TARGETING MICROENVIRONMENT AND CELLULAR IMMUNITY IN SARCOMAS WEEKLY TRABECTEDIN COMBINED WITH METRONOMIC CYCLOPHOSPHAMIDE IN PATIENTS WITH ADVANCED PRETREATED SOFT-TISSUE SARCOMAS
A PHASE I/II STUDY FROM THE FRENCH SARCOMA GROUP

Protocol *TARMIC*

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APPROVAL AND SIGNATURES OF PROTOCOL

Protocol title : Targeting Microenvironment and Cellular Immunity in Sarcomas Weekly trabectedin combined with Metronomic Cyclophosphamide in Patients with Advanced Pretreated Soft-tissue Sarcomas. A Phase I/II study from the French Sarcoma Group.

Competent authority	Name : ANSM	Date de l'autorisation initiale Autorisation de la modification substantielle 1 Autorisation de la modification substantielle 2 Autorisation de la modification substantielle 3 Autorisation de la modification substantielle 4 Autorisation de la modification substantielle 5	19/10/2015 10/03/2016 29/12/2016 13/10/2017 02/05/2018 06/02/2019
		Référence :	151077A-12
Ethic Committee	Name : CPP du Sud-Ouest et d'Outre-Mer III	Date de l'avis favorable initial Autorisation de la modification substantielle 1 Autorisation de la modification substantielle 2 Autorisation de la modification substantielle 3 Autorisation de la modification substantielle 4 Autorisation de la modification substantielle 5	30/09/2015 24/02/2016 30/11/2016 31/05/2017 31/01/2018 27/02/2019
		Référence :	2015/94

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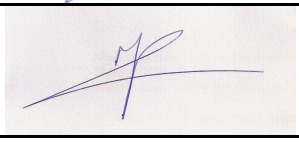
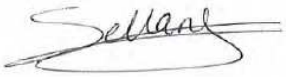
Biostatistician	Marina PULIDO Institut Bergonié – Bordeaux Tél:05.24.07.19.29/Fax: 05.24.07.19.49 Mail : m.pulido@bordeaux.unicancer.fr	11/12/2018	
Clinical Research Assistant	Sabrina SELLAN-ALBERT Institut Bergonié – Bordeaux Tél:05.56.33.78.05/Fax:05.56.33.04.85 Mail : s.albert@bordeaux.unicancer.fr	11/12/2018	
Pharmacist	Emilie TOULZA Institut Bergonié – Bordeaux Tél:05.47.30.60.53/Fax: 05.56.33.04.85 Mail : e.toulza@bordeaux.unicancer.fr	11/12/2018	

I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the Good Clinical Practice (decision of 24 November 2006), the Public Health Law No. 2006-806 of August 09, 2004 and the implementing Decree n° 2006-477 of April 26, 2006 and as described in this document.

I assume my responsibilities as referent investigator including:
- Collection of informed consent, dated and signed by patients before any selection procedure in the protocol,
- Validation of case report forms, completed for each patient included in the study,
- Direct access to source documents for verification by the clinical research assistant (CRA) commissioned by the sponsor,
- Archiving of critical documents of the study for a 15 year-period.

Name and address of the hospital

Name of the Coordinating Investigator :

Date : |__|__| |__|__| |__|__|__|__| Signature :

Title of the study	**Targeting Microenvironment and Cellular Immunity in Sarcomas Weekly trabectedin combined with Metronomic Cyclophosphamide in Patients with Advanced Pretreated Soft-tissue Sarcomas. A Phase I/II study from the French Sarcoma Group**
Abbreviation of the trial	**TARMIC**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Professor Antoine ITALIANO** **Department of Medical Oncology**
Number of investigational sites planned	**Phase I:** 1 centre - Institut Bergonié **Phase II:** 1 centre - Institut Bergonié
Number of patients	**Phase I:** 12 - 24 patients **Phase II**: 47 patients
Duration of the study	Planned enrollment period: 48 months Treatment duration : until progression Follow-up: 12 months Study period: 5 years
Medical conditions	Adult patients with unresectable locally advanced or metastatic soft-tissue sarcoma
Study design	**Phase I:** Monocentric Phase I trial based on a dose escalation study design (3+3 traditional design). **Phase II**: One-arm, monocentric Phase II trial based on two-stage optimal Simon's design.
Objectives	**<u>Phase I:</u>** **Primary objective:** To establish the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the dose limiting toxicities (DLT) of trabectedin given in combination with CP. **Secondary objectives:** • To evaluate preliminary signs of antitumor activity of trabectedin given in combination with CP in terms of objective response under treatment (as per RECIST v1.1 criteria), 6-month non-progression (as per RECIST v1.1 criteria), 1-year progression-free survival (PFS) (as per RECIST v1.1 criteria) and 1-year overall survival (OS). • To describe the pharmacokinetics (PK) of trabectedin given in combination with CP. • Biomarker study: To perform pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points). • Ancillary study: To assess pharmacodynamics changes of Tissue Associated Macrophage (TAM) infiltration and additional tumor markers on fresh pre-treatment and on-treatment tumor biopsies. **<u>Phase II:</u>** **Primary objective:** To evaluate the antitumor activity of trabectedin in association with CP in terms of non-progression at 6 months (complete or partial responses or stable disease more than 24 weeks, as per RECIST v1.1 criteria) after centralized radiological review, in patients with advanced STS who already failed anthracycline-containing chemotherapy (CT). **Secondary objectives:** • To evaluate the antitumor activity of trabectedin in association with CP in terms of objective response under treatment (as per RECIST v1.1 criteria), 1-year progression free survival (PFS) (as per RECIST v1.1 criteria) and 1-year overall survival (OS). • To evaluate the toxicity of trabectedin in association with CP (NCI-CTC v4). • Optional biomarker study: To perform pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points).

