reject an inactive drug based on current knowledge) - success in 20% of the cases will be considered as unacceptable, and would not warrant further investigation. ♦ P1 will be taken as 40% (based on the expected success rate of an active drug) - success in 40% of the cases will be considered as an acceptable result warranting further investigation of the drug in this histology. ♦ Type I error and type II error are fixed at 10% (Error: alpha = beta = 0.10). Under these hypotheses, a total of 37 eligible and treated patients will be treated and followed for the assessment of the primary end-point. Two steps are planned. In step 1, 17 eligible and treated patients will be included. If 3 or less successes are observed among these 17 patients, the trial will be stopped, with the conclusion that the drug should not be further investigated. Otherwise patients will continue to be accrued until 37 eligible patients have been enrolled and started therapy. If 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation of the drug.

Biobanking	For patients who consented, tumor material will be centrally stored for future research projects.

1 Background and introduction

1.1 Background Disease Information

Soft tissue sarcomas (STS) are a rare group of malignant tumors arising from mesenchymal cells and represent approximately one percent of all cancers (Ref. 1, Ref. 6). They comprise a heterogeneous group of more than 50 histological subtypes with distinct genetic, pathological and clinical profiles, and varying patterns of tumor spread. Differential chemosensitivity is seen, even between tumors within the same histological subtype group (Ref. 2, Ref. 3, Ref. 4, Ref. 5).

Few patients with metastatic disease achieve long term survival and, in the case of dedifferentiated (DD) liposarcoma, a recent series has reported a median survival of only 13.9 months (Ref. 18). Survival and response rates to chemotherapy vary amongst STS subtypes (Ref. 3, Ref. 4, Ref. 6, Ref. 7) but, until recently, treatment approaches have generally treated STS as a single group. There is clearly a need to differentiate more between the many STS subtypes and to improve treatment options through clinical trials tailored towards individual histological subtypes.

Currently, the optimal cytotoxic treatment for patients with advanced DD liposarcoma remains uncertain. Single agents which are most effective include doxorubicin and ifosfamide but, as with STS in general (Ref. 5, Ref. 8, Ref. 9, Ref. 10, Ref. 11, Ref. 17, Ref. 34, Ref. 35, Ref. 38), objective response rates and progression free survival (PFS) times are very modest. A relatively large but retrospective study looking at 208 patients receiving first-line chemotherapy for advanced well or DD liposarcoma revealed an objective response rate of just 12% by RECIST criteria, with a median PFS of just 4 months for DD liposarcoma (Ref. 18).

Cumulative use of doxorubicin is limited by the risk of cardiotoxicity, while ifosfamide regimens can be limited by a greater risk of myelosuppresion and encephalopathy (Ref. 8, Ref. 9, Ref. 10, Ref. 11, Ref. 17, Ref. 34, Ref. 35, Ref. 38). Other drugs which have demonstrated modest activity in STS include taxanes, gemcitabine, trabectedin and more recently a novel anti-microtubular agent eribulin (Ref. 12, Ref. 13, Ref. 14, Ref. 15). Combination regimens may improve response rates but this does not appear to translate into an overall survival benefit (Ref. 8, Ref. 18), with no randomized trial having shown a survival benefit to date. The results of the phase III EORTC 62012 study indicates that while combination chemotherapy can improve response rates, it is not associated with statistically significant improvement in survival and comes at the cost of increased toxicity (Ref. 40). For these reasons, single-agent treatment is often favored at present (Ref. 8).

In contrast to other STS subtypes, adipocytic sarcomas unfortunately do not appear to benefit from the recently-licensed pazopanib (Ref. 33). However, they do appear to be particularly sensitive to eribulin (Ref. 15). In the eribulin phase II STS study, the adipocytic sarcomas in general had the highest response rate (46.9%), with DD liposarcoma similarly achieving a 47.6% response rate (Ref. 41). A global phase III study sponsored by the makers of eribulin (Eisai) is recruited liposarcoma (and leiomyosarcoma) patients who have failed at least two prior lines of chemotherapy, with randomization between eribulin and dacarbazine (DTIC) (Trial NCT01327885) (Ref. 42). Thus there is this option for patients in third line

However there is a need and an opportunity for a second line study for DD liposarcoma patients in Europe, and this current protocol will provide an option in this setting.

Since eribulin, an anti-microtubular agent, demonstrated some activity in STS and specifically DD liposarcoma, it is reasonable to explore whether other anti-microtubular agents have a role in this subtype. Cabazitaxel, like other taxanes, exerts its effect through inhibition of microtubular disassembly. It has been investigated in a number of early phase trials and has been shown to be a relatively safe, effective and well-tolerated anti-microtubular agent. In 2010 the FDA approved the use of cabazitaxel for patients with metastatic hormone refractory prostate cancer based on the outcome of the phase III TROPIC study. This

demonstrated an improved survival benefit with acceptable toxicity despite the relatively elderly study population.

Inclusion of sarcoma patients in phase II trials is always limited by virtue of the rarity of the disease, and hence direct experience of cabazitaxel in this disease is presently limited. However, during phase I trials of cabazitaxel, it was noted that a patient with previously resected well differentiated liposarcoma, in whom dedifferentiation was suspected, with microscopic invasion of the pancreas, and with radiology indicative of development of dedifferentiated disease extensively in the retroperitoneum, who had documented progressive disease during treatment with combination doxorubicin and ifosfamide, higher dose single agent ifosfamide and combination docetaxel and gemcitabine, had been successfully treated with cabazitaxel continuously for over four years without progression. After cessation of treatment, the disease has since remained stable for a further 2 years, without development of any metastatic sites outside the retroperitoneum (as at the time of writing). This durable stability cannot in an individual case be definitively attributed to a treatment effect of course, as it might reflect unexpected biological indolence of the disease. Nonetheless it is of some interest when taken in the context of the more general evidence quoted above (in the case of eribulin) suggesting a potential role for anti-microtubular agents in liposarcoma. Together these observations led to the development of this phase II study protocol. Cabazitaxel will be evaluated for further development (or not) by reference to progression-free survival criteria established for phase II studies in STS by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) (Ref. 19)

One recent example of such a trial is the case of eribulin where, despite very limited published preclinical or phase I sarcoma-specific data for the drug, the STBSG ran a successful stratified phase II study (EORTC 62052) in multiple sarcoma subtypes (Ref. 41) with a decision rule to continue further investigation similar to the one we intend to use, based on the benchmark previously established by the STBSG (Ref. 19). Of note, the data from this trial (EORTC 62052), as judged in this way, were found sufficient to motivate the clinical community and the pharmaceutical company concerned (Eisai) to pursue a global phase III randomized controlled trial against DTIC in third line treatment of liposarcoma and leiomyosarcoma (Trial NCT01327885) showing a survival advantage for eribulin over dacarbazine in this third line setting (Ref. 42). Note that this eribulin study is third line and does not therefore compete with our protocol, which is for second line patients.

Thus the STBSG stratified phase II design has served its primary purpose in the case of eribulin, efficiently identifying a drug with sufficient clinical activity in two sarcoma subtypes (liposarcoma and leiomyosarcoma) to merit a further definitive phase III study.

The current protocol has the same purpose. We hope to follow the example of the EORTC 62052 study, by efficiently identifying a regimen of interest in second line in this disease, and thus motivate another definitive randomized phase III trial. The 2-stage design ensures an early stopping rule to minimize recruitment of patients to inactive treatment and if insufficient activity is observed amongst the first 17 patients the trial will be terminated. Thus the full proposed recruitment of 50 patients will ONLY proceed if promising indicators of activity are observed in the first stage of the study.

The original design of this current study EORTC 1202-STBSG, as described in the previous version 2.0 of this protocol, was to evaluate two different chemotherapy regimes in second line, in two independent Simon 2-stage phase II trials run in parallel, one addressing cabazitaxel, the other addressing prolonged infusional ifosfamide. However recruitment issues have led us to make this current amendment, suspending further recruitment to the prolonged infusional ifosfamide study, and focusing all recruitment efforts on the cabazitaxel phase II study, per this current protocol version 3.0.Turning to the issue of translational science and clinical studies of targeted agents for liposarcoma: mdm2 and cdk4 amplifications characterize DD liposarcoma, and drugs targeting these molecules are in development. However the drugs concerned are still in their early phase of clinical development, safety signals need further definition, and it will likely be some or many months before studies are ready to launch. Thus this current second line

protocol will not compete with molecularly targeted studies if and when those become available. Indeed we would expect that patients whose disease progresses on cabazitaxel in this protocol might become eligible for molecularly targeted therapy where available or for treatment with eribulin or other chemotherapeutic agents.

Furthermore up-front central pathology review will be required for molecularly targeted studies, because prior STBSG studies have demonstrated a significant rate of subtype mis-assignment, even in the hands of experienced sarcoma pathologists. This need for central review can present a formidable recruitment hurdle especially for trials exploring molecularly targeted agents which are of course critically dependent for success on the selection of the appropriate patient group.

With reference to the most recent (February 2013) WHO classification of tumors of soft tissue and bone sarcoma (Ref. 37), the diagnosis of DD liposarcoma rests on the presence of a transition between a low-grade well differentiated liposarcoma and a high-(or intermediate) grade non-lipogenic, poorly differentiated sarcoma.

In practice however it is unlikely that both components could be seen in small pre-treatment biopsies or even in open surgical biopsies and often the interpretation of these small biopsies for clinical purposes requires correlation with radiology. In the absence of both components, immunohistochemistry alone does not allow to readily distinguish between DD liposarcomas and undifferentiated pleomorphic sarcomas, previously called malignant fibrous histiocytoma (MFH). These two sarcomas subtypes are the most frequent in the retroperitoneal area.

Other less common intra-abdominal pleomorphic neoplasms also enter the pathological differential diagnosis too, for example sarcomatoid carcinomas or pleomorphic gastrointestinal stromal tumor (GIST).

On the other hand the range of morphology in DD liposarcoma (defined molecularly) is much wider than was previously thought – inflammatory MFH-like, myxofibrosarcomatous, inflammatory myofibroblastic tumor-like, pleomorphic sarcoma-like and low-grade variants are now recognized.

A useful molecular diagnostic tool thankfully exists for confirmation of the diagnosis of DD liposarcoma, namely FISH (fluorescent in situ hybridization) with an MDM2 probe, and this can be performed on small biopsy specimens. Demonstration of MDM2 amplification would thus ensure the diagnosis of DD liposarcoma is reliable.

