The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma Following Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

Demetri, et al

DOI: 10.1200/JCO.2015.62.4734

Janssen Research & Development*

Clinical Protocol

A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma

Protocol ET743-SAR-3007; Phase 3

R279741 (trabectedin)

AMENDMENT INT-4

*YONDELIS, ET-743 (trabectedin), is being codeveloped by Janssen Research & Development, LLC pursuant to a licensing arrangement with Pharma Mar, S.A. Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Issue/Report Date: 12 November 2014
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-14393045:5.0

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

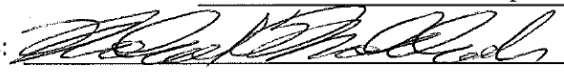
Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Roland Knoblauch, MD, PhD

Institution: Janssen Research & Development LLC

Signature:  Date: 10 Nov 2014

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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PROTOCOL AMENDMENTS

Original Protocol issued 20 October 2010.

Amendments are listed beginning with the most recent amendment.

Amendment INT-4 (11 November 2014)

The overall reason for the amendment: The overall reason for the amendment is to add an optional extension phase (OEP) to the protocol and to allow subjects randomized to the dacarbazine group the option to have access to trabectedin. Although the study is continuing for final OS analysis, the Sponsor feels an improved clinical benefit has been demonstrated with trabectedin over dacarbazine, and the option of trabectedin therapy for those subjects randomized to the dacarbazine group is warranted. Subjects must be in the treatment or follow up phase of the study, and meet eligibility criteria. If trabectedin becomes commercially available, it is expected that any ongoing subjects be switched over to the commercially available supply within 3 months. The Sponsor will make drug available up to 3 months after it becomes commercially available The study can be closed any time at the sole discretion of the Sponsor.

Applicable Section(s)	Description of Change(s)
Rationale: To add OEP to allow subjects to have access to trabectedin after being randomized to dacarbazine.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 5 Treatment Allocation; 9.1.1 Overview; 9.1.5 Optional Extension Phase	This phase was referenced and details, including data collection during this phase and new criteria for the study close, were added or clarified in all relevant sections.
Rationale: To clarify cross-over conditions	
9.1.3 Treatment Phase	A statement about disallowing a cross over to trabectedin was removed.
Rationale: To clarify inclusion/exclusion criteria in OEP	
9.1.5 Inclusion/Exclusion Criteria	Documentation for Inclusion criteria #2 and #3 do not need to be reviewed by Sponsor. Collection of the specimen described in inclusion criterion # 5 is not applicable. Documentation of inclusion criteria # 8 and #9 will be reviewed by the sponsor before enrollment on OEP may occur. Exclusion #1 does not apply. Exclusion # 9 with reference to dacarbazine does not apply. Exclusion criterion #2 was modified to specify subjects who are less than 3 weeks from systemic anticancer therapy are not eligible.
Rationale: Minor edits were made.	
Throughout the protocol	Minor revisions were made including changes in wording, added text, and grammatical and formatting changes.

Amendment INT-3 (12 January 2012)

The overall reason for the amendment: The overall reasons for this amendment were to revise the criteria for subject inclusion and to clarify the conditions for the continuation of dosing.

Applicable Section(s)	Description of Change(s)
Rationale: Due to the change in inclusion criteria, the study title was changed.	
Title page; Synopsis	The following text was deleted from the title: "Previously Treated with an Anthracycline and Ifosfamide".
Rationale: To update the company name.	
Title page	Johnson & Johnson Research & Development L.L.C. was changed to Janssen Research & Development, LLC. The names of the various legal entities were updated accordingly.
Rationale: Inclusion criterion #1 was revised to clarify the age of subjects at screening.	
Synopsis, Overview of Study Design, Study Population; Section 3, Overview of Study Design; Section 4.2, Inclusion Criteria	Inclusion criterion #1 was changed from 15 years of age or older to 15 years of age or older at the time of screening.
Rationale: Inclusion criterion #3 was revised to increase subject enrollment. The inclusion criterion is still based on standard chemotherapy for L-sarcoma.	
Synopsis, Primary Objective, Hypothesis, Overview of Study Design, Study Population; Section 2, Objectives, Primary Objective, Hypothesis; Section 3, Overview of Study Design; Section 3.1, Study Design; Section 3.2, Study Design Rationale; Section 4.1, General Considerations; Section 4.2, Inclusion Criteria	Inclusion criterion #3 was changed from "Treated with an anthracycline and ifosfamide administered either in combination or as sequential regimens" to Treated in any order with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.
Rationale: For clarity, text was revised to include the collection of a biopsy during screening for those potential subjects where a pathology specimen (eg, FFPE tumor block or unstained slides) is not available.	
Time and Events Schedule Footnotes	Text was revised to note that where a pathology specimen (eg, FFPE tumor block or unstained slides) is not available, a biopsy may be conducted to during screening to obtain a specimen.

Applicable Section(s)	Description of Change(s)
Rationale: For clarity, inclusion criterion #9 was revised.	
Section 4.2, Inclusion Criteria	The text regarding acceptable ALP limits was revised to "ALP ≤2.5 X ULN: if the ALP is >2.5 X ULN, then an ALP liver fraction or 5' nucleotidase must be obtained and ≤ULN".
Rationale: For clarity, inclusion criterion #11 was revised to specify the reproductive precautions to be taken by women before study entry, throughout the study, and for 3 months thereafter.	
Section 4.2, Inclusion Criteria	The text regarding reproductive precautions for women was revised to state "Female subjects must be postmenopausal (no spontaneous menses for at least 2 years), surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), abstinent (at the discretion of the investigator), or if sexually active, be practicing an effective method of birth control (eg, prescription hormonal contraceptive, intrauterine device, double-barrier method [eg, condoms and occlusive cap (diaphragm or cervical/vault caps)] with spermicidal foam, cream, gel, film, suppository), before entry, and must agree to continue to use the same method of contraception throughout the study and for 3 months thereafter."
Rationale: For clarity, text throughout the protocol was revised or added to reflect the informed consent/assent of subjects 15 years of age and up to the age of legal consent in the jurisdiction in which the study is to take place.	
Synopsis, Overview of Study Design; Time and Events Schedule (including footnotes); Section 3.1, Study Design; Section 4.2, Inclusion Criteria; Section 9.1.1, Overview; Section 9.1.2, Screening Phase; Section 9.1.3, Treatment Phase; Section 10.2, Discontinuation of Treatment; Section 10.3, Withdrawal From the Study; Section 16.1, Study Specific Design Considerations; Section 16.2.2, IEC or IRB; Section 16.2.3, Informed Consent; Section 16.2.4, Privacy and Personal Data; Section 17.2.2, Required Prestudy Documentation	Subject consent/assent was added to the screening procedures. Inclusion criterion #12 was revised accordingly. Study specific considerations and informed consent procedures were revised to include a legally-acceptable representative for subjects 15 years of age and up to the age of legal consent in the jurisdiction in which the study is to take place.

Applicable Section(s)	Description of Change(s)
Rationale: Text was added to specify the criteria that subjects undergoing de-bulking surgery must meet in order to continue study treatment	
Section 4.4, Prohibitions and Restrictions	Text was added to indicate that if a decision is made to undertake de-bulking surgery during study treatment, the principal investigator at the site should discuss the case with the medical monitor prior to the surgery. Thereafter, 4 specific criteria must be met in order for the subject to continue treatment with the study medication after surgery. These criteria were added to the study protocol.
Rationale: Additional instructional text was provided for clarity.	
Section 6.1, Dosage	The following text was added "If a subject cannot tolerate 20 mg of dexamethasone, please contact the medical monitor."
Rationale: Additional text provided to clarify conditions for the continuation of dosing.	
Section 6.2, Criteria for Continuation of Treatment	Text was added and modified regarding anemic subjects, subjects with liver function test abnormalities, and subjects receiving benefit from the study treatment. Specific conditions for discontinuing treatment, continuing treatment, or modifying treatment were added.
Rationale: Additional text provided to clarify the criteria for dose reductions due to nonhematologic toxicity.	
Section 6.3.2, Dose Reductions Due to Nonhematologic Toxicity and Table 5	Text was added and modified regarding subjects with liver function test abnormalities. Table 5 was revised accordingly to match the text.
Rationale: The definition of progression free survival (PFS) was revised based on RECIST (Version 1.1) criteria, which allow disease progression to be determined by symptomatic deterioration.	
Section 9.2.2.2, Secondary Endpoints	The definition of progression free survival was changed from "the time from randomization to the occurrence of radiographic disease progression or death, whichever occurs first" to "the time from randomization to the occurrence of disease progression or death, whichever occurs first".
Rationale: To a safety alert for the handling of dacarbazine.	
Section 14.4, Preparation, Handling, and Storage	The following text was added: "Dacarbazine is a cytotoxic anticancer medicinal product, and caution should be exercised during handling.
Rationale: Text regarding country selection was modified for clarity.	
Section 16.2.5, Country Selection	The following text was changed from "this study will only be conducted in those countries where the intent is to help ensure access to the developed product" to "this study will only be conducted in those countries where trabectedin is not approved for the treatment of soft tissue sarcoma".
Rationale: To ensure subject confidentiality, text was edited to remove the reference to subject initials.	
Section 17.3, Subject Identification, Enrollment, and Screening Logs	The term "initials" was removed from the following sentence "All reports and communications relating to the study will identify subjects by assigned number only".

Applicable Section(s)	Description of Change(s)
Rationale: Text was deleted for clarity.	
Section 17.4, Source Documentation	The following bullet was deleted "History of all nicotine use, eg, cigarettes, cigars, chewing tobacco, patch, gum".
Rationale: To provide the most recent version of the MDASI form.	
Attachment 2	The 1999 version was replaced with the 2000 version.
Rationale: To provide minor clarifications to the Time and Events Schedule	
Time and Events Schedule	It was clarified (schedule marked) that adverse events and concomitant medications should be collected every 6 for 36 weeks; then every 9 weeks until PD. Text was added to footnote "d" indicating that BSA may be calculated during screening for ordering vials of drug. Screening for inclusion and exclusion criteria was added.
Rationale: Minor edits were made.	
Throughout the protocol	Minor revisions were made including changes in wording, added text, and grammatical and formatting changes. IVRS was expanded to include IWRS. The units of measure for inclusion criterion 8 were corrected.

Amendment INT-2 (24 June 2011)

The overall reason for the amendment: The overall reasons for the amendment are to highlight that every assessment of disease status will be conducted consistently and on schedule and should include radiographic imaging of the chest (with lung views), abdomen, and pelvis; and to provide clarification to the dosing instructions for subjects with liver laboratory abnormalities as noted in Section 6.2, Criteria for Continuation of Treatment. Section 6.2 was updated to indicate that subjects experiencing liver abnormalities that include all of the following within the same cycle should discontinue treatment: bilirubin ≥2 x upper limit of normal [ULN], transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) ≥3 x ULN, and alkaline phosphatase [ALP] ≤2 x ULN; unless there is evidence of benefit (eg, tumor shrinkage, disease stabilization) and the subject recovers within 3 weeks. In addition, clarification was provided for the following: the timing of evaluations and procedures, inclusion criteria, and exclusion criteria.

Applicable Section(s)	Description of Change(s)
Rationale: Text deleted and added regarding the Sponsor name and the legal entity for the local operating company, respectively.	
Title page	The following text was deleted "Ortho Biotech Oncology Research and Development, a Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C", and the following text was added "Janssen Research & Development". In addition, a footnote regarding the Janssen Research & Development organization was added.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification regarding assessment of disease status using radiographic techniques.	
Synopsis Overview of Study Design; Time and Events Schedule Footnotes; Section 3.1 Study Design; Section 9.1.2 Screening Phase; Section 9.2.1.2 Disease Assessment	Text added specifying that radiographic imaging of the disease should include radiographic images of the chest (with lung views), abdomen, and pelvis.
Time and Events Schedule; Section 3.1 Study Design; Section 9.2.1.2 Disease Assessment	Text added specifying that radiographic imaging of the disease is to be consistent and on schedule.
Rationale: Clarification regarding the timing of the placement of a central venous catheter, when applicable.	
Synopsis Dosage and Administration; Section 3.1 Study Design	Text was revised to indicate that if a subject does not already have a central venous catheter or central venous access is not in place, placement of a central venous catheter may be performed during the 96-hour period permitted between randomization and the first dose of trabectedin.
Rationale: Clarifications regarding the dosing window of each 21-day treatment cycle and for laboratory evaluations on Days 8 and 15.	
Synopsis Dosage and Administration; Time and Events Schedule Footnotes; Section 3.1 Study Design; Section 6.1 Dosage	Added dosing window of up to +2 days, with each treatment cycle being at least 21 days apart.
Synopsis Safety Evaluations; Time and Events Schedule Footnotes; Section 3.1 Study Design; Section 9.5 Safety Evaluations	Added ±2 days to the blood sample collection window for hematology and chemistry evaluations on Days 8 and 15 of each treatment cycle.
Rationale: Clarification regarding the dacarbazine (DTIC) infusion time.	
Synopsis Dosage and Administration; Time and Events Schedule; Section 3.1 Study Design; Section 5 Treatment Allocation; Section 6.1 Dosage	The DTIC infusion time was changed from 20 minutes to 20-120 minutes.
Section 6.1 Dosage	Added references supporting the 20-120 minute infusion time
References	Added the Oncology Dilution Database 2011 reference to the reference list to support the 20-120 minute infusion time.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications for inclusion criterion #2 regarding eligible subtypes of metastatic liposarcoma and for exclusion criterion #5 regarding subjects with liver disease.	
Synopsis Study Population; Section 4.1 General Considerations; Section 4.2 Inclusion Criteria	Text added regarding the eligible subtypes of metastatic liposarcoma: dedifferentiated, myxoid round cell, or pleomorphic.
Section 4.3 Exclusion Criteria	Potential subjects with known significant chronic liver disease, such as cirrhosis or active hepatitis (potential subjects who test positive for hepatitis B surface antigen or hepatitis C antibodies are allowed provided they do not have active disease requiring antiviral therapy) are to be excluded.
Rationale: Clarification provided regarding disease assessments in subjects who discontinue study drug before disease progression occurs.	
Time and Events Schedule; Synopsis Overview of Study Design; Section 3.1 Study Design; Section 9.1.3 Treatment Phase; Section 9.2.1.2. Disease Assessment	Text was revised to reflect: that subjects who discontinue study drug before disease progression occurs will continue to have assessments of disease status until disease progression or subsequent therapy; and that whenever possible, subsequent therapy should only be started after disease progression has been documented.
Rationale: Clarification regarding multiple gated acquisition scans (MUGA).	
Synopsis Safety Evaluations; Time and Events Schedule; Section 3.1 Study Design	Text was added, were appropriate, to indicate that echocardiograms may be used if MUGA is not available.
Rationale: Clarifications regarding the timing of pre-randomization activities.	
Time and Events Schedule Footnotes; Section 9.1.2 Screening Phase	Text added specifying that informed consent is to be obtained within 30 days before randomization.
Time and Events Schedule Footnotes; Section 3.1 Study Design; Section 9.1.2 Screening Phase	Text added to specify that screening assessments must be completed within 14 days before randomization.
Time and Events Schedule Footnotes; Section 3.1 Study Design; Section 9.1.2 Screening Phase; Section 9.2.1.2 Disease Assessment	Text added specifying that during the screening phase radiographic disease assessments, MUGA scans, and ECGs must be performed within 30 days before randomization.