	• Optional ancillary study: To assess pharmacodynamics changes of TAM infiltration and additional tumor markers on fresh pre-treatment and on-treatment tumor biopsies.
Inclusion criteria	1. Patients with soft-tissue sarcoma histologically confirmed by central review (Pr. Coindre team), except in case of diagnosis was already confirmed by the RRePS Network, 2. Metastatic or unresectable locally advanced disease, 3. Age ≥ 18 years, 4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, 5. Life expectancy > 3 months, 6. Measurable disease according to RECIST v1.1 (lesion in previously irradiated field can be considered as measurable if progressive at inclusion according to RECIST v1.1), 7. For patients included in phase II study, progressive disease according to RECIST v1.1 criteria diagnosed on the basis of two CT scan or MRI obtained at an interval less than 6 months in the period of 12 months prior to inclusion and confirmed by central review. PET-CT are also acceptable (two PET-CT or a CT scan compared with a PET-CT), under the following conditions: a. Target lesions must be evaluable on PET-CT according to RECIST v1.1. This will be determined by the central radiologist at the time of the review. If target lesions are not evaluable according to RECIST v1.1, patient will not be eligible. b. PET-CT is acceptable only for the central review. If not available, an additional CT scan (or MRI) must be performed within four weeks prior to Day 1 of cycle 1 (+1 week tolerance) to be used as baseline tumor assessment. Patient must be then followed using the same technique throughout the duration of the protocol, 8. Previous use of Anthracyclines, 9. Have provided tissue from an archival tissue sample, 10. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy, 11. Adequate hematological, renal, metabolic and hepatic function: a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, leukocyte count ≥ 2.5 x 10^9/l and platelet count ≥ 100 x 10^9/l b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of extensive liver involvement) and alkaline phosphatase (AP) ≤ 2.5 x ULN c. Total bilirubin ≤ ULN. d. Albumin ≥ 25 g/l e. Serum Creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 30 ml/min (according to Cockroft formula). f. Creatine Phosphokinase (CPK) ≤ 2.5 x ULN 12. Women of childbearing potential must have a negative serum pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier, 13. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 14. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0), 15. Patients with a social security in compliance with the French law, 16. Voluntarily signed and dated written informed consent prior to any study specific procedure.
Non Inclusion criteria	1. Previous treatment with Trabectedin, 2. Currently active bacterial or fungus infection (> grade 2 CTC [CTCAE]), HIV1, HIV2, hepatitis B or hepatitis C infections, 3. History of chronic alcohol use and/or cirrhosis, 4. The following unstable cardiac conditions are not allowed: - Congestive heart failure - Angina pectoris - Myocardial infarction within 1 year before registration