We will encourage participating centers to perform FISH for MDM2 routinely to assist in their pathological interpretation of biopsies from possible DD liposarcomas. But in addition central pathology review in this current protocol will include molecular analysis by FISH for MDM2 amplification (if not already performed locally) for the presence of this characteristic molecular target and tissue will be stored centrally. Patients in this trial whose disease progresses on treatment, and for whom central pathology review will already have been performed, will therefore form a natural well defined pool for recruitment to targeted therapy studies as they become available.

In summary, STS have a historical lack of investment in research due to their rarity but there is a recognized need to improve treatment options through clinical trials tailored to individual subtypes. In the case of DD liposarcoma, anti-microtubular agents show promise and the aforementioned index patient's experience suggests that cabazitaxel, for which extensive safety data is available, should be formally assessed. The relative paucity of alternative treatment options with clinically meaningful benefit for this group of patients, who are often young and fit, has led to the development of this phase II study, assessing progression-free survival rates at 12 weeks with cabazitaxel as second-line treatment in metastatic or inoperable locally advanced DD liposarcoma.

We believe this current protocol fits well in an informal but coordinated STBSG approach to the DD liposarcoma subtype. It will have a clinical translational impact directly, by providing up front molecular characterization essential for recruitment to future translational studies of targeted agents, it will contribute

to the ongoing efforts of the STBSG to generate a central subtype specific sarcoma tissue collection for later, separately funded, translational science projects, and it will thus maximize the utility of central pathology review and the efficiency of patient recruitment and associated translational research. This provides an example of coordinated effort to yield maximum benefit to the patients concerned and accelerated progress in the field.

1.2 Background Therapeutic Information

Cabazitaxel is a new taxoid which, like other taxoids (Ref. 22, Ref. 23), binds to tubulin, the protein component of microtubules, to promote assembly and inhibit depolymerization, resulting in cell cycle arrest. Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of adult patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Data reported in this section are mainly based on the Summary of Product Characteristics (Ref. 36).

1.2.1 Pharmacokinetics

A population pharmacokinetic analysis was carried out in 170 patients including patients with advanced solid tumors (n=69), metastatic breast cancer (n=34) and metastatic prostate cancer (n=67). These patients received cabazitaxel at doses of 10 to 30 mg/m² weekly or every 3 weeks.

Absorption

After 1-hour intravenous administration at 25 mg/m² cabazitaxel in patients with metastatic prostate cancer (n=67), the Cmax was 226 ng/ml (Coefficient of Variation (CV): 107%) and was reached at the end of the 1-hour infusion (Tmax). The mean AUC was 991 ng.h/ml (CV: 34%).

No major deviation to the dose proportionality was observed from 10 to 30 mg/m² in patients with advanced solid tumors (n=126).

Distribution

The volume of distribution (Vss) was 4870 l (2640 l/m² for a patient with a median BSA of 1.84 m²) at steady state.

In vitro, the binding of cabazitaxel to human serum proteins was 89-92% and was not saturable up to 50,000 ng/ml, which covers the maximum concentration observed in clinical studies. Cabazitaxel is mainly bound to human serum albumin (82.0%) and lipoproteins (87.9% for HDL, 69.8% for LDL, and 55.8% for VLDL). The in vitro blood-to-plasma concentration ratios in human blood ranged from 0.90 to 0.99 indicating that cabazitaxel was equally distributed between blood and plasma.

Biotransformation

Cabazitaxel is extensively metabolised in the liver (>95%), mainly by the CYP3A isoenzyme (80% to 90%). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued form O-demethylations), with the main one accounting for 5% of parent exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and faeces.

Based on in vitro studies, the potential risk of inhibition by cabazitaxel at clinically relevant concentrations is possible towards medicinal products that are mainly substrate of CYP3A.

However a clinical study has shown that cabazitaxel (25 mg/m² administered as a single 1-hour infusion) did not modify the plasma levels of midazolam, a probe substrate of CYP3A. Therefore, at therapeutic doses, co-administration of CYP3A substrates with cabazitaxel to patients is not expected to have any clinical impact.

There is no potential risk of inhibition of medicinal products that are substrates of other CYP enzymes (1A2, 2B6, 2C9, 2C8, 2C19, 2E1, and 2D6) as well as no potential risk of induction by cabazitaxel on medicinal products that are substrates of CYP1A, CYP2C9, and CYP3A. Cabazitaxel did not inhibit in vitro the major biotransformation pathway of warfarin into 7-hydroxywarfarin, which is mediated by CYP2C9. Therefore, no pharmacokinetic interaction of cabazitaxel on warfarin is expected in vivo.

In vitro cabazitaxel did not inhibit Multidrug-Resistant Proteins (MRP): MRP1 and MRP2 or Organic Cation Transporter (OCT1). Cabazitaxel inhibited the transport of P-glycoprotein (PgP) (digoxin, vinblastin), Breast-Cancer-Resistant-Proteins (BCRP) (methotrexate) and Organic Anion Transporting Polypeptide OATP1B3 (CCK8) at concentrations at least 15 fold what is observed in clinical setting while it inhibited the transport of OATP1B1 (estradiol-17β-glucuronide) at concentrations only 5 fold what is observed in clinical setting. Therefore the risk of interaction with substrates of MRP, OCT1, PgP, BCRP and OATP1B3 is unlikely in vivo at the dose of 25 mg/m^2. The risk of interaction with OATP1B1 transporter is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of the infusion.

Elimination

After a 1-hour intravenous infusion [14C]-cabazitaxel at 25 mg/m² in patients, approximately 80% of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the faeces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel and metabolites account for less than 4% of the dose (2.3% as unchanged medicinal product in urine).

Cabazitaxel had a high plasma clearance of 48.5 l/h (26.4 l/h/m² for a patient with a median BSA of 1.84 m²) and a long terminal half-life of 95 hours.

1.2.2 Pharmacodynamic effects

Cabazitaxel demonstrated a broad spectrum of antitumor activity against advanced human tumors xenografted in mice. Cabazitaxel is active in docetaxel-sensitive tumors. In addition, cabazitaxel demonstrated activity in tumor models insensitive to chemotherapy including docetaxel.

The efficacy and safety of cabazitaxel in combination with prednisone or prednisolone were evaluated in a randomized, open-label, international, multi-center, phase III study, in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

This Phase 3 study TROPIC was a randomized, open-label, multicenter, multinational study in patients with metastatic hormone-refractory prostate cancer whose disease had progressed following a first-line docetaxel-containing regimen (Ref. 16). This pivotal study compared 25 mg/m^2 cabazitaxel (CBZ) every 3 weeks, plus prednisone, to 12 mg/m^2 mitoxantrone (MTX) every 3 weeks, plus prednisone. A total of 755 patients were recruited (378 patients in CBZ arm and 377 patients in MTX arm); of these patients 19 % (MTX arm) and 18 % (CBZ arm) were ≥ 75 years old. A statistically significant increase in OS was observed in patients treated with CBZ plus prednisone compared to patients treated with MTX plus prednisone (15.1 months versus 12.7 months, HR of 0.70, log-rank p-value of 0.0001). Cabazitaxel is now licensed for use in this setting by the FDA (2010) and in the EU and other countries (2011).

The secondary endpoints supported the positive data regarding OS. Progression-free survival (2.8 months versus 1.4 months, HR of 0.74, p<0.0001), PSA response rate, radiological response rate and time to progression all showed a statistically significantly improvement. Pain response and time to pain progression with CBZ were as good as with MTX.

Grade 3-4 neutropenia was the most common treatment emergent adverse events (TEAEs), reported in 81.7% of the patients treated with cabazitaxel, with febrile neutropenia reported in 7.5%. The most common all grade non-haematologic TEAEs were diarrhea (46.6%), fatigue (36.7%), nausea (34.2%), vomiting (22.6%), asthenia (20.5%), constipation (20.5%) and haematuria (16.7%) in patients receiving

cabazitaxel. The most common Grade 3-4 non-haematologic TEAEs were diarrhea (6.2%), fatigue (4.9%), asthenia (4.6%), back pain (3.8%), and nausea (1.9%). This is consistent with the other cabazitaxel trials and the pattern of toxicity will be familiar to clinicians using docetaxel in this setting, although the incidences of oedema, peripheral neuropathy, stomatitis and alopecia appear be lower with cabazitaxel.

Hematuria (occurred in 16.7% versus 3.8% in the MTX arm), was also seen in the ARD6191 and TCD6945 studies in metastatic breast cancer, where 6 patients experienced cystitis without local infection, including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported for 18 patients (5%) in the CBZ group versus 3 (<1%) in the MTX group. Of the 18 deaths in the CBZ group, 8 were the result of neutropenia and/or infection, 4 were due to cardiac events (2 cardiac arrest, 1 cardiac failure and 1 ventricular fibrillation), 4 were due to pre- or post-renal events leading to renal failure, and 2 were due to other causes, including a death of unknown etiology and a death from a cerebral hemorrhage following a fall in a patient taking concomitant clopidogrel.

A very useful recent abstract (Heidenreich et al, ESMO 2012) and subsequent publication (Ref. 39) describes a detailed safety analysis of the European compassionate use and early access program of cabazitaxel in the same indication, with prophylactic or therapeutic use of G-CSF according to ASCO recommended (but not mandated) guidelines. 746 patients were treated, 325 of them were over 70 years including 145 over 75 years. 90% had PS0 or 1 but 10% PS2. 92% had bone metastases, and of course involvement of bone marrow, and prior irradiation of bone marrow are both common in the prostate cancer population. 43% had prophylactic G-CSF with first cycle. The risk of treatment emergent adverse events possibly related to cabazitaxel and leading to death was 2.1% overall, mostly in the context of neutropenic infection. Febrile neutropenia or neutropenic sepsis occurred in 6.7% of patients. A multivariate analysis indicated baseline low total white count (OR 1.7), age >75 (OR 1.6), first cycle treatment (OR 5.1) and prophylactic G-CSF (OR 0.7) were significant independent predictors of the risk of grade 3 or complicated neutropenia. Given these observations we have set an upper age limit of 75 for this study, and restricted to those with PS 0 or 1.

The EMA has commented on the use of prophylactic G-CSF in their assessment of the use of cabazitaxel for patients with prostate cancer treated after prior failure of docetaxel. Our patients will also be treated in second line with the same dose (25mg/m^2 3 weekly). Involvement of bone marrow by disease is rare in sarcoma. In addition, our inclusion criteria (see below) will exclude patients >75 years or those with PS >1.