Applicable Section(s)	Description of Change(s)
Rationale: To indicate changes in the source documentation for trabectedin and dacarbazine..	
Section 6.1 Dosage; Section 14.4 Preparation, Handling, and Storage	Text regarding pharmacy manuals was deleted. Where appropriate, it was noted that the source document for the preparation, storage, and handling of trabectedin will be the Investigator Brochure and the source document for dacarbazine study drug will be the prescribing information.
Section 1.1 Background; References	Citations to the dacarbazine package insert were changed to the prescribing information.
Rationale: Clarification of dosing instructions for subjects with liver laboratory abnormalities**.**	
Section 6.2 Criteria for Treatment Continuation; Section 9.5 Safety Evaluations, Clinical Laboratory Tests	Text added to specify that subjects experiencing liver abnormalities that include all of the following within the same cycle should discontinue treatment: bilirubin ≥2 x ULN, transaminases (ALT or AST) ≥3 x ULN, and ALP ≤2 x ULN; unless there is evidence of benefit (eg, tumor shrinkage, disease stabilization) and the subject recovers within 3 weeks.
Rationale: Clarification provided regarding the use of colony stimulating factors.	
Section 6.3.1 Dose Reductions Due to Hematologic Toxicity; Section 8 Prestudy and Concomitant Therapy	Text prohibiting the use of colony stimulating factors during Cycle 1 was deleted and revised to indicate that colony stimulating factors may be used according to institutional or ASCO Guidelines (ASCO 1999b).
Rationale: Clarification regarding the number of unstained slides.	
Section 9.1.2 Screening Phase	The exact number of unstained slides was deleted.
Rationale: Clarification to the ALP liver fraction and 5' nucleotidase evaluations.	
Section 9.5 Safety Evaluations Clinical Laboratory Tests	Text changed to indicate that if ALP is >2.5 x ULN, then ALP liver fraction or 5' nucleotidase should be measured.
Rationale: Clarification regarding the infusion pumps provided.	
Section 14.4 Preparation, Handling, and Storage	Specific examples of infusion pumps were deleted.
Rationale: To update the list of supplies to be provided.	
Section 15 Study Specific Materials	The list of supplies to be provided to the Investigators was updated. The list now includes: e-CRFs, Site Investigational Product Binder, PRO questionnaire, Laboratory supplies to process samples that will be sent to the central laboratory including study manual, Pharmacogenomic sample collection and shipping instructions; and IVRS manual and codes.
Rationale: Text regarding the timing of data entry was deleted.	
Section 17.5 Case Report Form Completion	The exact timeline for data entry was deleted.
Rationale: Clarification regarding the handling of dacarbazine was added.	
Section 14.4 Preparation, Handling, and Storage	Text was added to specify that dacarbazine is light sensitive.

Applicable Section(s)	Description of Change(s)
Rationale: Minor clarifications or errors were noted, and minor formatting changes were made.	
Throughout the protocol	Minor spelling or typographical changes were made. Trailing zeros were deleted from numerical values. Changes related to the consistent use of defined abbreviations were made. Minor changes in formatting were made.

Amendment INT-1 (9 December 2010)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to revise the inclusion and exclusion criteria; to clarify that subjects whose disease has progressed and are in the dacarbazine (DTIC) arm may not cross over and receive trabectedin; and to add additional text regarding the documentation and review by investigators for subjects who may be experiencing the adverse event of sepsis.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of specific inclusion and exclusion criteria	
Synopsis Study Population; Section 4.2 Inclusion Criteria; Section 3 Overview of Study Design;	Inclusion criteria of age was changed from being 18 to 15 years of age and older.
Section 4.3 Exclusion Criteria	The following text thought to be confusing was deleted from the exclusion criteria: "has progressed on ALL prior therapy."
Rationale: Clarification that subjects who are in the dacarbazine treatment group may not cross over to receive trabectedin if they experience disease progression.	
Section 9.1.3 Treatment Phase	Text was added identifying that subjects who are randomized to the dacarbazine treatment group, if they experience disease progression may not cross over to receive trabectedin.
Rationale: To have a proactive review and documentation of the adverse event of sepsis by study investigator**s.**	
Section 9.5 Safety Evaluations	Additional text was added to include "Potential cases of sepsis will be thoroughly investigated. Investigators will complete a supplemental CRF section and provide additional supporting documentation for all subjects who experience the adverse event of sepsis."
Rationale: Minor typo was noted	
Introduction Section: Efficacy of Trabectedin in Soft Tissue Sarcoma	Deleted the word VELCADE and replaced with the word trabectedin

SYNOPSIS

A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma

YONDELIS® (trabectedin, ET-743) is a tris, tetrahydroisoquinoline alkaloid initially isolated from the marine ascidian ecteinascidin turbinate. It has a unique mechanism of action that involves the transcription dependent nucleotide excision repair system and is currently under development as an antineoplastic agent. Trabectedin has been approved in the European Union and other countries outside the United States for the treatment of soft tissue sarcoma (STS) and ovarian cancer.

OBJECTIVES

Primary Objective

The primary study objective is to evaluate whether overall survival (OS) for the trabectedin group is superior to the dacarbazine group for subjects with advanced L-sarcoma (liposarcoma or leiomyosarcoma) who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Secondary Objectives

Secondary objectives are to evaluate progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), symptom severity, and safety in the trabectedin group and dacarbazine group.

Hypothesis

Trabectedin treatment will improve OS compared with dacarbazine for subjects with advanced L-sarcoma who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine among adults (15 years of age and older at the time of screening) with unresectable, locally advanced or metastatic L-sarcoma, who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. The intent of the study is to determine whether trabectedin treatment is superior to dacarbazine treatment with regard to OS. The study will consist of 4 phases: Screening, Treatment, Follow-up, and Optional Extension.

During the Screening Phase, potential subjects will be assessed for study eligibility after providing informed consent/assent to participate in the study. Baseline radiographic disease assessments, including radiographic imaging of the chest (with lung views), abdomen, and pelvis, must be performed within 30 days before randomization. Approximately 570 subjects who satisfy all inclusion and exclusion criteria will be randomly assigned in a 2:1 ratio to either the trabectedin (n≈380) or dacarbazine (n≈190) treatment groups. Before randomization, subjects will be stratified by the number of lines of prior chemotherapy (1 versus 2 or more), Eastern Cooperative Oncology Group (ECOG) Performance Status score (0 versus 1), and L-sarcoma subtype (liposarcoma versus leiomyosarcoma).

During the Treatment Phase, subjects will receive study drug on Day 1 of each 21-day cycle. A subject will continue to receive study drug until there is documented disease progression or unacceptable toxicity. Disease response will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) guidelines. Radiographic assessment of disease, including radiographic imaging of the chest (with lung views), abdomen, and pelvis, will be performed every 6 weeks for the first 36 weeks on study and every 9 weeks thereafter, until disease progression occurs, the subject begins subsequent anticancer therapy, the study ends, or the subject dies. Subsequent therapy should only be started after disease progression has been documented. All adverse events will be reported from the time a subject (or a legally-acceptable representative) provides signed informed consent until 30 days after the subject's last dose of study drug.

During the Follow-up Phase, subjects will be monitored for survival status and the start of subsequent anticancer therapy at least every 60 days for the first 2 years after the last dose of study drug and every 90 days thereafter, until approximately 376 deaths have been observed. Subjects who discontinue study drug before disease progression occurs (eg, subjects who discontinue treatment due to unacceptable toxicity) should continue to have radiographic assessments of disease until disease progression or subsequent therapy. Whenever possible, subsequent therapy should only be started after disease progression has been documented.

Only those subjects who were randomized to the dacarbazine treatment group and are currently in treatment phase or follow-up phase will be eligible, at the investigator's discretion, for enrollment on the OEP. During this OEP subjects will be monitored for survival status, until clinical cutoff for final overall survival.

After the clinical cutoff date, only serious adverse events will be collected as described in Section 12.2.2, up to 30 days after last dose of study treatment for subjects still receiving study drug in the treatment phase or OEP.

An Independent Data Monitoring Committee (IDMC) will review the results of an interim analysis of OS, which will occur after approximately 188 deaths have been observed. The final OS analysis will be conducted when approximately 376 deaths have been observed.

Subsequent updates to the clinical study report will be provided as appropriate.

STUDY POPULATION

Eligible subjects must fulfill all study inclusion and exclusion criteria. Subjects will be 15 years of age and older at screening, with a documented histopathologic diagnosis of unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma, who have been treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. A pathology specimen (eg, formalin-fixed paraffin-embedded [FFPE] tumor block or unstained slides), to be archived for possible review of diagnosis and biomarker evaluation, must be submitted for each subject.

DOSAGE AND ADMINISTRATION

Study treatment occurs on Day 1 of each 21-day cycle (ie, each treatment cycle being at least 21 days apart) as follows:

- Trabectedin Group: 1.5 mg/m^2 as a 24-hour i.v. infusion once every 3 weeks (q3wk 24-h). A central venous catheter must be used to administer study drug to subjects in the trabectedin group. If a subject does not already have a central venous catheter or central venous access is not in place, placement of a central venous catheter may be performed during the 96-hour period permitted between randomization and the first dose of study drug. Subjects will be pretreated with 20 mg of dexamethasone i.v. (or the equivalent) on Day 1 of each treatment cycle, 30 minutes before study drug. A dosing window of up to +2 days will be allowed. Within the OEP, dosing will proceed along the same guidelines; catheter placement is mandatory prior to first dose, however timing of catheter placement is at the physician's discretion.
- Dacarbazine Group: 1 g/m^2 as a 20-120 minute i.v. infusion once every 3 weeks. A dosing window of up to +2 days will be allowed.

Investigators will review physical findings and the results of clinical laboratory tests before each dose of study drug and, if required, delay administration or reduce the dose according to predefined guidelines.

EFFICACY EVALUATIONS/CRITERIA

Survival status will be monitored throughout the study and will be used to calculate OS, the primary study endpoint. Investigators will assess disease response according to RECIST Version 1.1 guidelines.

Investigator assessment of these data will be used to calculate PFS, TTP, ORR, and duration of response (DR).

BIOMARKER AND PHARMACOGENOMIC EVALUATIONS

Biomarker evaluations will be performed using the required pathology specimen (eg, FFPE tumor block or unstained slides). A whole blood sample (10 mL) will be collected for pharmacogenomic research, as necessary (where local regulations permit).

SAFETY EVALUATIONS

The incidence and severity of adverse events will be assessed for all subjects who receive study drug. Clinical laboratory test results will be evaluated before dosing on Day 1 of each cycle. Blood samples will also be collected for clinical laboratory testing on Days 8 (±2 days) and 15 (±2 days) of each cycle and at the end of treatment. Electrocardiograms (ECG) and multiple gated acquisition scans (MUGA) (or echocardiograms if MUGA is not available) will be performed at baseline (within 30 days before randomization) and at the end of treatment to assess cardiac function.

The IDMC will assess safety data approximately every 3 to 4 months during the study.

STATISTICAL METHODS

Sample Size Justification

It was assumed that the hazards for the 2 treatment groups follow a proportional hazards model for OS. The test to detect a difference between a median OS of 10 months in the dacarbazine group and a median OS of 13.5 months in the trabectedin group (hazard ratio [HR]=0.74) at the 2-sided significance level of 0.05 with a power of 80% requires 376 events. Assuming an enrollment rate of 25 subjects per month over 23 months, a total sample size of approximately 570 subjects is planned for the study.

Primary Efficacy Endpoint

OS is defined as the time between randomization and death due to any cause. The primary analysis of OS is the comparison between the 2 treatment groups using the unstratified log-rank test. The distribution of OS will be estimated for each treatment group using the Kaplan-Meier method. The effect of prognostic factors such as age, lines of prior chemotherapy, ECOG Performance Status score, and L-subtype will also be examined in the supplementary analysis using the Cox proportional hazards model.