<table>
<tr><td></td><td>- Uncontrolled arterial hypertension defined as blood pressure ≥ 150/100 mmHg despite optimal medical therapy
- Arrhythmias clinically significant
5. Patients unable to receive corticotherapy,
6. Known central nervous system malignancy (CNS),
7. Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding,
8. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
9. Previous enrolment in the present study,
10. Patient unable to follow and comply with the study procedures because of any geographical, social or psychological reasons,
11. Known hypersensitivity to any involved study drug or any of its formulation components.
12. Recent vaccination (in the last 2 weeks before inclusion) for yellow fever.
13. Known urinary tract obstruction.
14. Cardiac dysfunction:
- LVEF (Left Ventricular Ejection Fraction) < 40% at baseline;
- or clinically symptomatic cardiac dysfunction (any % of LVEF at baseline)</td></tr>
<tr><td>Route of administration</td><td>Cyclophosphamide will be administered bi-daily (50 mg x 2), and given on a week on/week off schedule.
Trabectedin will be administered by intravenous 3-hour infusion weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks.</td></tr>
<tr><td>Treatment schedule</td><td>Phase I: Dose escalation part
<table>
<tr><th colspan="6">Regimen Description</th></tr>
<tr><th>Agent</th><th>Premedication</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th></tr>
<tr><td>CP</td><td>domperidone, metoclopramide, setrons allowed</td><td>50mg x 2</td><td>per os</td><td>1 week on /1 week off</td><td rowspan="2">4 weeks</td></tr>
<tr><td>Trabectedin</td><td>20 mg dexamethasone</td><td>Doses as appropriate for assigned dose level</td><td>IV</td><td>Days 1, 8 and 15 every 4 weeks</td></tr>
</table>
A treatment cycle consists of 4 weeks. Treatment may continue until disease progression or study discontinuation (withdrawal of consent, intercurrent illness, unacceptable adverse event or any other changes unacceptable for further treatment, etc.)
Patients will be allocated to 4 doses of Trabectedin following a 3 + 3 design:
<table>
<tr><th>Level</th><th>-1</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Trabectedin (mg/m²) - (3h)</td><td>0.25</td><td>0.3</td><td>0.4</td><td>0.5</td><td>0.6</td></tr>
</table>
Phase II: All patients will be treated at the RP2D of trabectedin defined in the preliminary phase I trial given in association with metronomic cyclophosphamide with the same schedule as in the phase I trial.</td></tr>
<tr><td>Safety and efficacy evaluations</td><td>Safety: Dose-limiting toxicities will be assessed for 4 weeks.
Toxicities will be assessed on Day 8, 15, 28 and every 4 weeks afterwards.
Efficacy will be assessed every 2 cycles (8 weeks).</td></tr>
<tr><td>Endpoints</td><td>Phase I trial:
Primary objective of the phase I trial is to establish the recommended phase II dose (RP2D), the maximum tolerated doses (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the dose limiting toxicities (DLT) of trabectedin given in association with metronomic cyclophosphamide.

Definitions
• Dose-limiting toxicity (DLT): A DLT is defined as an AE or laboratory abnormality that fulfills all the criteria below:
o Occurs during the first cycle (4 weeks) of treatment.
o Is considered to be at least possibly related to the study treatment.
o Meets one of the criteria below, graded as outlined or according to NCI CTCAEv4.0 :
▪ Any grade 4 toxicity (except for vomiting without maximal symptomatic/prophylactic treatment)
▪ Grade >= 3 non-haematological toxicity lasting > 7days (except for</td></tr>
</table>

1rst episode of nausea without maximal symptomatic/ prophylactic treatment and if toxicity is transaminitis, which may last > 7 days if total bilirubin is normal or grade =<1)

- Grade >=3 hematologic toxicity lasting for > 7days
- Grade 4 neutropenia with fever
- Grade > 2 thrombocytopenia with bleeding

- Is unrelated to disease, disease progression, inter-current illness, or concomitant medications.

In addition, any AE related to treatment and considered as clinically significant on the opinion on the sponsor and of the investigators

- Maximum tolerated dose (MTD): the MTD is defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced a DLT in the first treatment cycle.
- Recommended phase II dose (RP2D): will be identified by the steering committee based on the MTD, additional safety data (all cycles), PK and PD data. Data from all cycles will be used to define the dose level to be recommended for further investigations in phase II. An IDMC will be requested to assess safety data and validate the RP2D.

Primary Endpoints:

- Toxicity graded using the common toxicity criteria from the NCI v4.0.
- Incidence rate of DLT at each dose level on cycle 1.