Given the points above and the EMA assessments, consideration of prophylactic G-CSF will be recommended (but not mandated) using similar phraseology to that of the current EMA Summary of Product Characteristics thus:

Patients treated with cabazitaxel may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

1.2.3 Index patient treated with cabazitaxel for liposarcoma

A 40 year old male had a retroperitoneal mass excised at laparotomy in 2002. Histological examination demonstrated a well differentiatied liposarcoma (WDLS) with a single area of myxoid differentiation. However, Fluorescent In-Situ Hybridisation (FISH) showed no evidence of the CHOP-TLS hybrid gene, identified in 85% of pure myxiod liposarcomas.

Two-and-a-half years later, a recurrence with early evidence of tumor de-differentiation and microscopic pancreatic invasion was excised and he was given 6 cycles of ifosfamide (5 g/m²) and doxorubicin (50 mg/m²).

Unfortunately, he developed a further recurrence two years later, which could not be completely removed (R1 resection). Measurable disease became evident six months later (2008) and he was offered palliative chemotherapy. His disease progressed through a rechallenge with 3 cycles of ifosfamide (5 g/m²) and doxorubicin (50 mg/m^2) and continued to progress through a subsequent 3 cycles of higher dose single-agent ifosfamide (9 g/m^2). Finally, he received 4 cycles of gemcitabine (675 mg/m² d1 & d8) and docetaxel (80 mg/m² d8, q 21) and although the low density lipomatous elements of the gross tumor volume did not demonstrate progression, the solid, presumed DD components (on radiological grounds) had again progressed.

Prior to the availability of trabectedin, he consented to a phase I ADME trial of cabazitaxel (25 mg/m² d1, q21) in February 2009. A minor response according to Response Evaluation Criteria for Solid Tumors (RECIST) was achieved after four cycles. He required a 20% dose reduction for cycle 3 due to grade 4 neutropenia and changed schedule to 4 weekly with G-CSF cover from cycle 6 after delays to cycles 4 and 5 due to persistent neutropenia. The patient received more than 40 cycles without further adjustment and remained stable disease for a prolonged time (more than 4 years). Treatment was well tolerated, with short-lived G1 fatigue, diarrhea, sensory neuropathy or transaminitis at times, and a late adverse event of cataracts in September 2011, though the causal relationship of the latter with cabazitaxel therapy remains unproven.

After more than 4 years of continuous treatment cumulative fatigue and sensory neuropathy prompted cessation of treatment, the disease has remained stable for more than 2 years. This durable stability cannot in an individual case be definitively attributed to a treatment effect of course, as it might reflect unexpected biological indolence of the disease. Nonetheless it is of some interest when taken in the context of the more general evidence quoted above (in the case of eribulin) suggesting a potential role for anti-microtubular agents in DD liposarcoma. Together these observations led to the development of this cabazitaxel treatment phase II study protocol.

1.2.4 Safety

Elderly patients

In the population pharmacokinetic analysis in 70 patients of 65 years and older (57 from 65 to 75 and 13 patients above 75), no age effect on the pharmacokinetics of cabazitaxel was observed.

Hepatic impairment

Cabazitaxel is eliminated primarily via liver metabolism.

A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN) or moderate (total bilirubin >1.5 to ≤3.0 x ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated dose (MTD) of cabazitaxel was 20 and 15 mg/m², respectively.

In 3 patients with severe hepatic impairment (total bilirubin >3 ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment, indicating some effect of severe hepatic impairment on cabazitaxel pharmacokinetics. The MTD of cabazitaxel in patients with severe hepatic impairment was not established.

Based on safety and tolerability data, cabazitaxel dose should be reduced in patients with mild hepatic impairment cabazitaxel is contraindicated in patients with severe hepatic impairment.

2 Objective of the trial

2.1 General objective

The main objective is to determine whether cabazitaxel demonstrates sufficient antitumor activity (as measured by progression free survival at 12 weeks) in pre-treated patients with metastatic or inoperable locally advanced DD liposarcoma to justify further investigation in the phase III setting.

2.2 End-points

2.2.1 Primary end-point

The primary endpoint will be progression free survival, assessed at 12 weeks after start of treatment. Progression will be defined according to RECIST 1.1 (Ref. 20).

2.2.2 Secondary end-points

Secondary endpoints will include:

- Time to progression
- Progression free survival
- Overall survival
- Objective tumor response as defined by RECIST 1.1 (Ref. 20) where the dedifferentiated component is targeted for measurements of local disease (section 7.5.1.1)
- Objective tumor response as defined by RECIST 1.1 where both well differentiated and dedifferentiated components are included in measurements of local disease (measurements to be performed by central review only)
- Time to onset of response (for patients achieving an objective response)
- Duration of response (for patients achieving an objective response)
- Safety (CTCAE Version 4.0)

3 Patient selection criteria

Patient enrollment will follow a two-step procedure as illustrated in chapter 12 (registration step 1: registration and central pathological review and registration step 2: eligibility confirmation). Patients must meet all of the criteria described in sections 3.1 and 3.2 in order to be eligible for treatment with cabazitaxel.

3.1 Registration step 1

- Local diagnosis of DD liposarcoma.
- Mandatory availability for shipment of formalin-fixed, paraffin-embedded, tumor-containing tissue blocks from primary tumor and/or metastatic site. Information on previous histopathology reports and previous molecular analysis will be entered in an electronic CRF, to accompany the tissue sample(s).
- If a block cannot be provided, the following should be submitted:

- For cases that will be reviewed in UK (refer to chapter 15.3): 4 x 1 micron sections on coated slides, one thin H&E stained section and 20 unstained sections of usual thickness (2-4 micron) on coated slides.
- For cases that will be reviewed in France (refer to chapter 15.3): 3 x 4 micron sections on unstained (coated) slides for FISH and 15 unstained slides (4 micron) for immunohistochemistry.
- Before patient registration step 1, 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.

3.2 Registration step 2

- Central pathology confirmation of DD liposarcoma within 3 weeks after registration step 1.
- Radiological or histological diagnosis of inoperable locally advanced or metastatic disease, with evidence of disease progression within the past 6 months prior to registration step 2.
- Clinically and/or radiographically documented measurable disease within 28 days prior to registration step 2. At least one site of disease must be unidimensionally measurable according to RECIST 1.1
- Note: as DD liposarcoma commonly arises on a background of well differentiated liposarcoma, and as the latter well differentiated element can remain stable for prolonged periods without therapy, we recommend that when defining radiological measurable or target lesions per RECIST 1.1, especially in the region of the primary tumor mass if present, these should be chosen to include specifically the solid or higher density elements of the disease (which tend to correlate pathologically with the DD element), and not the low density fatty elements of the disease, which tend to correlate with the well differentiated element.
- One previous chemotherapy regimen for locally advanced or metastatic DD liposarcoma (this could include pre-operative chemotherapy for primary disease).
- Not more than 1 prior molecularly targeted therapy (e.g. CDK4 inhibitor). Any such prior therapy must be completed at least 2-4 weeks prior to registration step 2.
- Age 18-75 years old
- WHO performance status 0-1
- Adequate haematological, renal and hepatic function
  - Haematological: haemoglobin > 90 g/L or 5.6 mmol/L, absolute granulocytes > 1.5 x 10^9/L, platelets > 100 x 10^9/L
  - Renal: creatinine clearance (CrCl) * > 30 ml/min
  - Note: It is recommended that creatinine clearance is calculated using the estimated glomerular filtration rate (eGFR) methodology per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (21). If not supplied by the local laboratory, it can be calculated online using the link http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr. Direct measurement (e.g. EDTA) or other established methods of estimating creatinine clearance per local institution policies are acceptable.
  - Hepatic: Bilirubin ≤ 1.0 times upper limit of normal (1.0xULN) of institutional limits, ALT and/or AST≤1.5 x ULN.

- If isolated elevated bilirubin <2 x ULN and Gilberts syndrome suspected, suggest repeating bloods after food. If bilirubin improves to meet the criteria above this is acceptable. More severe persistent hepatic impairment of whatever cause would exclude the patient from treatment till resolved.

- Estimated life expectancy > 3 months
- No inflammation of the urinary bladder (cystitis)
- No symptomatic CNS metastases. If asymptomatic CNS metastases are present these should have been previously treated and stable for at least 3 months and patient should not require maintenance steroids.
- No other invasive malignancy within 5 years, with the exception of non-melanoma skin cancer, localized cervical cancer, localized and presumably cured prostate cancer or adequately treated basal or squamous cell skin carcinoma.
- No significant cardiac disease: i.e. active ischaemic heart disease or cardiac failure (NYHA (Appendix D) > class 1)
- No uncontrolled severe illness or medical condition (including acute infection, uncontrolled diabetes), other than the DD liposarcoma
- All related adverse events from previous therapies must have recovered to ≤ Grade 1 (except alopecia).
- 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) (listed in Appendix E).
- No known hypersensitivity to taxanes or their excipients (cabazitaxel, like docetaxel, is solubilized in polysorbate 80 and ethanol)
- Women of child bearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment.
- Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
- It is recommended that patients do not attempt to become pregnant or to breast feed after exposure to these chemotherapy agents, as there is no available data on safety. If despite this advice patients wish to do so, then it is recommended a minimum of 6 months should first be allowed to elapse from the last received dose.
- Men should use reliable contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of cabazitaxel.
- 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.

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial Design

This trial will be an international, multi-center, open label phase II trial where patients with metastatic or locally advanced DD liposarcoma will be treated with cabazitaxel.

Eligible patients will be registered at the EORTC Headquarters. Central review of tumor blocks to confirm the histological diagnosis before the final confirmation of eligibility is mandatory. If the DD liposarcoma diagnosis is confirmed, patients will start treatment within 72 hours after registration step 2:

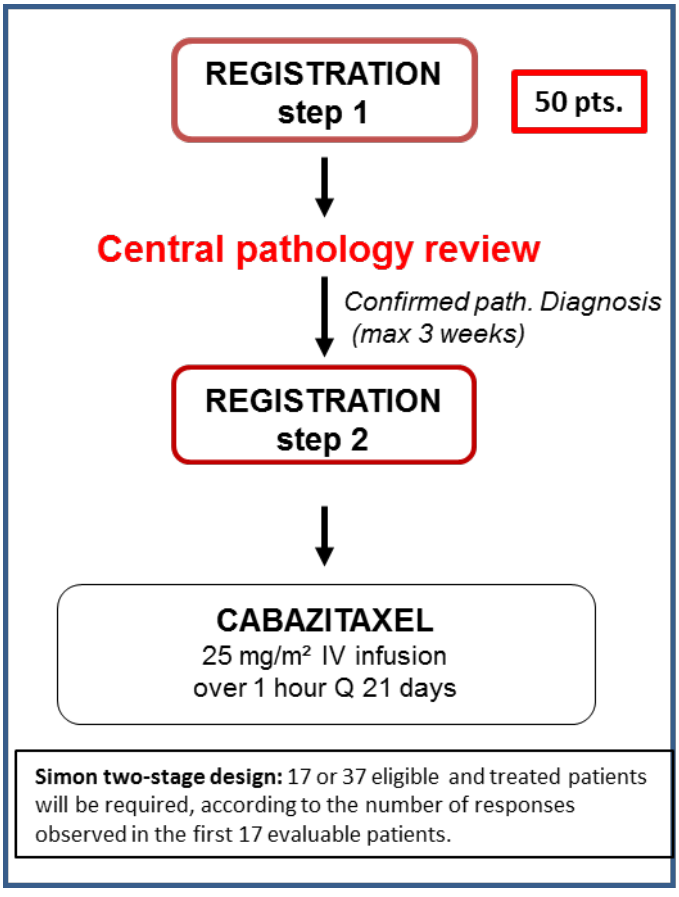
- Cabazitaxel 25mg/m² IV infusion over 1 hour every 21 days.
- The day of first treatment is defined as day 1 of cycle 1.