TIME AND EVENTS SCHEDULE

Assessment/ Activity	Screening[a] Phase	Each Treatment Cycle				Every 6 wks for 36 wks; then every 9 wks until PD	Treatment Discontinuation[b]	Follow-up Phase
		Day 1	Day 2	Day 8	Day 15			
Informed consent/assent	X							
Inclusion and exclusion criteria	X							
Medical history	X							
Physical examination[c]	X							
Vital signs[c]	X							
Body surface area (BSA)[d]		X						
ECOG Performance Status	X						X	
MUGA[e]/ECG	X[f]						X	
Adverse events[c]	X	X	X	X	X	X	X	X[g]
Concomitant medications	X	X	X	X	X	X	X	
LABORATORY								
Hematology	X	X[h]		X[i]	X[i]		X	
Chemistry and liver panels	X	X[h]		X[i]	X[i]		X	
Urine pregnancy test[j]	X							
Pharmacogenomic blood sample (10 mL)[k]		X						
Archived tumor sample[l]	X							
PREMEDICATION								
Dexamethasone 20 mg i.v.		X[m]						
STUDY DRUG ADMINISTRATION								
YONDELIS i.v. formulation 1.5 mg/m^2, 24-hour infusion		X[n]						
DTIC 1 g/m^2, 20-120 minute infusion		X[n]						
PATIENT REPORTED OUTCOMES								
MDASI questionnaire		X[o]					X[o]	
EFFICACY								
Tumor measurements	X[f]					X[p]	X	X[q]
Survival status / anticancer therapy								X[r]

BSA=body surface area; DTIC= dacarbazine; ECG=electrocardiogram; MDASI= M.D. Anderson Symptom Inventory; MUGA=multiple gated acquisition scan; PD=progressive disease; wks=weeks.

[a] Informed consent/assent is to be obtained within 30 days before randomization. Complete screening assessments within 14 days before randomization, except as noted for MUGA/ECG and tumor measurements (footnote "f"). Echocardiogram can be used if MUGA is not available (footnote "e").

[b] End-of-Treatment Visit should be performed within 4 weeks after the last dose of study drug and will document adverse events that occur within 30 days after the last dose of study drug.

[c] Document any clinically significant abnormal change in physical findings, including vital signs and ECOG Performance Status score, as an adverse events. PD should not be reported as an adverse event.

[d] BSA may be calculated during screening for ordering vials of drug. It is not necessary to recalculate BSA each cycle unless required to comply with institutional guidelines or a subject has a weight gain or loss >10% of body weight. For obese subjects (body mass index [BMI] >30), calculate BSA using the ideal body weight throughout the study.
[e] Echocardiogram can be used if MUGA is not available. The same procedure should be used for the screening and end-of-treatment evaluations.
[f] Obtained within 30 days before randomization.
[g] Record adverse events that occur within 30 days after the date of the last dose of study drug. Drug-related Grade 3 or Grade 4 toxicities will be monitored until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first. Grade 2 - 4 liver or cardiac toxicities will be monitored until Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first.
[h] Laboratory results must be obtained within 48 hours before dosing.
[i] To be completed on Day 8 (±2 days) and Day 15 (±2 days).
[j] Only for women of child bearing potential who are sexually active.
[k] Only for subjects who are eligible for the study and who provide separate informed consent/assent to participate in the pharmacogenomic analyses.
[l] Tumor specimen (eg, unstained slides or FFPE tumor block) will be collected before randomization. The specimen will be archived for possible review of diagnosis and biomarker analysis. In the event a pathology specimen is not available, a biopsy may be conducted during screening to obtain a specimen.
[m] Only for subjects in the trabectedin group. Administer 30 minutes before study drug.
[n] Study drug administration: Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (with each treatment cycle being at least 21 days apart). Results of all clinical laboratory assessments must be known before study drug is administered.
[o] Patient reported outcomes questionnaire should be completed on Day 1 of each treatment cycle and as part of the end-of-treatment evaluations before any other tests or procedures.
[p] Perform disease assessments using the same radiographic technique (CT scans or MRI) every 6 weeks for the first 36 weeks on study and every 9 weeks, thereafter. The disease assessments should include radiographic imaging of the chest (with lung views), abdomen, and pelvis.
[q] If disease progression has not occurred at the time of treatment discontinuation, continue radiographic assessments until there is evidence of disease progression or until the start of first subsequent anticancer therapy, whichever is earlier.
[r] Survival follow-up should occur at least every 60 days for the first 2 years after the last dose of study drug and then every 90 days, thereafter, until the end of the study.

ABBREVIATIONS

ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
BSA	body surface area
CI	confidence interval
CPK	creatine phosphokinase
CR	complete response
CRF	case report form (paper or electronic as appropriate for this study)
CSF	colony-stimulating factors
CT	computed tomography
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EORTC STBSG	European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group
FFPE	formalin-fixed paraffin-embedded
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
GCP	Good Clinical Practice
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MDASI	M.D. Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scans
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria of Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
qwk 3-h	weekly, 3-hour
q3wk 24-h	every-3-weeks, 24-hour
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
STS	soft tissue sarcoma
TTP	time to progression
ULN	upper limit of normal

1. INTRODUCTION

YONDELIS® (trabectedin, ET-743) is a tris, tetrahydroisoquinoline alkaloid initially isolated from the marine ascidian ecteinascidin turbinate. Trabectedin is an antineoplastic agent that has been approved in the European Union and other countries outside the United States for the treatment of soft tissue sarcoma (STS) and ovarian cancer.

Trabectedin has a unique and complex mechanism of action. It binds to the N^2 position of guanine in the minor groove of DNA to bend the DNA molecule towards the major groove. Trabectedin inhibits transcription of heat shock-inducible genes (Minuzzo 2000) and interacts with the transcription-coupled nucleotide excision repair system, resulting in formation of lethal DNA strands, cell cycle arrest, and apoptosis by a process that is p53 independent (Erba 2001, Takebayashi 2001). Trabectedin has potent in vitro activity against several tumor cell lines such as STS, leukemia, melanoma, breast, non-small-cell lung cancer, and ovarian cancer. Trabectedin has also shown significant anticancer activity against several adult human cancer xenograft models.

For additional information regarding the efficacy and safety of trabectedin, refer to the latest version of the Investigator's Brochure (IB) for trabectedin (Trabectedin IB 2010).

The term sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Soft-tissue Sarcoma

STS constitute a heterogeneous group of malignancies arising in extraskeletal connective tissues (muscle, fat, fibrous tissue, blood vessels, or other mesenchymally-derived tissues). The most frequent histopathologic types of STS are leiomyosarcoma and liposarcoma, which account for approximately 40% to 50% of all STS (Van Glabbeke 1999).

Current treatment options for patients with STS vary with clinical stage, but may include surgery, radiotherapy, and chemotherapy (Clark 2005). For patients with resectable disease, surgery is the standard treatment, as it results in the greatest chance for long-term disease-free survival. Radiation is used as the primary treatment modality for inoperable tumors as well as for palliative purposes. Approximately 50% of patients present with or develop advanced or metastatic disease. Despite available chemotherapy, the prognosis for these patients is very poor, with an estimated median survival of 8 to 13 months from the start of first-line anthracycline-based cytotoxic therapy, as shown in randomized studies performed over the last 2 decades (Bramwell 2003, Antman 1993, Le Cesne 2000,

Jelic 1997). The poor prognosis has not improved over this period. In addition, these patients are often debilitated by their sarcoma, as bulky disease may result in complications such as pain, intestinal obstruction, and other symptoms leading to end-stage organ failure and death.

At present, initial standard chemotherapy for advanced or metastatic STS consists of an anthracycline (mainly doxorubicin) given either as a single agent or in combination with ifosfamide (Verweij 1995). These are considered the most active agents, with an overall response rate (ORR) of approximately 15% to 20% for first-line therapy. Combination chemotherapy or dose intensification efforts have failed to improve survival of STS patients (Bramwell 2003, Le Cesne 2000, Santoro 1995, Schoenfeld 1982, Borden 1987, Bramwell 2000). The median survival for patients for whom conventional chemotherapy with an anthracycline and ifosfamide has failed is in the range of 6 months (Pazdur 1987, Rose 1998, Woll 1999, Reichardt 2003, Hartmann 2006).

Trabectedin

Efficacy of Trabectedin in Soft Tissue Sarcoma

In preclinical studies, trabectedin was highly active in multiple STS cell lines with a 50% inhibitory concentration (IC50) in the picomolar range.

The results of early Phase 1 studies indicated that trabectedin might have antitumor activity in STS. This observation prompted 3 Phase 2 studies of trabectedin involving 183 patients with advanced pretreated STS. The most common histologic types were L-sarcomas (leiomyosarcoma [41.0%] and liposarcoma [13.7%]), followed by synovial sarcoma (13.7%) and fibrohistiocytoma (4.9%). The overall response rate as per independent review was 7.7% (95% confidence interval [CI], 4.3-12.5%). Progression-free survival (PFS) rates at 3 months (44.0%) and 6 months (21.5%) exceeded the 39% and 14% values for 3- and 6-month PFS found by the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) for active agents in pretreated STS (Van Glabbeke 2002). Furthermore, these efficacy endpoints tended to show better results in L-sarcomas (liposarcoma or leiomyosarcoma), although the number of subjects with other STS subtypes was insufficient to draw definite conclusions. These observations led to Study ET743-STS-201 to further investigate single-agent trabectedin in a more homogeneous population of patients with L-sarcoma.

Study ET743-STS-201 was a Phase 2 investigation of 2 trabectedin dosing regimens in 270 randomized subjects with liposarcoma or leiomyosarcoma that had progressed after treatment with an anthracycline and ifosfamide. The design of Study ET743-STS-201 provided the basis for the design of the current study. Study ET743-STS-201 showed superior disease control with the 1.5 mg/m^2 trabectedin administered using an every3-weeks, 24-hour (q3wk 24-h) regimen compared with a regimen of 0.58 mg/m^2 administered as a weekly, 3-hour i.v. infusion (qwk 3-h), although the qwk 3-h regimen also demonstrated activity relative to historic control (Demetri 2009). Median time to progression (TTP) was 3.7 months for the q3wk 24-h group compared with 2.3 months for the qwk 3-h group (HR=0.734, p=0.0302). Median overall survival (OS) was 13.9 months for the q3wk 24-h group compared with 11.8 months for the qwk 3-h group. These efficacy parameters in both treatment groups compared favorably to historic data. In a large series of more than 350 subjects (Minchom 2010), the median OS for STS patients who received second line chemotherapy was 8 months.

Safety Results From Studies of Trabectedin

Myelosuppression (with neutropenia as the predominant component) transaminase elevations, and fatigue were the primary dose limiting toxicities associated with trabectedin in early Phase 1 dose-finding studies. An integrated analysis of safety data was performed that included 1,170 subjects participating in single-agent, Phase 2 trabectedin studies, including 575 subjects treated with the q3wk 24-h regimen at a starting dose of 1.5 mg/m^2. Grade 3 to 4 neutropenia was reported in 12% of all treated subjects regardless of treatment regimen. Neutropenia had a rapid onset, was reversible with appropriate medical management (including cycle delays) and was usually uncomplicated, with a low incidence of either febrile neutropenia or infection. Anemia, thrombocytopenia, leukopenia, and lymphopenia were less frequently reported components of myelosuppression (Trabectedin IB 2010). A Phase 1/2a study (Study ET743-OVC-1001) showed that trabectedin does not prolong the QTc interval as measured by electrocardiograms (ECGs) for subjects with advanced solid tumor malignancies when administered at a therapeutic dose.

Transaminase increases were commonly observed with single-agent trabectedin treatment. Grade 3 or 4 alanine transaminase (ALT) and aspartate transaminase (AST) elevations (51% and 41%, respectively) were observed for subjects treated with the q3wk 24-h infusion schedule. Transaminase elevations followed a predictable pattern of rapid onset, reversibility, and decreasing severity with succeeding cycles. There was no indication of cumulative toxicity, and early experience showed that dexamethasone

premedication appeared to decrease the frequency and severity of transaminase elevations.

The risk of nephrotoxicity with trabectedin is low. Across all studies, blood creatinine levels were normal or Grade 1 for subjects receiving trabectedin, and only 1% of subjects had on-treatment Grade 3 or 4 creatinine values. Renal and urinary disorder-related adverse events, when they were reported in Phase 2 or 3 studies, consisted mainly of laboratory abnormalities such as blood creatinine or blood urea increased.

The most commonly reported adverse event that led to treatment cycle delay/interruption or a permanent discontinuation of study treatment was neutropenia. The most commonly reported adverse events that led to a dose reduction were neutropenia, increased alkaline phosphatase (ALP), increased ALT, and increased AST.

The most common adverse reactions of any severity grade reported in Phase 2 clinical studies of 570 subjects assigned to the recommended monotherapy regimen in several cancer types, including STS, were nausea, fatigue, vomiting, anorexia, neutropenia, and increases in AST/ALT. Fatal adverse reactions have occurred in 1.9% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Dacarbazine for Treatment of STS

Dacarbazine is considered the third most active drug behind doxorubicin and ifosfamide for the treatment of STS (Gottlieb 1976, Buesa 1991). It is a recommended treatment option for STS by experts and guidelines after failure of anthracyclines and ifosfamide (NCCN 2009, Pazdur 2009). The commonly used schedules range from 800 to 1,200 mg/m^2 every 3 weeks (Zucali 2008).

Bone marrow suppression is the most common toxicity with dacarbazine. It involves primarily the leukocytes and platelets, although, anemia may sometimes occur. Hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis resulting in death, has been reported. Anorexia, nausea, and vomiting are the most frequently noted adverse reactions associated with dacarbazine use, with over 90% of patients affected after the initial few doses. These effects usually subside after the first 1 or 2 days. Other minor toxicities include influenza-like syndrome, alopecia, facial flushing, and facial paresthesia. Significant liver or renal test function test abnormalities have been reported, as have erythematous and urticarial rashes, and photosensitivity reactions (Dacarbazine Prescribing Information 2007).

Patient-Reported Outcomes

The psychometric properties of the M.D. Anderson Symptom Inventory (MDASI) have been extensively investigated and reported as reliable and valid for use in clinical trials (Cleeland 2000). The instrument is available in multiple languages.

Focus groups, clinician review, and cognitive debriefing has been used in the development of the MDASI (Cleeland 2000) and its modules (Armstrong 2005, Armstrong 2006, Fadol 2008, Gning 2009, Rosenthal 2007) to ensure that the content is both appropriate and relevant. Continuous validation of the MDASI core items in the modules and translations is performed to confirm the MDASI's content validity.

In the initial MDASI validation study (Cleeland 2000) principal axis factor analysis with oblimin rotation was used to test the construct validity. In the initial validation outpatient sample, the 13 core symptom items of the MDASI were found to measure 2 underlying constructs: a general symptom severity factor (pain, fatigue, disturbed sleep, distress [emotional], shortness of breath, drowsiness, dry mouth, sadness, difficulty remembering, and numbness or tingling) and a gastrointestinal factor (nausea and vomiting). Lack of appetite applies to both constructs.

1.2. Overall Rationale for the Study

At present, initial standard chemotherapy for advanced or metastatic L-type sarcomas consists of an anthracycline (mainly doxorubicin) given as a single agent or in combination with ifosfamide (Verweij 1995). No effective therapies are currently approved once conventional chemotherapy with anthracyclines and ifosfamide has failed. Despite numerous clinical studies, including those performed by major organizations such as the EORTC STBSG in Europe and the National Cancer Institute (NCI) cooperative groups in the United States, no new active agents have been registered in the United States, Australia, or Brazil for more than 20 years. The median survival for patients who have failed prior treatment with anthracyclines and ifosfamide is in the range of 6 months (Pazdur 1987, Rose 1998, Woll 1999, Reichardt 2003, Hartmann 2006). Thus, there is an unmet medical need for new therapeutic alternatives in this patient population.

2. OBJECTIVES

Primary Objective

The primary study objective is to evaluate whether OS for the trabectedin group is superior to the dacarbazine group for subjects with advanced L-sarcoma (liposarcoma or leiomyosarcoma) who were previously treated (in any order) with at least: a) an

anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Secondary Objectives

Secondary objectives are to evaluate PFS, TTP, ORR, symptom severity, and safety in the trabectedin group and dacarbazine group.

Hypothesis

Trabectedin treatment will improve OS compared with dacarbazine for subjects with advanced L-sarcoma who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

3. OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine among adults (15 years of age and older at the time of screening) with unresectable, locally advanced or metastatic L-sarcoma, who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. Approximately 570 adult subjects will be enrolled. An Independent Data Monitoring Committee (IDMC) will review safety data approximately every 3 to 4 months and will also review the results of the interim analysis of OS.

3.1. Study Design

The study is divided into a Screening Phase, Treatment Phase, Follow-up Phase, and Optional Extension Phase (OEP). The timing of all evaluations and procedures that occur in each phase of the study are detailed in the Time and Events Schedule that follows the Synopsis. A study flow diagram is provided in Figure 1.

During the Screening Phase, potential subjects will be assessed for study eligibility after providing signed informed consent/assent to participate. Baseline radiographic disease assessments (including radiographic imaging of the chest [with lung views], abdomen and pelvis), ECGs, and multiple gated acquisition scans (MUGA, or echocardiograms if MUGA is not available) must be performed within 30 days before randomization. All other evaluations required to establish eligibility must be completed within 14 days before randomization. A pathology specimen (eg, formalin-fixed paraffin-embedded [FFPE] tumor block or unstained slides), to be archived for possible review of diagnosis and biomarker evaluation, must be collected for each subject before randomization.

Eligible subjects will be randomly assigned to either the trabectedin or dacarbazine treatment groups in a 2:1 ratio within 96 hours before the first dose of study drug. Before randomization, the sponsor must verify a subject's L-sarcoma (leiomyosarcoma or liposarcoma) and prior treatment history with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy; regardless of the order. Subjects will be stratified by the number of lines of prior chemotherapy (1 versus 2 or more), ECOG Performance Status score (0 versus 1), and L-sarcoma subtype (liposarcoma versus leiomyosarcoma) before randomization. Approximately 570 subjects will be enrolled. Study treatment occurs on Day 1 (with a dosing window of up to +2 days) of each 21-day cycle (ie, with each cycle being at least 21 days apart) as follows:

- Trabectedin Group (n≈380): 1.5 mg/m^2 as q3wk 24-h i.v. infusion. A central venous catheter must be used to administer study drug to subjects in the trabectedin group. If a subject does not already have a central venous catheter or central venous access is not in place, placement of a central venous catheter may be performed during the 96-hour period permitted between randomization and the first dose of study drug. Subjects will be pretreated with 20 mg of dexamethasone i.v, or the equivalent, on Day 1 of each treatment cycle, 30 minutes before study drug. A dosing window of up to +2 days will be allowed. Within the OEP, dosing will proceed along the same guidelines; catheter placement is mandatory prior to first dose, however timing of catheter placement is at the physician's discretion.
- Dacarbazine Group (n≈190): 1 g/m^2 as a 20-120 minute i.v. infusion q3wk. A dosing window of up to +2 days will be allowed.

Investigators will review physical findings and the results of clinical laboratory tests before each dose of study drug and, if required, delay administration or reduce the dose according to predefined guidelines (see Section 6, Dosage and Administration). Subjects will receive study drug until there is documented disease progression or unacceptable toxicity.

Radiographic assessment of disease, using the same radiographic technique, should include radiographic imaging of the chest (with lung views), abdomen and pelvis. Assessment of disease will be performed every 6 weeks for the first 36 weeks on study and every 9 weeks thereafter, until disease progression occurs, the subject begins subsequent anticancer therapy, the study ends, or the subject dies. Subsequent therapy should only be started after disease progression has been documented. The end of the Treatment Phase is defined as 30 days after last dose of study drug.

The Follow-up Phase will begin immediately after the Treatment Phase. Subjects will be followed-up for the collection of survival status and the use of subsequent anticancer therapy every 60 days for the first 2 years after the last dose of study drug, and then every 90 days thereafter. Collection of survival status will continue until approximately 376 deaths have been observed, at which time clinical cutoff will occur. Subjects who discontinue study drug before disease progression occurs (eg, subjects who discontinue treatment due to unacceptable toxicity) should continue to have assessments of disease status until disease progression or subsequent therapy. Whenever possible, subsequent therapy should only be started after disease progression has been documented.

The OEP is available to those subjects who were randomized to the dacarbazine treatment group, and are currently in either the treatment phase or follow-up phase.

Survival status will be monitored throughout the study and will be used to calculate OS, the primary endpoint. Investigators will assess disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 guidelines (Attachment 1), and these data will be used to calculate PFS, TTP, ORR, and DR. One interim analysis of OS will be performed when approximately 188 deaths have been observed. The final analysis of OS will occur following clinical cutoff.

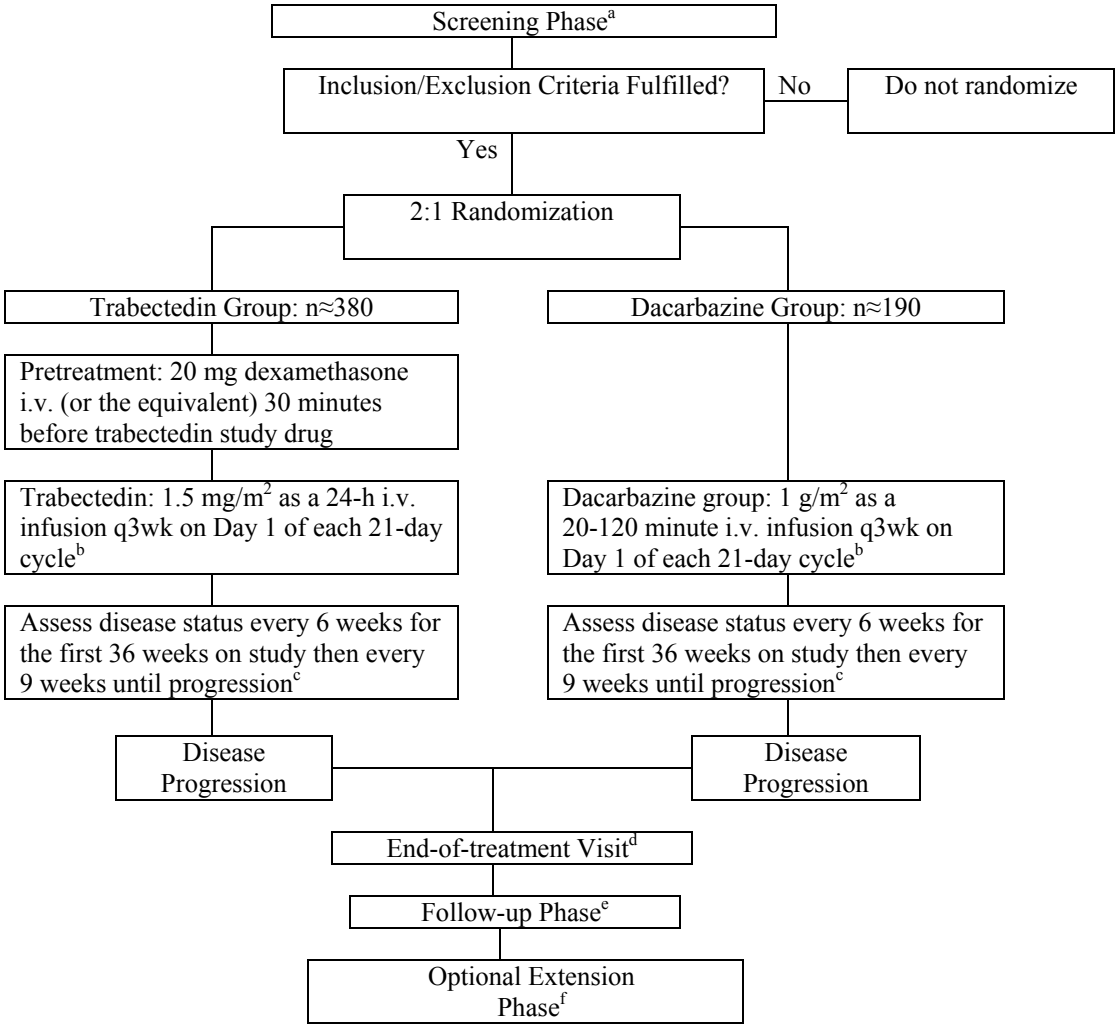
Symptom severity will be assessed using the MDASI questionnaire on Day 1 of each treatment cycle before any other tests or procedures. This information will be used to assess subjects' perceived symptom burden and determine the impact of treatment on symptom change or stability.

Subjects will be monitored for adverse events from the time signed informed consent is given until 30 days after the last dose of study drug in the treatment phase. The incidence and severity of adverse events will be assessed for all subjects who receive study drug. Clinical laboratory test results will be reviewed before dosing on Day 1 of each cycle. Blood samples will also be collected for clinical laboratory testing on Days 8 (±2 days) and 15 (±2 days) of each cycle and at the end of treatment. ECGs and MUGA scans (or echocardiograms if MUGA is not available) will be performed at baseline (within 30 days before randomization) and at the end of treatment to assess cardiac function.

An IDMC (See Section 11.5, Independent Data Monitoring Committee) will review safety data approximately every 3 to 4 months and will also review the results of the interim analysis of OS.

A pharmacogenomic blood sample will be collected from subjects who consent/assent separately to the pharmacogenomic component of the study where local regulations permit. Subject participation in pharmacogenomic research is optional. Additionally, biomarker-related analyses may be performed using the archived tumor specimens collected from all subjects.

Figure 1: Study Diagram



i.v.=intravenous; q3wk=every 3 weeks

[a] Perform disease status assessment, ECG, and MUGA scan (or echocardiograms if MUGA is not available) to determine study eligibility within 30 days before randomization; all other eligibility assessments within 14 days before randomization.

[b] Study drug administration: Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (with each treatment cycle being at least 21 days apart).

[c] Perform for all subjects, including those who discontinue study drug before disease progression.

[d] Complete within 30 days after treatment discontinuation or withdrawal from the study.

[e] Follow-up for survival status and use of subsequent anticancer therapy every 60 days for the first 2 years; every 90 days, thereafter.

[f] Only those subjects who were randomized to dacarbazine and are currently in treatment phase or follow-up phase are eligible for OEP.

3.2. Study Design Rationale

This study will enroll subjects with advanced STS who have previously received standard chemotherapy (in any order) with at least: a) anthracycline and ifosfamide containing

regimen or b) an anthracycline containing regimen and 1 additional cytotoxic agent. There is no other approved standard treatment option for these subjects. The rationale for limiting the population to only subjects with L-type sarcoma is based on the observation that trabectedin treatment yielded better outcomes in these patients. When data from earlier studies were analyzed, the clinical benefit rate (PR+CR+ stable disease [SD] ≥24 weeks) was 28.6% in L-type sarcoma versus 18.7% in the other histologic subgroups (data on file). In addition, interim OS data collected from 899 patients with locally advanced or metastatic STS who received trabectedin as participants in an expanded access program showed median survival of 16.1 months for patients with L-sarcoma and 8.4 months for patients with other histologic subtypes (Samuels 2010).

This will be an open-label study, as the distinctive toxicity profile of trabectedin (reversible and transient liver test abnormalities) would make determination of treatment group assignment obvious if a blinded study design were used. In addition, a blinded design would require use of central venous catheters in all subjects, thus unnecessarily exposing subjects in the dacarbazine group to the potential risks associated with the use of these devices.

Although the mechanisms are not completely understood, prophylactic use of dexamethasone reduces the incidence and severity of hepatic, renal, and to a lesser extent, hematologic toxicity of trabectedin. The impact of dexamethasone on both the pharmacokinetics and pharmacodynamics of trabectedin are thought to play a role in these beneficial effects (Trabectedin IB 2010). For this reason, prophylactic use of steroids at doses recommended by American Society of Clinical Oncology (ASCO) guidelines (ASCO 1999a) is required for all subjects assigned to the trabectedin group. Prophylactic use of steroids is optional for subjects in the dacarbazine group.