Treatment will be given until occurrence of withdrawal criteria (see section 5.8).

The Simon two-stage design will be applied: 17 or 37 eligible and treated patients will be required, according to the number of responses observed in the first 17 eligible and treated patients. As patients will only be evaluable for the primary end-point 12 weeks after start of treatment, the accrual will be temporarily stopped after the inclusion of 19 patients, to allow for 10% of untreated or ineligible patients. Up to 4 patients may be added to the total recruitment. Furthermore, to account for screening failure at central review, up to 50 patients will be enrolled.

A central review for imaging will be organized at the end of the trial. Refer to section 15.4.

The interval from registration Step 1 to Step 2 should be maximum 7 weeks.



5 Therapeutic regimen, expected toxicity, dose modifications

5.1 General drug information

- INN: Cabazitaxel
- Drug substance used: cabazitaxel acetone solvate
- Chemical name according to IUPAC:
  - (2α,5β,7β,10β,13α)-4-(acetoxy)-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate-propan-2-one
- The pH of the solution is about 3.5. The solution contains the following excipient: Polysorbate 80.

5.2 Drug supply

Cabazitaxel will be provided free of charge by Sanofi as a kit containing one single-use vial of cabazitaxel concentrate for solution for infusion and one single vial of solvent for dilution. Practicalities for drug supply will be detailed in the study pharmacy guidelines.

5.3 Packaging, dispensing and storage

5.3.1 Drug packaging

Cabazitaxel is supplied for parenteral administration as a sterile, nonpyrogenic, nonaqueous, yellow to brownish yellow concentrate for solution for infusion at 60 mg/1.5 mL and packaged in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. Each vial contains 60 mg of cabazitaxel, expressed on anhydrous and solvent-free basis, per 1.5 mL of solution.

The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 15 % v/v ratio of ethanol 95 % in water for injection. This solution is contained in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a colorless plastic flip off cap. The solution is a clear colorless liquid.

Storage conditions: vials should be stored according to their labeling and kept in their kit until use.

5.3.2 Drug preparation

Instructions on preparation of cabazitaxel infusion solution, infusion conditions and safe handling will be given in the pharmacy guidelines.

5.4 Drug reconciliation procedures

Accountability of the investigational study drug is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, issue dates, quantities (lowest unit) and stock balance. At the end of study, when all patients have stopped protocol treatment, complete drug

reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Standard accountability forms can be provided to the sites for the record of drugs accountability. However, the sites are permitted to use their own template providing they included all the required fields.

5.5 Initial dose and schedule

Cabazitaxel will be administered at a dose of 25 mg/m² by intravenous infusion, over 1 hour, on day 1 of each 21 day cycle.

Hepatic impairment

If isolated elevated bilirubin >1x ULN < 2 x ULN and Gilberts syndrome suspected, suggest repeating bloods after food. If bilirubin improves to the meet the criteria above this is acceptable. More severe persistent hepatic impairment of whatever cause would exclude the patient from treatment till improved.

Premedication

All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel.

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions can occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy. Patients with a hypersensitivity reaction must stop treatment with cabazitaxel (see section 5.8)

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent), and
- H2 antagonist (ranitidine or equivalent)

Supportive care see chapter 5.9.

5.6 Treatment duration

Treatment should be administered until the occurrence of a withdrawal criterion (section 5.8).

It is anticipated that the average treatment duration will be between 12 and 24 weeks (i.e. 4 to 8 x 21 day cycles of cabazitaxel).

5.7 Dose and schedule modifications

The following guidance has been provided by Sanofi.

5.7.1 General rules

Every effort should be made to administer the full dose regimen to maximize dose-intensity. If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to improve signs and symptoms including for example antiemetics for nausea and vomiting, antidiarrheals for diarrhea and antipyretics and/or antihistamines for drug fever.

However, doses may require adjustment for significant hematological and/or other adverse events.

Dose adjustments are to be made according to the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE). The major adverse effects of cabazitaxel which limit dose are neutropenia and gastrointestinal toxicity.

The guidelines below outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

5.7.2 Dose reduction

Dose can be reduced for cabazitaxel when necessary as described in the following sections. If a dose has been reduced as a result of toxicity, it must not be re-escalated. Only one dose reduction will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should discontinue study treatment.

Dose level	Cabazitaxel dose
0 (initial)	25 mg/m²
-1 (after first reduction required)	20 mg/m²
-2 (if second reduction required)	Withdraw from study treatment

5.7.3 Treatment delay

New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm³, platelet count ≥75 000/mm³, and non-hematological toxicities (except alopecia) have recovered to baseline. Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should discontinue cabazitaxel.

5.7.4 Hematological toxicity

Cabazitaxel dose modifications for hematological toxicity are summarized in Table 1.

Blood counts should be monitored weekly for the first cycle to determine if G-CSF or dosage modification is needed. Additional blood counts will be performed in case of fever or infection. Study treatment should not be given to patients with neutrophil counts $<1.5 \times 10^9$/L.

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF should be considered according to ASCO guidelines, EMA comments and local institutional policies. Infections concomitant with grade 3-4 neutropenia should be reported with the term “neutropenic infection” on case report form. The use of prophylactic G-CSF for subsequent cycles should be considered (but is not mandated) per local policy, ASCO guidelines and EMA comments (see current 2013 EMA phraseology in Summary Product Characteristics quoted in introduction).

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines or local policies).

Table 1 - cabazitaxel - dose modifications for hematological toxicity

Toxicity	Grade 2	Grade 3 Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to grade ≤1 (neutrophil ≥1.5 x 10^9/L). - 1st episode: no dose reduction required. - subsequent episodes: reduce by 1 dose level	No dose reduction if isolated and duration ≤ 7 days. If duration more than 7 days or not recovered on D21, delay** next infusion until ANC ≥1.5 x 10^9/L and: - If occurred despite prior prophylactic G-CSF then reduce the cabazitaxel dose -If no prior prophylactic G-CSF then consider that option or reduce the cabazitaxel dose - If further episode despite prior dose reduction then withdraw from treatment
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥1.5 x 10^9/L and: - If occurred despite prior prophylactic G-CSF then reduce the cabazitaxel dose -If no prior prophylactic G-CSF then consider that option or reduce the cabazitaxel dose - If further episode despite prior dose reduction then withdraw from treatment
Thrombocytopenia	Delay** next infusion until recovery to grade ≤ 1 (platelets ≥75 x 10^9/L). No dose reduction required.	Delay** infusion until platelets ≥75 x 10^9/L. If grade 3 without delay, no dose reduction required. If grade 4 with or without delay, or grade 3 with delay - 1st episode: reduce dose by 1 dose level. - 2nd episode: withdraw from study treatment

** maximum of 2 weeks delay, otherwise the patient will discontinue cabazitaxel

5.7.5 Allergy (anaphylactic and hypersensitivity reactions)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of the start of the first or of the second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of wellbeing and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (i.e. antihistamine, corticosteroids, epinephrine and bronchodilators for example aminophylline and beta 2-agonists) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, bronchodilator or aminophylline in case of bronchospasm,

etc) will be instituted per local institutional policies. In addition, it is recommended to take the measures listed below:

Table 2 - cabazitaxel - dose modifications for Allergy**Toxicity**	♦ Cabazitaxel
Mild Localized cutaneous reaction, such as pruritus, flushing, rash.	♦ Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside ♦ Complete cabazitaxel infusion at the initial planned rate.
Moderate: generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B.P. >80 mmHg	♦ Stop cabazitaxel infusion ♦ Give IV antihistamine e.g. diphenhydramine 50 mg and/or IV corticosteroid e.g. dexamethasone 10 mg. ♦ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. ♦ Re-administer premedication regimen as described in section 5.9 when cabazitaxel is reinfused more than 3 hours after the interruption ♦ Administer cabazitaxel over 2 hours for all subsequent infusions
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	♦ Stop cabazitaxel infusion ♦ Give IV antihistamine e.g.diphenhydramine 50 mg and/or IV dexamethasone 10 mg ♦ Add epinephrine and/or bronchodilators and/or IV plasma expanders if indicated per local institutional policies ♦ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible ♦ Re-administer premedication regimen as described in section 5.9 when cabazitaxel is reinfused more than 3 hours after the interruption ♦ Administer cabazitaxel over 2 hours for all subsequent infusions ♦ If a severe reaction recurs, patient will go off protocol therapy permanently
Anaphylaxis (Grade 4 reaction)	♦ Treat the acute reaction as above and per local institutional policies ♦ Withdraw from study treatment permanently.

5.7.6 Nausea/vomiting

A prophylactic anti-emetic treatment should be given to patients in all cycles. The use of metoclopramide or similar is recommended. More aggressive anti-emetic prophylaxis (e.g. ondansetron etc. per local institutional policies) should be given if the patient has experienced grade ≥ 3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, grade ≥ 3 nausea/vomiting still occurs, reduce the dose of cabazitaxel. If despite one dose reduction and prophylaxis, grade ≥ 3 nausea/vomiting still occur, the patient should be withdrawn from treatment with cabazitaxel.

5.7.7 Stomatitis

If grade 3 stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤ 1. Treatment may then be resumed, but the dose of cabazitaxel should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel.

5.7.8 Diarrhea

No prophylactic treatment for diarrhea is recommended in cycle 1. However, following the first episode of diarrhea, the patient should be treated with rehydration or antidiarrheal medications as needed. In case of Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose. If despite dose reduction, diarrhea still occurs at grade ≥ 3, the patient should be withdrawn from treatment with cabazitaxel.

5.7.9 Renal function

Renal function assessment by blood tests at baseline and before each treatment cycle is required.