Reports in the medical literature have described dacarbazine activity for patients with STS, and the drug has been identified for single-agent palliation treatment in the targeted patient population (Zucali 2008, Buesa 1991, Gottlieb 1976). The dose, regimen, and route of administration for the trabectedin group was selected based on the results of Study ET-743-STS-201, which showed that the 24-hour i.v. infusion regimen was superior to the alternative 3-hour i.v. infusion regimen. Furthermore, Study ET-B-022-00 showed that trabectedin administered as a 3-h infusion q3wk to subjects with STS had less favorable toxicity and efficacy profiles (CSR ET-B-022-00 2005). Single bolus dacarbazine administration has been shown to be as effective as the classical 5-day regimen (maximum tolerable dose 1,980 mg/m^2) (Buesa 1984). Therefore, similar dosing

regimens could be used for both treatment groups in this study, allowing symmetrical safety and efficacy evaluations to occur relative to dosing for the 2 treatment groups.

OS has been chosen as the primary efficacy endpoint as it is considered the gold standard in oncology studies for assessment of treatment efficacy and safety. Patient-reported perception of symptom severity will be gathered at each cycle to assess perceived symptom burden and determine the impact of treatment on symptom change or stability.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Before randomization, subjects will be stratified by the number of lines of prior chemotherapy (1 versus 2 or more), ECOG Performance Status score (0 versus 1), and L-sarcoma subtype (liposarcoma versus leiomyosarcoma), as these variables have been reported to affect clinical outcomes (data on file).

Some disease subtypes may be more sensitive to trabectedin treatment (Grosso 2007, Italiano 2010), and this more favorable sensitivity can be directly linked to molecular components involved in the mechanism of action of trabectedin. Therefore, FFPE tumor samples will be collected to allow for confirmation of previous study results showing superior response for subjects with myxoid round cell liposarcoma or for those with particular XPG status, the latter being a component of the TC-NER complex. Details are provided in Section 9.4, Pharmacogenomic and Biomarker Evaluations.

4. STUDY POPULATION

4.1. General Considerations

Eligible subjects will have unresectable, measurable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma following treatment (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. The study will enroll approximately 570 subjects in order to observe 376 deaths for the primary analysis of OS.

4.2. Inclusion Criteria

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before

enrolling the subject in the study. No waivers will be granted for inclusion or exclusion criteria.

1. Criterion modified per amendment
   1.1 15 years of age or older at the time of screening.
2. Histologically proven, unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma. Subjects must have a pathology report indicating the diagnosis of liposarcoma or leiomyosarcoma that has been reviewed by the sponsor before randomization may occur.
3. Criterion modified per amendment
   3.1 Treated in any order with at least:
      ◊ an anthracycline and ifosfamide containing regimen, or
      ◊ an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Previous treatment must be reviewed by the sponsor before randomization may occur.

4. Measurable disease at baseline in accordance with RECIST Version 1.1
5. Pathology specimens (eg, tumor blocks or unstained slides) for potential centralized pathology review and biomarker studies.
6. ECOG Performance Status score of 0 or 1
7. Adequate recovery from prior therapy; all side effects (except alopecia) have resolved to Grade 1 or less according to the National Cancer Institute – Common Terminology Criteria of Adverse Events (NCI-CTCAE) Version 4.0
8. Criterion modified per amendment
   8.1 Adequate organ function as evidenced by the following peripheral blood counts or serum chemistry values:
      ◊ hemoglobin ≥9 g/dL
      ◊ absolute neutrophil count (ANC) ≥1,500/μL
      ◊ platelet count ≥100,000/μL
      ◊ serum creatinine ≤1.5 x the upper limit of normal (ULN)
      ◊ creatine phosphokinase (CPK) ≤2.5 x ULN.
9. Criterion modified per amendment
   9.1 Adequate hepatic function as evidenced by the following serum chemistry values:
      ◊ total bilirubin ≤ ULN. If total bilirubin is > ULN, measure indirect bilirubin to evaluate for Gilbert's syndrome (if direct bilirubin is within normal range, subject may be eligible).
      ◊ ALP ≤2.5 x ULN;

if the ALP is >2.5 x ULN, then an ALP liver fraction or 5' nucleotidase must be obtained and ≤ ULN

- ◊ AST and ALT ≤2.5 × ULN.

10. Negative pregnancy test (urinary or serum β-HCG) at screening (applicable to women of child bearing potential who are sexually active).
11. Criterion modified per amendment
    11.1 Female subjects must be postmenopausal (no spontaneous menses for at least 2 years), surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), abstinent (at the discretion of the investigator), or if sexually active, be practicing an effective method of birth control (eg, prescription hormonal contraceptive, intrauterine device, double-barrier method [eg, condoms and occlusive cap (diaphragm or cervical/vault caps)] with spermicidal foam, cream, gel, film, suppository), before entry, and must agree to continue to use the same method of contraception throughout the study and for 3 months thereafter. Male subjects must agree to use an adequate contraception method as deemed appropriate by the investigator (eg, vasectomy, double-barrier, partner using effective contraception) and to not donate sperm for a minimum of 5 months after treatment discontinuation.
12. Criterion modified per amendment
    12.1 Sign (or their legally-acceptable representative must sign) an informed consent document indicating they understand the purpose of and the procedures required for the study and are willing to participate in the study. Assent is also required for subjects who are 15 years of age and up to the age of legal consent in the jurisdiction in which the study is to take place and who are capable of understanding the nature of the study (see Section 16.2.3, Informed Consent).

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Prior exposure to trabectedin or dacarbazine
2. Less than 3 weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent
3. Other malignancy within past 3 years. Exceptions: basal or nonmetastatic squamous cell carcinoma of the skin, cervical carcinoma in situ, or Federation Internationale de Gynecologie et d'Obstetrique (FIGO) Stage 1 carcinoma of the cervix
4. Known central nervous system metastasis
5. Known significant chronic liver disease, such as cirrhosis or active hepatitis (potential subjects who test positive for hepatitis B surface antigen or hepatitis C antibodies are allowed provided they do not have active disease requiring antiviral therapy).

6. Myocardial infarct within 6 months before enrollment, New York Heart Association Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
7. Uncontrolled intercurrent illness including, but not limited to, poorly controlled hypertension or diabetes, ongoing active infection, or psychiatric illness/social situation that may potentially impair the subject's compliance with study procedures
8. Unwilling or unable to have a central venous catheter
9. Known allergies, hypersensitivity, or intolerance to trabectedin, dacarbazine, dexamethasone, or their excipients (refer to Section 14, Study Drug Information)
10. Pregnant or breast-feeding
11. Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.

4.4. Prohibitions and Restrictions

Potential subjects must be willing/able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- No concurrent investigational agents are permitted.
- No concurrent antineoplastic agents are permitted.
- No radiotherapy is permitted.

Investigators should take caution when administering inducers or inhibitors of cytochrome CYP3A4 (see Section 8, Prestudy and Concomitant Therapy).

If a decision is made to undertake de-bulking surgery during study treatment, then the principal investigator at the site should discuss the case with the medical monitor prior to the surgery. The subject must meet the following conditions in order to continue treatment with the study medication after surgery:

- The subject must have completed at least 4 cycles of study treatment and the 12-week postbaseline tumor assessment prior to the surgery;
- The surgery was not undertaken to treat new or worsening tumor-related signs or symptoms that could be considered evidence of progressive disease;
- There was no evidence of tumor progression at the most recent RECIST assessment, which should have been completed within 2 weeks prior to the surgery; and
- There was no evidence of progression of disease at the time of the surgery.

5. TREATMENT ALLOCATION

This is an open-label study; therefore, blinding is not applicable. Eligible subjects will be randomly assigned to 1 of 2 treatment groups in a 2:1 ratio within 96 hours before Day 1 of Cycle 1 as follows:

- Trabectedin group (n≈380): 1.5 mg/m^2 as a 24-h i.v. infusion q3wk
- Dacarbazine group (n≈190): 1 g/m^2 as a 20-120 minute i.v. infusion q3wk.

Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by the number of lines of prior chemotherapy (1 versus 2 or more), ECOG Performance Status score (0 versus 1), and L-sarcoma subtype (liposarcoma versus leiomyosarcoma). The Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification (ID) and personal identification number (PIN) when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject.

In the optional extension phase, no randomization will be required and subjects who were previously randomized to the dacarbazine group will have the option to receive trabectedin at the discretion of the investigator. Study drug kits will be assigned for each subject in the OEP using the IVRS/IWRS.

6. DOSAGE AND ADMINISTRATION

6.1. Dosage

Study drug dose is dependent on the subject's body surface area (BSA), which will be calculated on Day 1 of Cycle 1 before the first dose of study drug using the subject's body weight and height. It is not necessary to recalculate BSA before each cycle unless required to comply with institutional guidelines or unless a subject has a weight gain or loss >10% of body weight. For subjects who are obese (body mass index >30), BSA will be calculated using the ideal body weight throughout the study.

Trabectedin and dacarbazine study drug will be provided by the sponsor. The following treatment regimens will be used:

Trabectedin Group

Trabectedin will be administered at a dose of 1.5 mg/m^2 via a central venous catheter as a 24-hour infusion on Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (ie, each treatment cycle being at least 21 days apart).

If a subject randomized to the trabectedin group does not already have a central venous catheter, one must be placed. Consideration of the 96-hour interval permitted between randomization and first dose of study drug must be taken into account before randomization.

- Refer to the IB (provided separately) for complete instructions regarding the storage, handling, and preparation of trabectedin for administration.
- All subjects will be pretreated with 20 mg of dexamethasone i.v. on Day 1 of each treatment cycle 30 minutes prior to each infusion of study drug. If dexamethasone is not available, an equivalent may be substituted. If a subject cannot tolerate 20 mg of dexamethasone, please contact the medical monitor.
- Subjects may receive multiple cycles of trabectedin as long as there is no documented disease progression or unacceptable toxicities.

Dacarbazine Group

Dacarbazine will be administered at a dose of 1 g/m^2 as a 20-120 minute infusion (Buesa 1991, Oncology Dilution Database 2011) on Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (ie, each treatment cycle being at least 21 days apart). Subjects may receive multiple cycles of dacarbazine as long as there is no documented disease progression or unacceptable toxicities, as determined by the investigator. Refer to the prescribing information for complete instructions regarding the storage, handling, and preparation of dacarbazine for administration.

6.2. Criteria for Continuation of Treatment

On Day 1 of each treatment cycle, the criteria specified in Table 1 must be met in order for treatment to occur. If the criteria in Table 1 are not met on Day 1 of a new cycle, the subject will be evaluated weekly and the new cycle will start upon recovery to the Day 1 criteria specified in Table 1. Dosing can be delayed for a maximum of 3 weeks to allow for recovery of laboratory toxicity or other nonhematologic drug-related effects. If toxicities have not recovered after 3 weeks of delay, the subject should discontinue treatment. If it is determined that a subject can continue treatment, it may be necessary to reduce the dose of study drug based on nadir values for critical analytes or toxicities, that occurred since the previous dose as described in Section 6.3, Dose Modification.

Table 1: Criteria for Continuation of Treatment

Variable	Day 1
Platelets	≥100,000/μL
ANC	≥1,500/μL
Bilirubin	≤ ULN
ALP[a]	≤2.5 x ULN
Transaminases	≤2.5 x ULN
Creatine phosphokinase	≤2.5 x ULN
Other nonhematologic, drug-related effects	Grade 1 or lower

ALP=alkaline phosphatase; ANC=absolute neutrophil count; ULN=upper limit of normal

[a] If ALP >2.5 x ULN, ALP liver fraction or 5' nucleotidase must be ≤ ULN.

Although there is no criterion for continuation of treatment for hemoglobin values, anemic patients should be monitored closely to ensure that they are clinically asymptomatic.

Subjects experiencing liver abnormalities within the same cycle that include all of the following should discontinue treatment:

- bilirubin ≥2 x ULN,
- transaminases (ALT or AST) ≥3 x ULN,
- ALP ≤2 x ULN

However, if there is evidence of benefit (eg, tumor shrinkage, disease stabilization) and the subject recovers within 3 weeks, in consultation with the sponsor, the subject may continue treatment.

For elevated ALP, a value >2.5 x ULN on Day 1 of any cycle, an ALP liver fraction or 5' nucleotidase test must be performed. If the ALP liver fraction or 5' nucleotidase value is ≤ULN, the subject may continue dosing.

If, at any time since the last dose of drug, either the liver fraction ALP or 5' nucleotidase is elevated, then a dose modification needs to be made. See Section 6.3.2 for dosing instructions.

6.3. Dose Modification

Dose reductions will be made on the basis of the worst drug-related toxicity that occurred since the previous dose, as outlined in the Section 6.3.1, Dose Reductions Due to Hematologic Toxicity, and Section 6.3.2, Dose Reductions Due to Nonhematologic Toxicity. Table 2 and Table 3 specify the dose levels that will be used when dose reductions are required for subjects in the trabectedin group or dacarbazine group,

respectively. Subjects who require more than 2 dose reductions should discontinue study treatment. Dose escalations are not allowed following a dose reduction.

Table 2: Dose Level Reductions – Trabectedin Group

Dose Level	Trabectedin
Starting level	1.5 mg/m^2
Level –1	1.2 mg/m^2
Level –2	1 mg/m^2

Table 3: Dose Level Reductions – Dacarbazine Group

Dose Level	Dacarbazine
Starting level	1 g/m^2
Level –1	0.8 g/m^2
Level –2	0.6 g/m^2

6.3.1. Dose Reductions Due to Hematologic Toxicity

Subjects in either treatment group who experience hematologic toxicity meeting either criteria cited in Table 4 will have a dose level reduction as specified in Table 2 (trabectedin group) or Table 3 (dacarbazine group). Subjects who require more than 2 dose reductions should discontinue study treatment.

Table 4: Dose Reduction Criteria for Hematologic Toxicity

Nadir toxicity	Nadir Value	Dose modification
ANC	<1,000/μL with fever/infection or <500/μL lasting >5 days	Decrease 1 level[a, b]
Platelets	<25,000/μL	Decrease 1 level[a]

ANC=absolute neutrophil count

[a] If toxicity reappears, decrease dose to Level –2.

[b] Colony-stimulating factor support may be added to the next cycle.

Note that the use of hematopoietic colony-stimulating factors (CSF) according to institutional or ASCO guidelines (ASCO 1999b) is permitted.

6.3.2. Dose Reductions Due to Nonhematologic Toxicity

Subjects in either treatment group who experience non-hematologic toxicity meeting any of the criteria cited in Table 5 will have a dose level reduction as specified in Table 2 (trabectedin group) or Table 3 (dacarbazine group). Subjects who require more than 2 dose reductions should discontinue study treatment.

If, at any time since the last dose of drug, either the liver fraction ALP or 5' nucleotidase is >ULN, then a dose modification needs to be made. At the first occurrence, 1 dose reduction is required. A second dose reduction is required at reoccurrence (see Table 2

and Table 5). Subjects who require more than 2 dose reductions should discontinue treatment.

Table 5: Dose Reduction Criteria for Nonhematologic Toxicity

Toxicity		Worst Grade	Dose modification
Nausea or vomiting despite adequate treatment[a]		≥3	Decrease 1 dose level
Transaminase elevation	Recovery to ≤2.5 x ULN by day of next dose or within 3 weeks after the day the next dose is due.	≥3	Decrease 1 dose level
	Not recovered after a 3-week delay	≥3	Off treatment unless clinical benefit, then decrease 1 dose level
ALP liver fraction or 5' nucleotidase elevation >ULN	First occurrence	≥1	Decrease 1 dose level.
	Worsening to or recurrence of ALP liver fraction or 5' nucleotidase >ULN despite 1st dose reduction.	≥1	Decrease 1 dose level.
Total bilirubin > ULN at any time		≥1	Decrease 1 dose level
Other		≥3	Decrease 1 dose level

ALP=alkaline phosphatase; ULN=upper limit of normal

[a] Before dose modification, use full antiemetic regimen to include anti-HT3+/ other/ dexamethasone.

7. TREATMENT COMPLIANCE

Treatment compliance (ie, administration of the correct dose according to the assigned schedule) will be assessed on the basis of the completion of the appropriate section of the case report form (CRF). Case report forms will be monitored by a site monitor designated by the sponsor.

8. PRESTUDY AND CONCOMITANT THERAPY

Only systemic medications taken by a subject (prescription or nonprescription) that are not the study drug must be documented in the concomitant therapy section of the CRF. This includes medications taken before and during the study and for up to 30 days after the administration of the last dose of study drug.

Premedication with dexamethasone (or its equivalent) is required for subjects in the trabectedin group. The use of dexamethasone for this purpose is not considered concomitant therapy and will be documented as a required pretreatment medication on the study drug administration section of the CRF. The use of dexamethasone (or its

equivalent) for reasons other than the required pretreatment of subjects in the trabectedin group should be documented in the concomitant therapy section of the CRF.

Prophylactic use of steroids for antiemetic prophylaxis is permitted for subjects in the dacarbazine group. Treatment consistent with ASCO guidelines is recommended (ASCO 1999a). Steroid use in the dacarbazine group should be recorded as concomitant therapy. Optional treatment with additional antiemetic drugs, such as 5HT3 antagonists or additional corticosteroids, is permitted. Note that the antiemetic Emend® (aprepitant) should be used with caution, as it is an inhibitor of CYP3A4 (see below).

Any new condition or a worsening of an existing condition that requires the use of concomitant therapy must be documented on the adverse events section of the CRF. Subjects may receive supportive care while receiving study medication, including transfusions, hematopoietic growth factors, antibiotics, analgesics, and antidiarrheal agents. Colony stimulating factors may be used according to institutional or ASCO Guidelines (ASCO 1999b).

Megestrol acetate may be used only for appetite stimulation. Concomitant administration of any other antineoplastic therapy is prohibited.

The use of the following concomitant medications or therapies should be documented in the CRF:

- Anti-infective medications (eg, antibiotics, antifungals, antivirals), from the time that the informed consent document is signed until 30 days after the last dose of study drug
- Hematopoietic cytokines from the first dose of study drug until 30 days after the last dose of study drug
- Any medications the subject was receiving when a serious adverse event started and medications administered to treat the serious adverse event will be reported from the time that the informed consent document is signed until 30 days after the last dose
- Blood product transfusions received from the time of the first dose of study drug until 30 days after the last dose of study drug (the events that lead to the need for blood product transfusion should be recorded as adverse events, but not the transfusions themselves)
- All inhibitors or inducers of cytochrome CYP3A4 (see below).

The metabolism of trabectedin may be modified by concomitant administration of compounds that induce or inhibit CYP3A4. Caution should be exercised if administration

of such agents becomes necessary. Inhibitors of CYP3A4 include but are not limited to the following:

- aprepitant
- clarithromycin
- clotrimazole
- diltiazem
- erythromycin
- fluconazole
- grapefruit juice
- indinavir
- itraconazole
- ketoconazole
- nefazodone
- nelfinavir
- ritonavir
- saquinavir
- telithromycin
- troleandomycin
- verapamil

Inducers of CYP3A4 include but are not limited to the following:

- barbiturates
- phenytoin
- carbamazepine
- rifabutin
- rifampin
- St. John's Wort

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into 4 phases: a Screening Phase to establish study eligibility and collect baseline assessments; a Treatment Phase, during which study drug is administered and subjects undergo safety and efficacy assessments until there is documented disease progression or unacceptable treatment toxicity; a Follow-up Phase for the collection of post-treatment adverse event information, anticancer therapy, and survival status, and an Optional Extension Phase, during which eligible subjects who were randomized to dacarbazine will receive optional treatment with trabectedin. The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, pharmacogenomic, safety, and other measurements applicable to this study.

All visit-specific patient-reported outcomes (PRO) assessments during a visit (ie, the MDASI questionnaire) should be conducted before any tests, procedures, or other consultations for that visit.

It is anticipated that the total volume of blood drawn for each subject for routine laboratory evaluations throughout the study is approximately 10 mL for screening serum biochemistry and hematology tests, 20 mL per cycle for serum biochemistry and hematology tests, 10 mL for the pharmacogenomic analysis (optional), and 10 mL for the end of treatment serum biochemistry and hematology tests. Repeat or unscheduled blood samples may be taken if required for safety reasons, and a small amount of blood will be discarded each time a sample is taken via intravenous cannula. The total blood volume to be collected from each subject who is on study for 5 months is approximately 120 to 130 mL.

A 10-mL blood sample will be collected from subjects who have consented/assented to participate in the pharmacogenomics component of the study. Procedures for the collection and shipment of pharmacogenomic samples will be provided separately. In the event of DNA extraction failure, a replacement pharmacogenomic blood sample may be requested from the subject. Signed informed consent/assent will be required to obtain a replacement sample.

9.1.2. Screening Phase

At the beginning of the Screening Phase, the risks and requirements of the study will be explained to each potential subject, after which the subject (or their legally-acceptable representative) will be asked to voluntarily sign an informed consent document. No study procedures may be performed before the informed consent/assent process is completed, and informed consent/assent is to be obtained within 30 days before randomization.

The purpose of the Screening Phase is to determine whether a subject is eligible for further study participation based on the inclusion and exclusion criteria specified in Section 4, Study Population, and to collect baseline data against which subsequent measurements will be compared for subjects who enter the Treatment Phase. A screening log will be kept at the study center to record the primary reason why subjects who do not proceed to the Treatment Phase did not satisfy eligibility criteria (see Section 17.3, Subject Identification, Enrollment, and Screening Logs).

Screening Phase procedures and assessments are specified in the Time and Events Schedule that follows the Synopsis. These must be completed within 14 days before randomization with the exception of baseline radiographic disease assessments (including radiographic imaging of the chest [with lung views], abdomen and pelvis), ECGs, and MUGA scans (or echocardiogram if MUGA is not available), which must be performed within 30 days before randomization.

Eligible subjects will be randomly assigned to 1 of 2 treatment groups within 96 hours before Day 1 of Cycle 1 and before the first administration of study drug, according to the procedures described in Section 5, Treatment Allocation. Arrangements for potential central venous catheter placement should therefore be considered before randomization. A pathology specimen (eg, FFPE tumor block or unstained slides) will be collected for possible centralized pathology review and biomarker studies before a subject can be randomized.

9.1.3. Treatment Phase

Treatment Phase procedures and assessments are specified in the Time and Events Schedule that follows the Synopsis. The Treatment Phase begins with the first administration of study drug, as described in Section 6, Dosage and Administration. In order to participate in the optional pharmacogenomic component of this study, subjects (or their legally-acceptable representative) must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent/assent for this component does not exclude a subject from participation in the clinical study. Subjects who consent/assent to this analysis will have a 10-mL blood sample drawn on Day 1 of Cycle 1.

A subject will discontinue study drug when he or she has documented disease progression or experiences unacceptable toxicity. Subsequent therapy should only be started after disease progression has been documented. An End-of-treatment Visit will occur within 30 days after the last dose of study drug for all subjects, regardless of the reason for study drug discontinuation (other than the death of the subject), including withdrawal from the study. Subjects who discontinue study drug before disease progression occurs should continue to have assessments of disease status until disease progression or subsequent therapy, as described in Section 9.2.1.2, Disease Assessment. Whenever possible, subsequent therapy should only be started after disease progression has been documented.

9.1.4. Follow-up Phase

The Follow-up Phase begins immediately after the Treatment Phase. Drug-related Grade 3 or Grade 4 toxicities will be monitored until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first. Grade 2 to 4 liver or cardiac toxicities will be monitored until the toxicity is Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first.

If follow-up information regarding subsequent anticancer treatment and survival status is obtained without having the subject visit the study center, written documentation of the communication must be available for review in the source documents. A subject will continue to be followed-up until his or her death is documented or the clinical cutoff is reached.

9.1.5. Optional Extension Phase

The OEP will be open only for those subjects who were randomized to dacarbazine treatment group and are currently in treatment phase or follow-up phase. If the investigator determines the subject may benefit from the treatment of trabectedin, these subjects may enroll in the OEP. Subjects will have to meet all inclusion criteria in Section 4.2 with the following exceptions:

- Documentation for inclusion criteria #2 and #3 do not need to be reviewed by the Sponsor
- Collection of the specimen described in inclusion criterion #5 is not applicable
- Documentation of inclusion criteria # 8 and #9 will be reviewed by the Sponsor before enrollment in the OEP may occur

Potential subjects who meet any of the exclusion criteria in section 4.3 will be excluded from participating in the OEP with the exception of the following:

- Exclusion criteria #1 does not apply
- Exclusion criteria #9 with reference to dacarbazine does not apply

Exclusion criteria # 2 will apply with modification as below:

- Exclusion # 2: Less than 3 weeks from last dose of systemic anticancer therapy, radiation therapy, or therapy with any investigational agent

Screening labs should be done within 14 days prior to enrollment. If duplicate laboratory assessments are performed at screening, the results performed closest to the date of dosing will be used to demonstrate eligibility. Treatment with trabectedin in the OEP should occur as in the treatment phase, as outlined in Section 6 (Dosage and Administration), and laboratory monitoring as outlined in Section 9.5 (Clinical Laboratory Tests). Discontinuation of treatment in the OEP will be performed as described in Section 10.2, Discontinuation of Treatment. Collection of subsequent therapies and survival status will continue until clinical cutoff for final overall survival.

During OEP, only the following data will be collected in eCRF:

- trabectedin start date as subsequent therapy
- survival status

Once a subject has completed treatment on the OEP, the follow up phase of the OEP will commence, following the same procedures discussed in Section 9.1.4.

Once clinical cutoff occurs, data collection will be performed as described below.

Clinical Cutoff

The sponsor will establish a clinical cutoff date after the required number of events (approximately 376 death events) has occurred for the analysis OS. The clinical study report will be written on the basis of this data, with updates provided as required. After the clinical cutoff date, only serious adverse events as described in Section 12.2.2 will be collected up to 30 days after last dose of study drug for subjects still receiving study drug in the treatment phase or OEP. The study can be closed anytime at the sole discretion of the Sponsor.

9.2. Efficacy

The timing of efficacy assessments is provided in the Time and Events Schedule that follows the Synopsis.

9.2.1. Evaluations

9.2.1.1. Survival Status

All subjects will be followed-up regularly during the study for the collection of survival status and the use of subsequent anticancer therapy. Collection of survival status information will continue until approximately 376 deaths have been observed.

9.2.1.2. Disease Assessment

Investigator assessments of disease progression will be used for the calculation of secondary efficacy endpoints. Every effort should be made to ensure that the same method of radiographic disease assessment is used at screening and during the study. Disease assessment procedures must be consistent with RECIST Version 1.1 guidelines for radiographic assessment, as presented in Attachment 1.

Baseline radiographic disease assessments (including radiographic imaging of the chest [with lung views], abdomen and pelvis) and determination of extent of disease must be performed within 30 days before randomization. Complete radiographic disease assessments consistently using the same radiographic technique and including radiographic imaging of the chest (with lung views], abdomen and pelvis) will be performed approximately every 6 weeks for the first 36 weeks on study and every

9 weeks thereafter, until disease progression occurs, the subject begins subsequent anticancer therapy, the study ends, or the subject dies. Disease status will be assessed using radiographic techniques, including computed tomography (CT) scans of the chest (with lung views), abdomen, and pelvis, or if necessary, magnetic resonance imaging (MRI) scans. Subjects who discontinue study drug before disease progression occurs should continue to have assessments of disease status until disease progression or subsequent therapy. Whenever possible, subsequent therapy should only be started after disease progression has been documented.

Assessments of disease progression must be done consistently, as scheduled, to ensure symmetrical assessment of tumor response and progression. Every effort should be made to ensure that these assessments are done on the required date, although a window of ±5 days will be accommodated. The date of progression will be defined as the date of the first imaging study that documents progression. In case of clinical or symptomatic progression, the same radiographic disease assessments will be performed to document the progression. If this examination falls outside of the timetable and progression is not documented, the scheduled radiographic disease assessments should also be performed as outlined in the Time and Events Schedule.