Consideration should be given to IV hydration for CT scans with contrast in case of eGFR < 60 ml/min per examples provided in Appendix F.

The following are also required:

1) Microscopic urinalysis/dipstick:

- at baseline (reference value)
- and during study treatment if creatinine increase by at least 1.5 x ULN from baseline value

2) Consideration of nephrologist advice in case of creatinine increase by at least 2 x ULN from baseline value or eGFR (according to CKD-EPI formula) decrease by 50%.

3) In case of renal function impairment, the local investigator should make every effort to identify the cause and to report the cause as an adverse event. The degree of the renal failure existing should be considered in the grading of the event. If no cause is identified, report the eGFR decrease itself as the adverse event.

Creatinine and eGFR should be assessed until recovery or stabilization. If mild to moderate renal impairment persists, continuation of cabazitaxel therapy is at the discretion of the local investigator.

5.7.10 Hematuria

An imbalance in the incidence of hematuria was observed in the EFC6193/TROPIC Phase III study of carbazitaxel and prednisolone as second-line treatment in metastatic hormone-refractory prostate cancer. More hematuria was reported in the cabazitaxel arm versus the mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In the cabazitaxel arm, no clear possible cause (such as local infection/ obstruction/ progression, or anticoagulation/ aspirin therapy, or thrombocytopenia) was found for 21 patients. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Hematuria may therefore be related to treatment and unless there is a clear possible cause, every effort should be undertaken to seek this (e.g. urine cultures, urinary tract ultrasound and, if no cause identified, cystoscopy with or without biopsy).

5.7.11 Peripheral neuropathy

Dose modification should be performed as follows:

- Grade ≤1: No change
- Grade 2: Delay treatment until improvement, then reduce cabazitaxel and retreat with reduced dose
- Grade 3: Patient will be withdrawn from treatment with cabazitaxel

5.7.12 Liver toxicity

Table 3 - cabazitaxel - dose modifications for liver toxicity

Toxicity	Cabazitaxel
Total bilirubin > 1 to ≤ 1.5 x ULN or AST >1.5 x ULN	Reduce cabazitaxel dose to 20 mg/m²
Total bilirubin > 1.5 to ≤ 3 x ULN and AST any	Reduce cabazitaxel dose to 15 mg/m²
Severe hepatic impairment (total bilirubin > 3 X ULN and AST = any)	Cabazitaxel should be discontinued.

5.7.13 Other toxic effects

For toxicities ≥ grade 3 except; fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be withheld for a maximum of 2 weeks from the planned date of reinfusion until resolution to ≤ grade 1, then reinstituted, if medically appropriate. A dose reduction for subsequent doses will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >1 dose reduction is needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator's judgment.

5.7.14 Contraindications

- Known hypersensitivity to taxanes or their excipients (cabazitaxel, like docetaxel, is solubilized in polysorbate 80 and ethanol). For list of excipients please refer to the Summary of Product Characteristics
- Neutrophil counts less than 1,500/mm³.
- Severe hepatic impairment (total bilirubin >3 x ULN).

Concomitant vaccination with a live attenuated vaccine.

5.8 Withdrawal criteria

Treatment should be continued until the occurrence of a withdrawal criteria listed below:

- Disease progression
- Unacceptable toxicity, including recommendations (section 5.7) for severe toxicity and dose and schedule modifications (like more than 1 cabazitaxel dose level reduction or treatment delay greater than 2 weeks).
- Patients with a hypersensitivity reaction, as mentioned in section 5.7.5 (Table 2) must stop treatment with cabazitaxel.
- Withdrawal of consent
- Physician's recommendation
- Occurrence of a second malignancy

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 best interest of the patient.

After progression, the treatment will be left to the discretion of the treating physician. Any anti-cancer therapy other than the study drug given as single agent will not be considered as part of the protocol treatment.

5.9 Concomitant treatments

5.9.1 Supportive Medications

Concomitant treatment with another anti-cancer or investigational therapy is not permitted while patients are on study.

Concomitant radiotherapy for palliation of pain is permitted, with the investigational agent on hold during that period. Target lesions should not be irradiated and treatment should not be delayed by more than two weeks. The use of palliative radiotherapy for symptom control of non-target lesions will not be regarded as evidence of progressive disease.

The Investigator may prescribe any other concomitant medications as deemed necessary. Other non-cytotoxic supportive or palliative measures would also be expected to be permitted taking into account interaction with other medications as described hereunder. If there are any uncertainties, these can be discussed with the Study coordinator and EORTC HQ team.

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent), and
- H2 antagonist (ranitidine or equivalent)

A supply of antiemetic to use as required is recommended and institutions may wish to follow the same protocols as they currently use for three-weekly docetaxel.

During the first cycle of treatment, visits on day 8 and 15 will be scheduled for assessment of toxicity and blood tests to document the extent of neutropenia.

The use of granulocyte colony stimulating factors (G-CSF) for primary or secondary prophylaxis of febrile neutropenia is at the discretion of the local investigators. Consideration of prophylactic G-CSF is recommended (but not mandated) per the phraseology of the current EMA Summary of Product Characteristics thus:

Patients treated with cabazitaxel may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

5.9.2 Interactions with other medications

In vitro studies have shown that cabazitaxel is mainly metabolised through CYP3A (80% to 90%).

CYP3A inhibitors

Repeated administration of ketoconazole (400 mg once daily), a strong CYP3A inhibitor, resulted in a 20% decrease in cabazitaxel clearance corresponding to a 25% increase in AUC. Therefore concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) should be avoided as an increase of plasma concentrations of cabazitaxel may occur.

Concomitant administration of aprepitant, a moderate CYP3A inhibitor, had no effect on cabazitaxel clearance.

CYP3A inducers

Repeated administration of rifampin (600 mg once daily), a strong CYP3A inducer, resulted in an increase in cabazitaxel clearance of 21% corresponding to a decrease in AUC of 17%.

Therefore concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) should be avoided as a decrease of plasma concentrations of cabazitaxel may occur. In addition, patients should also refrain from taking St. John’s Wort.

OATP1B1

In vitro, cabazitaxel has also been shown to inhibit the transport proteins of the Organic Anion Transport Polypeptides OATP1B1. The risk of interaction with OATP1B1 substrates (e.g. statins, valsartan, repaglinide) is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of

the infusion. A time interval of 12 hours is recommended before the infusion and at least 3 hours after the end of infusion before administering the OATP1B1 substrates.

Vaccinations:

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving cabazitaxel. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant vaccination with a live attenuated vaccine is contraindicated.

6 Clinical evaluation, laboratory tests and follow-up

The study will include a screening visit, study assessments and post-treatment follow-up visits. During the treatment phase the patients will undergo regular assessments for safety. Treatment activity will be assessed at regular intervals and objective response will be defined according to RECIST 1.1. The disease will be assessed regularly until documented progression, and treatment side effects will be assessed separately for each cycle of therapy.

Cabazitaxel visits will be scheduled on day 1 of each cycle for the duration of treatment on the study. During the first cycle, 3 visits will be scheduled to assess the tolerance to treatment.

6.1 Baseline investigations

6.1.1 Registration step 1

- Written informed consent must be obtained before registration step 1.
- Central pathology review (maximum 3 weeks from shipment to result): shipment of formalin-fixed, paraffin-embedded, tumor-containing tissue blocks from primary tumor and/or metastatic site. Information on previous histopathology reports and previous molecular analysis will be entered in an electronic CRF, to accompany the tissue samples. (Refer to chapter 15.3)
- If block cannot be provided, the following should be submitted:
  - For cases that will be reviewed in UK (refer to chapter 15.3): 4 x 1 micron on coated slides, one thin H&E stained section and 20 unstained sections of usual thickness on coated slides.
  - For cases that will be reviewed in France (refer to chapter 15.3): 3 x 4 micron unstained (coated) slides for FISH and 15 unstained slides for immunohistochemistry.

6.1.2 Registration step 2

The interval from registration Step 1 to Step 2 should be maximum 7 weeks.

6.1.2.1 Within 28 days prior to registration step 2

- Physical examination (including height, weight, pulse rate, blood pressure, temperature)
- Note: height is only requested at baseline
- Medical history (including performance status, existing signs and symptoms, adverse events, concomitant medications, other diagnoses)
- Radiological assessment. This should include scans of chest, abdomen and pelvis and any site of known disease involvement elsewhere if not clinically measurable by local investigator as target lesion for response evaluation, using CT or MRI scan.

6.1.2.2 Within 7 days prior to registration step 2

- Hematology including hemoglobin, absolute granulocytes, platelets.
- Biochemistry including urea, creatinine, CrCl, bilirubin, ALT and/or AST, alkalin phosphatase, albumin

6.1.2.3 Within 72 hours prior to registration step 2

- Pregnancy test: for females with child bearing potential within 72 hours prior to the first dose of study treatment

6.2 During treatment

First cycle of treatment should start within 72 hours of registration-step 2.

6.2.1 Day 1 of each cycle of chemotherapy (+/- 2 days)

Day 1 cycle 1 is defined as day first cabazitaxel treatment given, day 1 subsequent cycles the day treatment is given for that cycle.

On day 1 of each cycle of chemotherapy the following tests will be performed or recent results reviewed as indicated:

- Physical examination (including weight, pulse rate, blood pressure, temperature).
- Note on weight: dose should be adjusted if weight changes by > 5% of baseline value.
- Medical history (including performance status, assessment of all adverse events that have occurred since the previous visit and ongoing events from previous cycles, concomitant medications and other diagnoses)*
- Hematology (see section 6.1.2.2)*
- Biochemistry (see section 6.1.2.2)*
- Pregnancy test if menstruation cycle is prolonged beyond 28 days.

For cycle 1: as the original eligibility blood tests and patient assessments will have been performed prior to registration step2, they may be more than seven days old and if so will need to be repeated prior to day 1 of cycle 1. For that first cycle these tests must be available dating from a maximum of seven days prior to day 1 and must continue to meet eligibility criteria.

6.2.2 Days 8 and 15 during the first cycle of chemotherapy (+/-1 day)

- Physical examination (including pulse rate, blood pressure, weight, temperature)
- Medical history (including performance status, assessment of all adverse events that have occurred since the previous visit and ongoing events from previous cycles, concomitant medications and other diagnoses)
- Hematology (see section 6.1.2.2)
- Biochemistry (see section 6.1.2.2)
- Pregnancy test if menstruation cycle is prolonged beyond 28 days.

6.2.3 Every 12 weeks

Tumor assessments will be performed every 12 weeks using CT/MRI scans. Scans should include the chest, abdomen and pelvis and any site of known disease involvement elsewhere if not clinically measurable and judged relevant by local investigator as target lesion for response evaluation.