Other signs or symptoms deemed related to disease that are suggestive of progression, including escalating pain not referable to another cause, increased ascites, declining performance status, and examination findings consistent with disease progression, are valid reasons to consider an unscheduled assessment of tumor status.

Subjects who discontinue study drug but do not withdraw from the study will be followed-up as described in Section 9.1.4, Follow-up Phase. In particular, radiographic disease assessment should be performed according to the protocol schedule until a subsequent anticancer therapy is started.

9.2.2. Criteria

9.2.2.1. Primary Endpoint

Overall Survival

Survival status information will be used to calculate OS, the study's primary endpoint. OS is defined as the time between randomization and death. Subjects who die, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to follow-up before the end of the study or who are withdrawn from the study will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date when the subject is known to be alive.

9.2.2.2. Secondary Endpoints

Disease response based on investigator assessments using RECIST Version 1.1 (Attachment 1) will be used to evaluate PFS, TTP, ORR, and DR.

Progression-Free Survival

Disease progression based on RECIST Version 1.1 guidelines (Attachment 1) will be used to calculate PFS, defined as the time from randomization to the occurrence of disease progression or death, whichever occurs first. If a subject has not progressed and is still alive as of the clinical cutoff date, the subject will be censored at the date of his or her last radiographic assessment. If a subject starts subsequent anticancer therapy without prior disease progression, then he or she will be censored at the last disease assessment date before or on the first day of the start of the first subsequent anticancer therapy.

Time-to-Progression

TTP is defined as the time between randomization and disease progression. Subjects who progressed or died with documented disease progression will be considered to have had an event. Subjects who died without evidence of disease progression will be considered censored at time of the last radiographic disease assessment before death. Subjects who are lost to follow-up or still being treated without documented disease progression will be censored at the date of the last radiographic disease assessment. If a subject starts subsequent anticancer therapy without prior disease progression, then he or she will be censored at the last disease assessment date before or on the first day of the start of the first subsequent anticancer therapy.

Objective Response Rate

ORR is defined as having complete response (CR) or partial response (PR) as best overall response based on reconciled radiographic disease assessment.

Duration of Response

Duration of response (DR) is defined only for subjects who have CR or PR as best overall response and is calculated from the date of the first documentation of response to the date of disease progression or death, whichever occurs first. Subjects who have neither progressed nor died will be censored at their last disease assessment date. If a subject starts subsequent anticancer therapy without prior disease progression, then he or she will be censored at the last disease assessment date before or on the first day of the start of the first subsequent anticancer therapy.

9.3. Patient-Reported Outcomes

MDASI scores will be used to assess subjects' perceived symptom burden and determine the impact of treatment on symptom change or stability. The MDASI is a 19-item self-reported questionnaire designed to measure the severity of cancer symptoms or treatment-related symptoms and the degree to which the symptoms interfere with daily function (Attachment 2). There are 13 items related to symptom severity "at its worst" (pain, fatigue, nausea, disturbed sleep, being distressed or upset, shortness of breath, remembering things, lack of appetite, feeling drowsy [sleepy], dry mouth, feeling sad, vomiting, and numbness or tingling). Six items measure how much these symptoms have interfered with 6 daily activities (general activity, mood, work, relations with others, walking, and enjoyment of life). All items are rated on a 10-point numeric rating scale. Anchors for the symptom severity items are 0 "not present" and 10 "as bad as you can imagine". Anchors for the interference items are 0 "did not interfere" and 10 "interfered completely". High scores reflect greater symptom severity or burden. The recall period is the past 24 hours and the time required to complete the questionnaire is approximately 5 minutes.

The endpoints for the PRO analysis will be the change from baseline in mean score of all symptom severity items, mean score of all symptom interference items, and each individual item score. The change in these PRO scores between baseline and postbaseline assessments will be summarized.

9.4. Biomarker and Pharmacogenomic Evaluations

9.4.1. Biomarker Evaluation

FFPE tumor samples from diagnosis collected as part of this study may be utilized for biomarker analyses. Research on these samples will be limited to genes involved in the mechanism of action of trabectedin, or dacarbazine, or to the diseases for which they are developed. Samples may be analyzed to assist in development of these drugs in L-type sarcomas.

9.4.2. Pharmacogenomic Evaluation

There are 2 parts to the optional pharmacogenomic component of this study (whole blood sample collection).

Analysis Related to the Study (Part 1)

Part 1 of pharmacogenomic research allows for the analysis of genes may be relevant to trabectedin, or dacarbazine, or soft-tissue sarcoma. Candidate genes will only be genotyped, if it is hypothesized that this may help resolve issues with the clinical data. The genes that are currently hypothesized to potentially be relevant to trabectedin and

soft-tissue sarcoma are provided in Attachment 3. Genotyping of any of these candidate genes would be performed on identifiable samples.

Additional genes may be analyzed on identifiable samples if these genes are hypothesized to be relevant to trabectedin, or dacarbazine, or soft-tissue sarcoma between the time that the clinical protocol has been issued and the samples have been made nonidentifiable.

DNA Storage for Future Research (Part 2)

Part 2 of the pharmacogenomic research allows for the storage of DNA samples for future genetic research related to trabectedin, or dacarbazine, or the indication(s) for which they are developed. Stored DNA samples and relevant clinical data will be made nonidentifiable after the Clinical Study Report has been issued. This involves removing personal identifiers and replacing the study subject identifier with a new number to limit the possibility of linking genetic data to a subject's identity.

Subjects will be given the option to participate in Part 1 only, Part 2 only, both parts, or neither part of the pharmacogenomic component of this study where local regulations permit.

9.5. Safety Evaluations

Details regarding the IDMC are provided in Section 11.5.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Drug-related Grade 3 or Grade 4 toxicities will be assessed until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first. Grade 2 to 4 liver or cardiac toxicities will be monitored until the toxicity is Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. For randomized subjects, clinical laboratory testing of blood samples should be performed no more than 48 hours before Day 1 of each cycle, midcycle on Days 8 (±2 days) and 15 (±2 days), and at the end of treatment. Physician review of clinical laboratory results must occur before study drug can be administered. See Section 6.2, Criteria for Continuation of Treatment, for additional information.

The following tests will be performed by the local laboratory. The ALP liver fraction or 5' nucleotidase should be measured if total ALP is >2.5 x ULN. If the local laboratory is unable to measure these analytes, they will be measured by a central laboratory, and the results will be sent directly to the site and entered into the CRF.

- Hematology Panel

  -hemoglobin -platelet count
  -ANC -white blood cell count

- Serum Chemistry Panel

  -creatinine -albumin
  -AST -ALP liver fraction*
  -ALT -5' nucleotidase*
  -ALP -total (direct and indirect) bilirubin
  -CPK

  * ALP liver fraction or 5' nucleotidase should be measured only if total ALP is >2.5 x ULN.

- Serum or urine pregnancy testing for women of childbearing potential is required only during the Screening Phase.

Potential cases of hepatotoxicity will be thoroughly investigated. Investigators will complete a supplemental CRF section and provide additional supporting documentation for all subjects who experience all of the following within the same cycle: total bilirubin values ≥2 x ULN, elevated transaminase values (AST or ALT) ≥3 x ULN, and ALP values ≤2 x ULN.

Potential cases of sepsis will be thoroughly investigated. Investigators will complete a supplemental CRF section and provide additional supporting documentation for all subjects who experience the adverse event of sepsis.

MUGA Scans

MUGA scans performed up to 30 days before randomization and as part of the end-of-treatment evaluations are required to assess cardiac function. Echocardiograms can be substituted for MUGA if the latter is not available. The same modality should be used for both screening and end-of-treatment evaluations.

Electrocardiogram

ECGs will be performed during the Screening Phase and as part of the end-of-treatment evaluations. Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by an appropriately trained investigator (eg, a cardiologist or internist).

Vital Signs (oral temperature, respiration, pulse, blood pressure)

Vital signs will be recorded only during the Screening Phase. Any clinically significant change in vital signs during the study should be reported as an adverse event.

Physical Examination

A physical examination including height and weight measurement will be performed during the Screening Phase. Subject weight will be measured with the subject lightly clothed and without shoes. Any clinically significant change in physical findings noted during the study should be reported as an adverse event.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has experienced a clinical endpoint that precludes further study (eg, early mortality in a mortality endpoint study).

10.2. Discontinuation of Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The subject has disease progression
- The subject experiences unacceptable toxicity
- Concurrent medical conditions for which the investigator believes that it is in the best interest of the subject to stop treatment

- The subject begins a subsequent anticancer therapy
- The subject becomes pregnant
- The subject withdraws consent/assent to continue study treatment.

If a subject discontinues study treatment before disease progression has occurred, obtain end-of-treatment evaluations and continue survival follow-up and radiographic disease assessments as described in Section 9.2.1.1, Survival Status, and Section 9.2.1.2, Disease Assessment.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for either of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent

In case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

A subject who withdraws from the main part of the study will have the following options regarding pharmacogenomic research:

- The DNA extracted from the subject's blood will be retained and used in accordance with the subject's original pharmacogenomic informed consent/assent.
- The subject may withdraw consent/assent for pharmacogenomic research, in which case the DNA sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the pharmacogenomics representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From Pharmacogenomic Research Only

The subject may withdraw consent/assent for pharmacogenomic research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed. The sample destruction process will proceed as described above.

However, all samples will be made nonidentifiable after the clinical study report is issued and thereafter cannot be identified for destruction. If the sample has already undergone conversion to the nonidentifiable format, the sponsor will notify the investigator in writing.

11. STATISTICAL METHODS

11.1. Efficacy Analyses

Efficacy analyses will be performed using the intent-to-treat population. The overall 2-sided significance level for the primary endpoint will be 0.05. Analyses of all secondary efficacy endpoints will not use group sequential methods, and no adjustments for multiplicity due to repeated testing will be performed for these endpoints. The exact timing of the analysis will be carried out according to the pre-specified required number of events for each endpoint. The final analysis of OS is planned after approximately 376 deaths have been observed.

11.1.1. Primary Endpoint

The primary analysis of OS is the comparison of OS between the 2 treatment groups using the unstratified log-rank test. The distribution of OS will be estimated for each treatment group using the Kaplan-Meier method. The median times to event with 2-sided 95% CIs will be estimated. The estimate of the hazard ratios (HR) and their 95% CI will also be provided. The effect of prognostic factors such as age, lines of prior chemotherapy, ECOG Performance Status score, and L-subtype will also be examined in the supplementary analysis using the Cox proportional hazards model.

11.1.2. Major Secondary Endpoints

Methods similar to those used to evaluate OS will be used to analyze PFS and TTP. Comparison of the ORR between the 2 treatment groups will be made using the Fisher's exact test. Response rate and the associated 95% CI will be provided for each treatment group. For DR, descriptive statistics will be provided. No statistical testing will be performed.

11.2. Sample Size Determination

It was assumed that the hazards for the 2 treatment groups follow a proportional hazards model for OS. The test to detect a difference between a median OS of 10 months in the dacarbazine group and a median OS of 13.5 months in the trabectedin group (HR=0.74) at an overall 2-sided significance level of 0.05 with a power of 80% requires 376 events. Assuming an enrollment rate of 25 subjects per month over 23 months, a sample size of approximately 570 subjects is planned for the study.

11.3. Safety Analyses

The safety population will used for safety analyses.

Adverse Events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. The severity of adverse events will also be summarized.

Special attention will be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

A listing of subjects with any laboratory results outside the reference ranges will be provided. Clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding the study medication (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of a concomitant therapy should be reported.

The NCI-CTCAE, Version 4.0, will be used to grade the severity of adverse events and to summarize clinical laboratory results.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross tabulations (with classes for below, within, and above normal ranges, as defined by the local laboratories). A listing of subjects with any laboratory results outside the reference ranges will be provided. These results will be summarized according to the NCI-CTCAE, Version 4.0, as appropriate.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations.

11.4. Interim Analysis

The OS endpoint analysis incorporates group sequential design by including 1 interim analysis and 1 final analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. This method ensures that the type I error rate is not inflated. The interim analysis is planned at 50% of the required number of events. The study will be stopped early should the data strongly favor treatment with trabectedin compared with DTIC in terms of the primary endpoint, OS. The cumulative alpha spent will be 0.003 and 0.050 for the 2 analyses, respectively. This study will reach the primary endpoint (OS) in approximately 32 months.

11.5. Independent Data Monitoring Committee

An IDMC will be established to monitor data to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives. The details will be provided in a separate IDMC charter. The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter. The IDMC will review safety data approximately every 3 to 4 months and will also review the results of the interim analysis of OS, which will be performed when approximately 188 deaths have been observed (See Section 11.4, Interim Analysis).

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For a comparator product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The NCI-CTCAE Version 4.0 will be used to grade the severity of adverse events.

12.2. Procedures

12.2.1. All Adverse Events

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until 30 days after the last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Drug-related Grade 3 or Grade 4 toxicities will be assessed until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first. Grade 2 to 4 liver or cardiac toxicities will be monitored until the toxicity is Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first.

Disease progression will not be reported as an adverse event, as this information will be used for the assessment of secondary efficacy endpoints. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless

of whether they are protocol-specific assessments. All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- reasons described in the protocol, eg, drug administration, protocol-required testing
- prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event
- preplanned reasons (ie, planned prior to the start of treatment on study – must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study medication remains a reportable serious adverse event.
- as part of a standard procedure for protocol therapy administration will not be reported as a Serious Adverse Event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- for the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- as part of a procedure for protocol/disease related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling), or hospitalization or prolonged hospitalization for a complication of such a procedure.