- All sites that were found to be involved at the initial assessment will be re-investigated by the same method.
- All lesions chosen as target lesions during the initial assessment will be measured by the same method and, if possible, by the same person.
- All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

The evaluation at 12 weeks after start of treatment is mandatory for all patients unless disease progression has been documented earlier.

At the end of the trial a central review will be organized (see section 1.1).

6.3 At the end of the treatment

The following will be performed within 30 days after the last treatment administration:

- Physical examination (including weight, pulse rate, blood pressure, temperature)
- Medical history (including performance status, assessment of all adverse events that have occurred since the previous visit and ongoing events from previous cycles, concomitant medications and other diagnoses)
- Hematology (see section 6.1.2.2)
- Biochemistry (see section 6.1.2.2)
- Pregnancy test if menstruation cycle is prolonged beyond 28 days.

6.4 After the end of treatment (Follow-up)

6.4.1 In case of discontinuation without progression

If discontinued for reasons other than progression, scheduled scans should continue to be performed every 12 weeks until progression.

For patients who withdraw due to toxicity/adverse event(s), appropriate follow-up will continue until any associated toxicity/adverse event(s) has been resolved.

6.4.2 In case of discontinuation due to progression

After disease progression, the patient should be followed every 3 months for survival and further antitumor therapy.

6.5 Summary table

	Registration step 1	Registration step 2			During Treatment			End of treatment[8]	After treatment	
Required Investigations		Within 28 days	Within 7 days	within 72 hrs	D1 each cycle	Cycle 1 D8 & 15	Every 12 wks		Discontinu-ation due to toxicity and until recovery	After progression every 12 wks
Informed consent	X[0]									
Histology (central pathology review)	X[1]									
Physical [2] examination and medical history[3]		X			X	X		X	X	
Haematology[4] and biochemistry[5]			X		X	X		X	♣	
Tumor assessment (CT/MRI[6])		X					X		X	
Pregnancy test[7]				X	X[7]	X[7]		X[7]		
Survival										X

X in all cases ♣ if clinically indicated

0. Before registration step 1 patient must have signed the consent form

1. Central pathology review: maximum 3 weeks from shipment to result (6.1.1).

2. To include: weight, pulse rate, blood pressure, temperature on day 1 of each cycle. Height only requested at baseline

3. To include: performance status, assessment of all adverse events that have occurred since the previous visit and ongoing events from previous cycles, concomitant medications, other diagnoses. At baseline, it includes also existing signs and symptoms.

4. To include: hemoglobin, granulocytes, platelets, note timelines for these bloods specified in section 6.2.1.

5. To include: urea, creatinine, CrCl, bilirubin, ALT and/or AST, alkaline phosphatase, albumin, note timelines for these bloods specified in section 6.2.1.

6. Scans should include chest, abdomen, pelvis and other known sites of disease involvement elsewhere if not clinically measurable and judged relevant as target lesion.

7. For women with childbearing potential: pregnancy test within 72 hours prior to the first dose of study treatment and at day 1 of each treatment cycle if menstruation cycle is prolonged beyond 28 days.

8. Tests performed within 30 days after the last treatment administration

7 Criteria of evaluation

7.1 Progression free survival at 12 weeks

The primary endpoint of the study is progression free survival at 12 weeks, measured as a binary variable, based on the locally assessed disease evaluation performed 12 weeks after start of treatment. Patients will be considered as "success" if this assessment indicates "stable disease" or a "response" as defined by RECIST v1.1 (see hereunder); all other cases will be considered as failures (including patients who have progressed, symptomatically deteriorated or died before the 12 week evaluation, patients with an unknown progression status at 12 weeks, or patients who started new anti-tumor therapy in the absence of progressive disease).

A central review for imaging will be organized at the end of the trial (see chapter 15.4).

7.2 Time to progression

Time to progression will be computed from the date of start of treatment to the first documented date of progression (measured according to the RECIST v1.1 - see hereunder) or death due to progressive disease, whichever occurs first. Patients free from progression at the time of analysis will be censored at the date of last follow-up.

7.3 Progression free survival

Progression free survival will be computed from the date of start of treatment to the first documented date of progression (according to RECIST v1.1 - see hereunder) or death, whatever the cause, whichever occurs first. Patients alive and free from progression at the time of the analysis will be censored at the date of last follow-up.

7.4 Overall survival

Overall survival will be computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis will be censored at the date of last follow-up.

7.5 Objective tumor response

Objective tumor response (CR + PR) will be measured according to RECIST v1.1 (see hereunder).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document (Ref. 20) also available at http://www.eortc.org/RECIST.

7.5.1 Measurability of tumor lesions at baseline

7.5.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and

have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Note: as DD liposarcoma commonly arises on a background of well differentiated liposarcoma, and as the latter well differentiated element can remain stable for prolonged periods without therapy, we recommend that when defining radiological measurable or target lesions per RECIST 1.1, especially in the region of the primary tumor mass if present, these should be chosen to include specifically the solid or higher density elements of the disease (which tend to correlate pathologically with the DD element), and not the low density fatty elements of the disease, which tend to correlate with the well differentiated element.

- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a *short* axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5 is to be calculated and recorded.

- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.5.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.

7.5.2 Tumor response evaluation

All patients will have their BEST RESPONSE from start of treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 3: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this category also requires**
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 12 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration*". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

7.5.2.1 Frequency of tumor re-evaluation

Tumor assessments will be performed at baseline, week 12 after start of treatment and every 12 weeks thereafter until progression. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 12 weeks, unless they have started a new anti-cancer therapy.

7.5.2.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met.

7.5.3 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

7.5.4 Time to onset of response

Time to onset of response will be measured from the date of start of treatment until the criteria for CR/PR (whichever is first recorded) are met.

7.5.5 Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that progressive disease is objectively documented.

7.6 Evaluation of safety

7.6.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

Only the worst grade per CTCAE category will be recorded per reporting period e.g. cycle.

The collection period will start from registration step1.

All adverse events must be followed until resolution or stabilization.

7.6.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page www.eortc.org\investigators-area\ctc.

The highest CTCAE grading per cycle and per patient will be computed at the EORTC HQ for analysis.

Planned safety analysis and tabulations are described in the statistics section.

7.6.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this PROTOCOL (see chapter on Reporting Serious Adverse Events)

7.6.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.6.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

Progression free survival at 12 weeks (taken as a binary indicator of success (i.e. progression-free at 12 weeks) or failure (i.e. dead or with progressive disease at or before week 12); see section 7.1) has been chosen as primary endpoint of the trial and was used to derive the sample size calculations described below.

The Simon optimal two-stage design will be used to test the null hypothesis H0: $P \leq P0$ versus HA: $P > P0$. The power and sample size is computed under the alternative hypothesis that $P = P1$. The following design characteristics and decision rules apply:

- P0 will be taken as 20% (the threshold to reject an inactive drug based on current knowledge) - success in ≤ 20% of the cases will be considered as unacceptable, and would not warrant further investigation.
- P1 will be taken as 40% (based on the expected success rate of an active drug) - success in ≥ 40% will be considered to definitively warrant further investigation of the drug in this histology.
- These two reference values are based on a retrospective analysis of the EORTC STBSG database of patients treated with 2nd line therapy (Ref. 19).
- Type I error and type II error are fixed at 10% (alpha = beta = 0.10).

Under those hypotheses, a total of 17 or 37 eligible patients will need to be treated and followed for the assessment of the primary end-point.

Two steps are planned. In step 1, 17 eligible and treated patients are required. If 3 or less successes are observed among these 17 patients, the trial will be stopped, with the conclusion that the drug should not be further investigated. Otherwise patients will continue to be accrued. For step 2, an additional 20 eligible

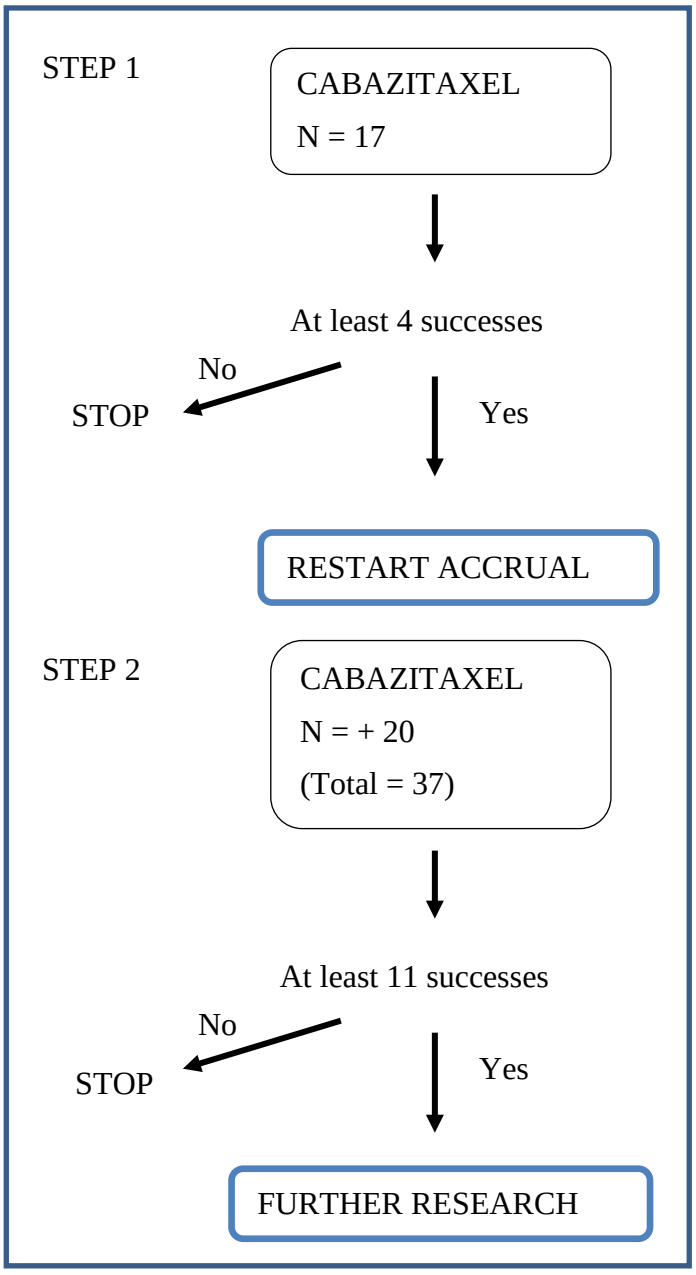
and treated patients are required (adding up to 37 patients). If 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation of the drug in this disease.