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the study drug may have an effect on sperm, or if the effect is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The trabectedin (YONDELIS® i.v. formulation) supplied for this study is a white to off white powder for reconstitution, dilution, and i.v. infusion. Inactive ingredients are sucrose, potassium phosphate monobasic, phosphoric acid and potassium hydroxide. Each vial of trabectedin for injection is a single-use vial.

Dacarbazine will be supplied as a colorless to ivory-colored solid.

14.2. Packaging

The study drug will be packaged in individual kits.

Trabectedin

Study drug is provided by the sponsor as a sterile lyophilized product in single-use vials containing 1 mg of YONDELIS.

Dacarbazine

Dacarbazine is supplied in vials and is provided by the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Detailed information describing the requirements for storage, reconstitution and dilution, accountability, and disposal of trabectedin can be found in the IB for trabectedin and in the prescribing information for dacarbazine study drug.

Trabectedin

Trabectedin is a cytotoxic anticancer medicinal product, and caution should be exercised during handling.

No incompatibilities have been observed between YONDELIS and Type 1 glass vials, polyvinylchloride, polyethylene, polyethylene and polypropylene mixture bags, polyvinylchloride or polyethylene tubing, or titanium or plastic resin implantable vascular access systems.

Only calibrated infusion pumps with the above product contact surfaces should be used to deliver the drug over a 24-hour infusion period.

All trabectedin study drug must be stored at controlled temperatures ranging from 2ºC to 8ºC (36ºF to 46ºF).

Dacarbazine

Dacarbazine is a cytotoxic anticancer medicinal product, and caution should be exercised during handling. All dacarbazine study drug must be stored at controlled temperatures ranging from 2ºC to 8ºC (36ºF to 46ºF). Dacarbazine is light sensitive.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form. Investigational product (used and unused vials) must be documented by kit number on the Institution's Investigational Product Destruction Form. This information must be made available for verification of drug accountability at the sponsor's on-site monitoring visits.

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- e-CRFs
- Site Investigational Product Binder
- PRO questionnaire
- Laboratory supplies to process samples that will be sent to the central laboratory including study manual
- Pharmacogenomic sample collection and shipping instructions
- IVRS/IWRS manual and codes

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

There are no currently approved therapies in the United States, Australia, or Brazil for subjects with advanced or metastatic STS once single-agent anthracycline treatment or combination treatment with an anthracycline and ifosfamide has failed. Although dacarbazine is not approved for the treatment of STS, it was selected as the active control in the current study as it is considered to have antitumor activity based on literature and practice guidelines. Therefore, the dacarbazine control group in this study will allow the comparison of trabectedin with a widely used treatment in this population. A 2:1 randomization is employed to enable more patients to receive trabectedin.

The open-label study design is appropriate as the primary endpoint of OS relies on the objective assessment of subject survival. Although a double-bind study design is possible, it would be unethical to expose subjects in the dacarbazine group to the potential risks associated with the use of central venous catheters. Furthermore, it is unlikely that a double-blind design would effectively reduce investigator bias, as the adverse event profile for trabectedin would make treatment assignment obvious.

Subject safety will be protected by frequent contact with study personnel to assess and manage adverse events. An IDMC will review cumulative safety data every 3 to 4 months during the study and will also review the results of the interim analysis of OS.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent/assent voluntarily will be enrolled. When referring to the signing of the informed consent form, the terms legal guardian and legally-acceptable representative refer to the legally appointed guardian of subjects 15 years of age and up to the age of legal consent in the jurisdiction in which the study is taking place. For each subject, his or her parent(s) (preferably both parents, if available) or legally-acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from subjects who are 15 years of age and up to the age of legal consent and capable of understanding the nature of the study. For the purposes of this study, all references to

subjects who have provided consent/assent refers to the subject (assent as applicable) and his or her parent(s) or the subject's legal guardian(s) or legally-acceptable representative(s) who have provided consent according to this process. Subjects who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The study requires radiographic disease assessments, which may necessitate the use of diagnostic imaging techniques that may expose subjects to X-ray radiation.

The total blood volume to be collected from a subject who is on study for 5 months is approximately 120 to 130 mL, which is considered to be less than that which would be collected from a standard blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent and assent forms (and any other written materials to be provided to the subjects)
- Investigator’s Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator’s curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)

- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent and assent forms, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the pharmacogenomic research component of the clinical study and for the pharmacogenomic informed consent and assent forms must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenomic research.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form, assent form (if applicable), and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent/assent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject (or a legally-acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form and assent form that are used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects or their legally-acceptable representative the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject or their legally-acceptable representative is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed or to obtain information about his or her survival status.

The subject or their legally-acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally-acceptable representative's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

Subjects will be asked to consent/assent to participate in a pharmacogenomic research component of the study (where local regulations permit). After informed consent for the clinical study is appropriately obtained, the subject or his or her legally-acceptable representative will be asked to sign and personally date a separate pharmacogenomic informed consent form indicating agreement to participate in optional pharmacogenomic research. A copy of the signed pharmacogenomic informed consent form will be given to the subject. Refusal to participate will not result in ineligibility for the clinical study.

If the subject or legally-acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject or legally-acceptable representative is obtained.

Assent must be obtained from subjects who are 15 years of age and up to the age of legal consent in the jurisdiction in which the study is to take place and who are capable of understanding the nature of the study. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for subjects 15 years of age and up to the legal age of consent in the jurisdiction in which the study is to take place. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent and/or legally-acceptable representative.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or

accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject (or his or her legally-acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

For those subjects who gave consent/assent to store DNA samples for future genetic research (Part 2), samples and corresponding relevant clinical data will be made nonidentifiable by the removal of personal identifiers. Samples will be stored until completely used. Only research related to the drug or the indications for which the drug is developed will be done on stored samples. For data generated on identifiable samples (Part 1), the sponsor will provide the individual raw data, through the investigator, to subjects who submit a written request. The sponsor cannot make decisions as to the significance of any findings resulting from this pharmacogenomic research, and cannot, therefore, provide genetic counseling. Genotypic data generated on nonidentifiable samples (Part 2) cannot be returned to individual subjects.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where trabectedin is not approved for the treatment of soft tissue sarcoma.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant

competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, assent form (if applicable), any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)

- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; tumor assessments; follow-up for survival status; date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRFs and will be considered source data:

- Race
- Blood pressure/heart rate (if not primary efficacy or significant safety issue)
- Height/weight (except if primary efficacy or significant safety issue)
- Details of physical examination
- PRO.

17.5. Case Report Form Completion

Case report forms are provided for each subject in printed or electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor. The electronic file will be considered to be the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager can generate a query (field data correction form) for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor

to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding trabectedin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of trabectedin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomic results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy

approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1:
RECIST Guidelines

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The following information was extracted from Section 3, Section 4, and Appendix I of the New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication.

Measurability of tumor at baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Non-measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by 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. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter 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 suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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 on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

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. As is described in Appendix II, 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). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix II.

Attachment 1: (Continued)
RECIST Guidelines

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response (CR).

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two 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*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

A sum of the diameters (longest for non-nodal lesions,) for all target lesions will be calculated and reported as the *baseline sum diameters*. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Attachment 1: (Continued)
RECIST Guidelines

Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Timepoint response

It is assumed that at each protocol specified timepoint, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Best overall response: all timepoints

The *best overall response* is determined once all the data for the patient is known.

Attachment 1: (Continued)
RECIST Guidelines

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 - Timepoint response: patients with Target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.

Table 2 - Timepoint response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = inevaluable.

[a] Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–2.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

Attachment 1: (Continued)
RECIST Guidelines

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of progressive disease).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Attachment 1: (Continued)
RECIST Guidelines

Summary of major changes RECIST 1.0 to RECIST 1.1[a]

	RECIST 1.0	RECIST 1.1	Rationale
Minimum size measurable lesions	CT: 10 mm spiral; 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable.
	Lymph node: not mentioned	CT: ≥15 mm short axis for target ≥10 - <15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive.
Special considerations on lesion measurability	-	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions.
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site.
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes.
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error.
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding.
New lesions		New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD).
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline.
		Special notes: How to assess and measure lymph nodes; CR in face of residual tissue; Discussion of 'equivocal' progression	Frequently asked questions on these topics.

Attachment 1: (Continued)
RECIST Guidelines

Summary of major changes RECIST 1.0 to RECIST 1.1[a] (Continued)

	RECIST 1.0	RECIST 1.1	Rationale
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint.
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint. Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III; 9 categories collapsed into 5; In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently.
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomized studies where response is not the primary endpoint makes separate 'rules' unnecessary.
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT. Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience.
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1; Appendix III: frequently asked questions	

PD = progressive disease
[a] See publication for references applicable to this table.

Attachment 2:
M.D. Anderson Symptom Inventory

Date: _____

Participant Initials: _____

Participant Number: _____

Institution: _____

Hospital Chart #: _____

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Attachment 2: (Continued)
M.D. Anderson Symptom Inventory

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Attachment 3:
Candidate Gene List for Part 1 of Pharmacogenomics

Absorption, Distribution, Metaboli**sm**, and Excretion Genes: *ABCB family, ABCC family, ABCG2, ADH family, AHR, ALDH family, AOX1, ARNT, ATP7A, ATP7B, BDH2, CDA, CHST family, COMT, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP1A2, CYP1B1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP27A1, CYP2A13, CYP2A6, CYP2A7, CYP2B6, CYP2B7, CYP2C family, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP39A1, CYP3A family, CYP46A1, CYP4B1, CYP4F family, CYP4Z1, CYP51A1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, DHRS family, DHRSX, DPYD, EPHX1, EPHX2, FMO family, FOM3, GPX family, GSR, GSS, GSTA family, GSTCD, GSTK1, GSTM family, GSTO1, GSTO2, GSTP1, GSTP2, GSTT1, GSTT2, GSTZ1, HAGH, HNMT, MAOA, MAOB, MGST1, MGST2, MGST3, MPO, NAT1, NAT2, NFE2L2, NNMT, NQO1, NR1I2, NR3C1, POR, PPARA, PPARD, PPARG, RALBP1, RLIP76, SLC10A1, SLC10A2, SLC13A1, SLC15A1, SLC15A2, SLC16A1, SLC19A1, SLC22A family, SLC28A family, SLC29A1, SLC29A2, SLC5A6, SLC7A5, SLC7A7, SLCO1A2, SLCO1B1, SLCO1B3, SLCO1C1, SLCO2A1, SLCO2B1, SLCO3A1, SLCO4A1, SLCO4C1, SLCO5A1, SLCO6A1, SPG7, STE, SULT1A1, SULT1A2, SULT1B1, SULT1C1, SULT2A1, SULT2B1, SULT4A1, TPMT, UGT1A family, UGT2A1, UGT2B family, UGT8, XDH.*

MHC Related Genes: *ABCB2, ABCB3, ABCF1, AGER, AGPAT1, AIF1, ApoM, APT, ATP6G, B30.2-L, B3GALT4, BAT1, BAT2, BAT3, BAT4, BAT5, BF, BING1, BING3, BING4, BING5, BTL-II, C2, C4B, CAT56, CAT75X, CDSN, CLIC1, COL11A2, COL11A2p, COX3-L, CREBL1, CSK2B, CYP21A2, DAXX, DDAH2, DDR, DDX16, DHFRP, DOM3L, FLOTILLIN, G10, G16, G18, G4, G5b, G5c, G6b, G6c, G6d, G6e, G6f, G7B, G7c, G8, G9a, GLN-tRNA, GNL1, GT257, HCGI, HCGII-1, HCGII-2, HCGII-3, HCGII-4, HCGII-5, HCGII-6, HCGII-7, HCGII-8, HCGIV-1, HCGIV-10, HCGIV-11, HCGIV-2, HCGIV-3, HCGIV-4, HCGIV-5, HCGIV-6, HCGIV-7, HCGIV-8, HCGIV-9, HCGIX-1, HCGIX-2, HCGIX-3, HCGIX-4, HCGIX-5, HCGVII, HCGVIII-1, HCGVIII-2, HCR, HKE2, HLA-16, HLA-17, HLA-21, HLA-30, HLA-54, HLA-59, HLA-70, HLA-75, HLA-80, HLA-90, HLA-92, HLA-A, HLA-B, HLAC, HLA-DMA, HLA-DMB, HLA-DNA, HLA-DOB, HLA-DPA1, HLA-DPA2, HLA-DPA3, HLA-DPB1, HLA-DPB2, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DQB3, HLA-DRA, HLA-DRB1, HLA-DRB2, HLA-DRB3, HLA-DRB9, HLA-E, HLA-F, HLA-G, HLA-X, HLA-Z1, HNRPA1, HSPA1A, HSPA1B, HSPA1L, HTEX4, IER3, IPP2, KE6, KIAA0055-hom, KIAA0170, KNSL2, LST1, LTA, LTB, MICA, MICB, MICC, MICD, MICE, MICF, MSH5, NEU1, NFKBIL1, NG22, NG23, NG3, NG36, NG5, NG7, NOB1, NOB2, NOB3, NOB4, NOB5, NOTCH4, P5-1, P5-10, P5-11, P5-12, P5-13, P5-14, P5-15, P52, P5-2, P5-3, P5-4, P5-5, P5-6, P5-7, P5-8, P5-9, PBX2, POU5FI, PPP1R10, PPT2, ROA-hom, PSMB8, PSMB9, PTD017, RANBP1, RD, RGL2, RING1, RING13, RING14, RING3, RING8, RING9, RNF5, RNF9, rPL12-L, RPL32-L, rPL35A-L, RPL3-hom, RPL7A, RPL7B, RPS18, RXRB, SACM2L, SEEK1, SKI2W, SPR1, STG, STK19, TAPBP, TAT-SF1-L, TCF19, TNF, TNXB, TSBP, TUBB, Val-TRS, ZNF173, ZNFB7, ZNF-L, ZNRD1.*

DILI Related Genes: *HCP5/HLAB, HLA-DQB1, HLA* class 3, *ADAMTS9, RAD54L2/TEX264.*

LAST PAGE