As patients will only be evaluable for the primary end-point 12 weeks after start of treatment, the accrual will be temporarily stopped after the inclusion of 19 patients, to allow for 10% of untreated or ineligible patients. Once 17 eligible and treated patients are assessable for the primary endpoint, a decision will be taken: either to restart accrual as soon as 4 successes are documented or to discontinue as soon as 14 failures are reported among the first 17 eligible and treated patients

In previous trials on liposarcoma performed at the EORTC (Ref. 15, Ref. 33) 20-25% of the patients were wrongly diagnosed according to a panel review. Therefore, taking into account ineligibility, untreated patients and screening failure at central review, up to 50 patients will be enrolled.

At the time of submission of this amendment (v3.0) to the protocol, 1 patient had started treatment with cabazitaxel. It is anticipated that the remaining number of patients will enter the study at the average rate of 1 patient/month during the first 3 months, 2 patients/month during months 4-6, and 3 patients/month thereafter. The duration of accrual is expected to vary between 10 months and 20 months from activation of this amendment (v3.0), if the results of the first step are promising (30-40 months from first patient in (FPI)). This is based on the assumption that that the accrual will be stopped for approx. 3 months to perform the evaluation of the first step.

The final analysis of the primary endpoint will be performed when all patients have been treated for at least 12 weeks and an evaluation of the disease has been performed and reported.


STEP 1
CABAZITAXEL
N = 17
At least 4 successes
No
STOP
Yes
RESTART ACCRUAL
STEP 2
CABAZITAXEL
N = + 20
(Total = 37)
At least 11 successes
No
STOP
Yes
FURTHER RESEARCH

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

Primary and secondary end-points are defined in the chapter "Criteria of evaluation".

8.2.2 Analysis populations

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

Consider the following analysis populations

- Per protocol population: All patients who are eligible and have started their allocated treatment (at least one dose of the study drug.
- Safety population: All patients who have started their allocated treatment (at least one dose of the study drug.

The evaluation of the decision rules will be based on the per protocol population at the end of each step: the 17 first eligible treated patients assessable for the primary end-point at the end of the first step and the 37 first eligible treated patients assessable for the primary end-point at the end of the second step.

The analysis of the activity and efficacy endpoints (progression free survival at 12 weeks, time to progression, progression free survival, overall survival and objective tumor response) will be based on the per protocol population. Furthermore, time to onset of response and duration of response will be based on those patients who achieved a documented objective response.

Analyses of safety end-points will be based on the safety population.

8.2.3 Statistical methods

The decision rules described in section 8.1.1 will be applied.

Progression free survival at 12 weeks after start of treatment will be taken as a binary indicator of success or failure (see section 7.1) and will be reported as a proportion with a conditional 95% confidence interval (Ref. 43).

The rate of objective tumor response (CR+PR) will be computed with its 95% confidence interval (from the exact binomial distribution). Patients in response categories progression, early death or unknown will be considered as failures. Time to onset of response and duration of response will be reported as median and range in days, in responding patients.

Time to progression, progression free survival and overall survival will be estimated by the Kaplan-Meier method. The full curve will be included in the report. Estimates at 3 months intervals will be tabulated with their standard error; median will be provided with its 95% confidence interval.

8.2.4 Pre-planned sensitivity or exploratory analyses

Patients are not expected to start any new anticancer treatment in the absence of documented progression. If this happens before the 12 weeks evaluation, patients will be considered as failure for the primary end-point. If this happens in more than 10% of the patients (at any time), two sensitivity analyses of PFS and time to progression will be carried out, a) considering the start of a new therapy as failure, and b) censoring the patient at the time of start of the new therapy.

8.2.5 Follow-up analyses

A follow-up analysis will be performed one year after the last patient entered the study to provide a more mature estimate of the time to event endpoints (time to progression, progression free survival and overall survival).

8.2.6 Data recoding and display

Frequencies will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the Case Report Forms (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of conformation of eligibility (date of conformation of eligibility – date of past event + 1) and presented using the median and range. For example, on the eligibility checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of conformation of eligibility on study (date of conformation of eligibility – last administration/diagnosis +1).

Other delays (eg. pre-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

The dose intensity of the treatments will be calculated on actual treatment dose received (mg/m^2 for cabazitaxel) and actual treatment duration (in weeks). The relative dose intensity will be calculated as the ratio of the actual dose intensity and the theoretical dose intensity indicated by the protocol, expressed in %. The dose intensity parameters will be presented using median and ranges.

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have either stopped protocol treatment

2. The trial is mature for the analysis of the primary end-point as defined in the protocol

3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Independent Data Monitoring Committee (IDMC) will review all safety problems identified by the EORTC Headquarters for which an advice is sought. Experts on the IDMC performing this review will be selected to have the relevant early trials/drug development expertise and will provide a review process independent of that of the Medical Review. In principle, no access to outcome data is necessary for safety reviews. However, the IDMC will also provide recommendations as an initial step in phase III trials to advise if a full review of all study data and endpoints is needed.

The EORTC IDMC is charged with the interim review (planned in the protocol or ad hoc) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Biobanking

10.1 Introduction

The Soft Tissue and Sarcoma Group is developing a research platform for liposarcoma tumors and would like to collect tumor material in order to conduct translational research projects aiming at detecting molecular targets to predict response to treatment and therefore to improve the strategy of treatment.

In this trial, tumor material will be collected to confirm the pathological diagnosis and for those patients who consented for future research, the material will be biobanked.

10.2 Material for biobanking

For biobanking the following material is requested:

- In case block is provided for the central review, if block is to be returned after the review, 10 slides will be cut before sending back the block, otherwise the entire block will be stored.
- In case slides are provided for the central review, 10 additional unstained slides of usual thickness (2-4 micron) on coated slides should be submitted with the material for the review.

The possible left-over from central review may also be kept for biobanking.

10.3 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Separate technical appendices will be jointly developed for each project. These appendices will be written before starting any analysis and will specify the analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be realized according to applicable procedures in each organization.

10.4 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

In this study, biological material will be first centralized and stored at laboratories of reference pathologists see chapter 15.3. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects defined in the future.

The following principles apply to storage of HBM:

- The collected HBM should be documented, i.e. the amount remaining and its location.

The Study Steering Committee (SSC) and the Soft Tissue and Bone Sarcoma Group committee will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a SSC, responsibilities of the SSC are transferred to the Group and/ or EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the SSC/Group committee. Additional expertise may be sought through advisory non-SSC/Group committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate SSC and Group committee.
- The SSC and the Group committee will prioritize the TR projects. Access procedures defined by the SSC and the Group committee will build on the following key points:
- Project prioritization
- Should be strongly based on scientific merit,
- Should consider the contribution of the different investigators to the trial and TR project,
- Will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
- Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still

retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.

- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once SSC and Group committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC and Group committee and the TR project leader(s), as needed.

11 Investigator authorization procedure

Investigators will be authorized to register patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of normal ranges for the investigator’s institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator’s institution.
- The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the CIF.

- The Study Agreement between EORTC and investigator's institution.A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- The full name, address, phone numbers and e-mail address of the local pathologist who will be responsible for sending tumor material, pathology reports and information on previous molecular analysis to reference pathologist.

- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to randomize patients in the trial as soon as

- All the above mentioned documents are available at the EORTC Headquarters.
- All applicable national legal and regulatory requirements are fulfilled.

Patient randomization from centers not (yet) included on the authorization list will not be accepted.

12 Patient registration & confirmation of eligibility

12.1 Registration/confirmation of eligibility of individual patients

Patient registration/confirmation of eligibility will only be accepted from authorized investigators (see chapter on "investigator authorization procedure").

Patients should be registered/confirmation of eligibility directly on the **EORTC online randomization system**
(ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to register patients via the EORTC call center. Registration/confirmation of eligibility via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet: http://orta.eortc.be/
In case of problems registration by phone: +32 2 774 16 00

A patient can only be registered after signature of the Patient Informed Consent

A patient can only be entered into the trial after verification of eligibility. The eligibility check must be done before the start of the protocol treatment.

12.2 Registration step 1

A short list of questions needs to be answered during the registration (step 1).

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1202
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics,* a unique code to help identify the patient within your institution)

- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- Local diagnosis of DD liposarcoma
- Availability for shipment of formalin-fixed, paraffin-embedded, tumor-containing tissue blocks for primary tumor and or metatastic site
- date of written informed consent (*day/month/year*)

Once eligibility has been verified, a **sequential patient identification number ("seqID")** will be assigned at the end of the registration step 1 procedure. The seqID will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

A patient who has not been registered at the EORTC before the first treatment administration will not be accepted for the study at a later date.

12.3 Central review of Pathology

This intermediate step has been introduced in the registration procedure, compared to the study design (2 steps) to allow automatic notification to investigators about the eligibility status of patients based on result of the central pathology review.

During registration step 1, tumor material will be sent for central review by the reference pathologist to confirm pathology/eligibility of the patient.

At the end of registration step 1, the investigators will be notified whether the patient can proceed to registration step 2.

12.4 Registration step 2

Patient eligibility checks will only be allowed after patient has been registered (step 1) and pathology of the patient is confirmed by EORTC HQ.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1202
- step number: 3
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics,* a unique code to help identify the patient within your institution)
- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- date foreseen for protocol treatment start

Once eligibility has been verified, the treatment will be started for the patient within 72 hours of the registration step 2.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE and pregnancy forms which are paper CRFs.

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be registered and eligibility confirmed in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one hour after the registration on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper SAE/pregnancy form which need to be signed and dated individually by the responsible investigator or one of his/her authorized staff members.

13.2 Data flow

The forms must be completed electronically, with the exception of the SAE and pregnancy forms according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

The data corrections will appear in the VISTA/RDC system and the EORTC data manager will subsequently apply the corrections into the database.

More details on the data flow can be found in the Guidelines for completion of Case Report Forms.

13.3 HBM* sample registration and tracking

Once the patient is registered, this procedure might take up to one hour, the investigator or his/her authorized staff must log on "Samples" website at https://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be

"Samples" is a web based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

14 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

14.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, AE as a result of an overdose, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

14.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.

- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference document:

- Cabazitaxel: Investigator's Brochure.

14.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the day the patient signed the Informed Consent until 30 days after last protocol treatment as specified in the table below. This procedure applies also for any SAE that occurs outside of the SAE detection period (as specified in table below), only if it is considered to have a reasonable possibility to be related to the investigational product or study participation (e.g. SAEs related to biopsy for tumor block, or to other screening procedure).

Signed Patient Informed Consent till study treatment started	Only SAEs related to study procedure (e.g. related to biopsy for tumor block, to screening procedure) or if it causes the subject to be excluded from the trial
From study treatment startedtill 30 days after last protocol treatment:	All SAEs
From day 31 after last protocol treatment:	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

14.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable.

The EORTC Pharmacovigilance Unit will take in charge the production and distribution of the DSUR as appropriate.

14.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

15.3 External review of histology

15.3.1 Forms

Two electronic "Pathology Review Forms" will be used for this review and will be available on the VISTA/RDC website (http://rdc.eortc.be or http://www.eortc.org/)

- Local Pathology Form will be completed by the site
- Central Pathology Review Form will be completed by the reference pathologist

15.3.2 Tumor material

Formalin-fixed, paraffin-embedded, tumor-containing tissue blocks from primary tumor and/or metastatic site should be available.

If block cannot be provided, the following should be submitted:

- For cases that will be reviewed in UK: 4 x 1 micron sections on coated slides, one thin H&E stained section and 20 unstained sections of usual thickness (2-4 micron) on coated slides.
- For cases that will be reviewed in France: 3 x 4 micron sections unstained (coated) slides for FISH and 15 unstained slides (4 micron) for immunohistochemistry.

15.3.3 Shipment of tumor samples

The local pathologist will send tumor material, his/her pathology report and information on previous molecular analysis (FISH results) to the reference pathologist. Personal data of the patient must be anonymized and replaced by the EORTC sequential identification number allocated to this patient at the time of registration.

- Copies of informed consent cannot be provided.
- Samples need to be logged on to the Samples website prior to shipment (see section 13.3).
- For procedures and contact details please refer to "Pathology guidelines".

15.3.4 Reference pathologist

- Will complete the Central Pathology Review Form
- For patient who did not consent for biobanking: the reference pathologists will return left- over tumor material to the sites after review.
- For patients having consented to biobanking: reference pathologists will store left-over tumor material after review. Refer to chapter 10.

15.3.4.1 List of reference pathologists

List of reference pathologists for the EORTC investigators is reported below

U. K. Belgium The Netherlands	C. Fisher Dept of Histopathology Royal Marsden Hospital - Chelsea, London Fulham Road 203 London SW3 6JJ Great Britain (United Kingdom) Email: cyril.fisher@rmh.nhs.uk Phone: +44 2078082631 Fax: +44 2078082578	France Italy	F. Collin Dept of Pathology Centre Georges-Francois-Leclerc 1, rue du Professeur Marion 21079 Dijon CEDEX France Email: fcollin@cgfl.fr Phone: +33 380737514 Fax: +33 380671915	Germany	G. Mechtersheimer Institute of Pathology Universitaetsklinikum Heidelberg – Kopfklinik Im Neuenheimer Feld 400 DE 69120 Heidelberg Germany Phone: +49 6221 5639909 Fax: +49 6221 565251 E-mail: gunhild.mechtersheimer@med.uni-heidelberg.de

15.4 Other central review procedures

15.4.1 Scan submission, Quality Assurance and Quality Control in imaging

The EORTC HQ will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Scans will be provided by the participating centers to the EORTC HQ. Please refer to the imaging guidelines for more details.

15.4.1.1 Central review

- A Blinded Independent Central Review (BICR) will be organized to review all scans. Centers are requested to submit all scans, which will be collected during the course of the study. The BICR will perform a central reading of all scans of all patients retrospectively.
- The BICR will remain blinded regarding the treatment group of the patients. Furthermore, the reviewers will be blinded regarding the site's assessment which will only be unblinded to the study coordinator.

16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

16.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data

- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

17 Administrative responsibilities

17.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

Richard Larry Hayward
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Crewe Road South
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Fax: +44 131 7773520
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17.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
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Fax: +32 2 7723545

17.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

EORTC Soft Tissue and Bone Sarcoma group

Chairman:

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18 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

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Financial support is provided by Sanofi and the EORTC Soft Tissue and Bone Sarcoma Group.

19 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

20 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.02 dated 19/03/2012.

The final publication of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

Rules of authorship will be applied according to the statutes of the EORTC STBSG. The title of all manuscripts will include “EORTC Soft Tissue and Bone Sarcoma Group”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies (NCI, cancer leagues, supporting company…).

Prior to submission, all publications (papers, abstracts, presentations…) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters and to all co-authors. They will also be submitted to Sanofi allowing a period of at least 30 days for review (at least 7 days for abstracts and poster presentations).

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

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Appendix B: Abbreviations

ADME	Absorption Distribution Metabolism Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate Aminotransferase
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BCRP	breast cancer-resistant protein
B.P.	Blood Pressure
BSA	Body Surface Area
CBZ	Cabazitaxel
CDK4	Cyclin-dependent Kinase 4
CHOP-TLS	Characteristic translocation of myxoid liposarcoma
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
Cmax	Maximum Concentration
CNS	Central Nervous System
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate use program
CV	Coefficient of Variation
CYP	Cytochrome P450
DD	De-differentiated
DLT	dose limiting toxicity
DTIC	Dacarbazine
EAP	Expanded access program
eGFR	Estimated Glomerular Filtration Rate
EM(E)A	European Medicines Agency

EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FISH	Fluorescent In-Situ Hybridisation
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factors
HDL	High-density-lipoproteïne
HR	Hazard Ratio
HQ	Headquarters
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IV	Intravenous
LDL	Low-density-lipoproteïne
LFT	Liver Function Tests
LS	Liposarcoma
Mdm2	Murine Double Minute oncogene 2
Mdr-1	Multidrug Resistance
MRI	Magnetic Resonance Imaging
MRP	multidrug-resistant protein
MTD	maximum tolerated dose
MTX	mitoxantrone
NYHA	New York Heart Association classification
ORR	Overall response rate
OR	Overall Response
ORTA	Online Randomized Trials Access
OS	Overall survival
PD	Progressive disease
PEG	Polyethylene Glycol
PET	Positron Emission Tomography
PFS	Progression free survival
P-gp	P-glycoprotein
PIS/IC	Patient Information Sheet/Informed Consent
PK	Pharmacokinetics
PR	Partial response

PS	Performance Status
PSA	Prostate Specific Antigen
PVC	Polyvinyl Chloride
QA&C	Quality Assurance and Control
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable disease
SeqID	Sequential Identification
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
STS	Soft Tissue Sarcomas
STBSG	Soft Tissue and Bone Sarcoma Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
Tmax	Time at which the Cmax is observed
Trt	Treatment
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
VISTA	Visual Information System for Trial Analysis
VLDL	Very-low-density-lipoproteïnen
Vss	Volume of distribution
WDLS	Well Differentiatied Liposarcoma
WHO	World Health Organization
WOCBP	Women of child bearing potential

Appendix C: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix D: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix E: CYP3A mediated interactions

1.1 List of potent CYP3A inhibitors

List of CYP3A Inhibitors

Precipitant	Therapeutic Class	Object (oral)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUC_r > 5)					
ritonavir	Protease Inhibitors	triazolam	**40.70**	16513448	2006 Mar
indinavir	Protease Inhibitors	vardenafil	**16.25**	NDA # 021400	2003 Aug
ketoconazole	Antifungals	midazolam[1]	**15.90**	8181191	1994 May
troleandomycin	Antibiotics	midazolam	**14.80**	15536460	2004 Dec
itraconazole	Antifungals	midazolam	**10.80**	8181191	1994 May
voriconazole	Antifungals	midazolam	**9.40**	16580904	2006 Apr
saquinavir / RIT	Protease Inhibitors	maraviroc	**9.23**	18333863	2008 Apr
mibefradil	Calcium Channel Blockers	midazolam	**8.86**	14517191	2003 Oct
clarithromycin	Antibiotics	midazolam	**8.39**	16432272	2006 Feb
lopinavir / RIT	Protease Inhibitors	aplaviroc	**7.71**	16934050	2006 Sep
nelfinavir	Protease Inhibitors	simvastatin	**6.07**	11709322	2001 Dec
telithromycin	Antibiotics	midazolam	**6.0**	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	midazolam	**5.95**	12953340	2003 Aug
conivaptan	Diuretics	midazolam	**5.76**	NDA # 021697	2005
nefazodone	Antidepressants	midazolam	**5.44**	14551182	2003 Nov
saquinavir	Protease Inhibitors	midazolam	**5.18**	10430107	1999 Jul

1.2 List of inducers of CYP3A isoenzymes

Amobarbital
Carbamazepine
Dexamethasone
Efavirenz
Modafinil
Nevirapine
Norethindrone
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifampicin
Rifapentin
Ritonavir
Secobarbital
St John's Wort
Troglitazone

Referenced using University of Washington database (May 2007)

Appendix F: Suggestions of protocols of intra-venous hydration for CT-scan with contrast (1), (2)

Intra-venous hydration at the time of CT-scan with contrast is recommended when creatinine clearance <60 mL/mn.

Step 1: identify the population at risk:

- all patients with an eGFR <60 ml/min/1.73 m^3,
- especially in diabetic and cardiovascular patients with eGFR <60 ml/min/1.73m^2.

(PS: eGRF is the estimated GFR from the EPI formula).

Step 2: stop NSAID the day before and the day of the radiocontrast examination and make sure that the patient is well hydrated (eventually diuretics "on hold" and additional fluid intake is advised - if medically possible)

Step 3 (advisable, not obligatory): the day before and the day of the radiocontrast examination, the patient is taking acetylcysteine 600 mg x 2 orally

Step 4: (write down for your radiologist to) use the lowest possible volume of (iso-/low-osmolar) radiocontrast.

Step 5: before the contrast examination IV fluid is started; oral hydration is not sufficient.

A/ Radiocontrast kidney injury prevention with isotonic NaCl 0.9%:

Prehydratation: IV NaCl 0.9% at 1 ml/kg/h during 12h before radiocontrast and during the radiocontrast examination

Posthydratation: continue IV same NaCl 0.9% at 1 ml/kg/h during 12h.

OR

B/ Radiocontrast kidney injury prevention with isotonic NaHCO3:

Prehydratation: prepare IV 850 ml GLU 5% + 150 mEq NaHCO3 and infuse at 3.5 ml/kg/h during 1h before radiocontrast and during the radiocontrast examination.

Posthydratation: IV same preparation 850 ml GLU 5% + 150 mEq NaHCO3 at 1 ml/kg/h during 6h.

OR

C/ Alternative scheme in case of "URGENT - Emergency" radiocontrast administration: IV NaCl 0.9% at 3 ml/kg/h during 1 h before and during the radiocontrast examination; continue IV NaCl 0.9% for 6-12h at 1 ml/kg/h after the radiocontrast examination. (PS: 6 h post only in patients in whom a sustained volume expansion is not possible).

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