Secondary Endpoints:

- Objective response under treatment defined as complete (CR) or partial response (PR) as per RECIST v1.1 criteria. Objective response (CR or PR) under treatment is recorded from study treatment initiation until the end of treatment, with confirmation of responses ≥ 4 weeks after initial documentation, as per RECIST 1.1. Objective response under treatment is determined once all the data for the patient is known.
- 6-month non-progression defined as CR, PR or stable disease more than 24 weeks according to RECIST v1.1 criteria.
- 1-year Overall Survival (OS) defined as the time from study treatment initiation to death (of any cause).
- 1-year Progression-Free Survival (PFS) defined as the time from study treatment initiation to disease progression (defined as per RECIST v1.1) or death (of any cause), whichever occurs first.
- PK measurements expressed as the AUC, the half-life of trabectedin, CP and concentration peak.
- Pharmacodynamic study:
  - Blood: Serum/plasma cytokines levels (INFγ, TNFα, IL2,4,6,10) by ELISA ; Serum/plasma VEGF and TPS-1 levels by ELISA, monocytes, Treg, CD4+, CD8+ and DR lymphocytes subpopulations monitoring, CD4+/CD8+ ratio (Flow Cytometry),
  - Tumor: Fresh pre-treatment and on-treatment tumor biopsies will be collected to assess pharmacodynamics changes of TAM infiltration and additional tumor markers. Frozen biopsy samples will be analyzed for:
    - Hematoxylin and eosin staining (H&E).
    - Immunohistochemistry (IHC) assessments include, but are not limited to the following markers: CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers. The analysis will be prioritized based on the amount of material available.

Phase II trial:
Primary Endpoints:

- 6-month non-progression as defined above for the phase I escalation study.
- Disease status at 6 months will be reviewed by an expert radiologist. Reviewed data will be used for this primary endpoint analysis.

Secondary Endpoints:
Toxicity, objective response under treatment, 1-year OS and 1-year PFS defined above for the phase I escalation study except for the PD study which is optional in this phase II trial.

Statistical considerations	**Sample Size Considerations:** Phase I (Dose escalation part): based on a 3 + 3 traditional design with 4 dose levels with a minimum of 3 patients and a maximum of 6 patients per dose level: 24 eligible and assessable patients maximum will be needed. Patients fulfilling the inclusion criteria will be enrolled in successive cohorts of 3 to 6 patients. If no DLT is observed during the first 4 weeks of study treatment in 3 patients, the dose of trabectedin will be escalated to the dose level (DL) immediately above. If One DLT is observed among 3 patients, the cohort will be expanded to 6 evaluable patients. If two patients out of 3 or 2 /6 patients experience a DLT, the dose will be considered intolerable and the DL immediately below will be further explored. The recommended phase II dose (RP2D) will be defined based on safety, PK data and PD data (optimal biological dose). Phase II: The EORTC suggest that 3 and 6-month non-progression rates (NPR) are relevant endpoints in STS phase II trials. We rely on an optimal two-stage Simon's design. Using unacceptable and acceptable 6-month non-progression rates of 20% and 40% respectively, a 5% type I error rate (bilateral), and a 20% type II error rate (80% power), a total of 43 eligible and assessable subjects will be necessary, with 13 subjects recruited to the first stage. At the end of the first stage, the trial will be terminated if 3 or less responses are observed. Otherwise, the second group of 30 subjects will be recruited, and a total of 13 responses or more will be required to claim activity of the drug. Assuming, 10% are not eligible or cannot be assessed for the primary endpoint, 47 patients will be recruited. **Definition of study populations** Phase I trial Population assessable for safety (primary analysis): all patients who completed the DLT assessment period or who developped DLT are included in the analysis. *Patient's replacement* - If a patient cannot complete the full DLT evaluation period (28 days) and goes off-treatment for reasons other than toxicity, this patient can be replaced. - Patients with DLT will never be replaced. - All patients will be fully described in the analysis. - Only patients who completed the DLT assessment period or who develop DLT are included in the analysis for escalation. Phase II trial • Eligible population: All patients included without major violation of eligibility criteria. • Population evaluable for efficacy: - All patients eligible and for whom the following conditions are satisfied: o Diagnosis of STS at inclusion is confirmed after central review, except in case of diagnosis was reviewed in the RRePS Network, o For STS: Diagnosis of progressive disease at inclusion is confirmed after central review of the inclusion scans or MRI, o Received at least one administration of the treatment, o At least one disease measurement recorded not less than eight weeks after treatment onset. • The following patients will also be included in the population evaluable for efficacy; they will be considered as failures for the primary endpoint (i.e. disease progression at six months for STS) and not be replaced in the primary efficacy analysis: - Any eligible patients who received at least one administration of the treatment and experienced disease progression or died due to disease progression prior to response evaluation (will be considered as an "early progression"). - Patients withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment. - Patients who received at least one administration of the treatment AND withdrawn due to significant clinical deterioration of unknown reason AND without any tumor assessments after the start of study treatment. ▪ ▪ Safety population: all patients having received at least one treatment administration. *Patient's replacement*

Any patient not eligible or not assessable for efficacy will be replaced.
However, any patient who received at least one administration of the study drug will be included in the safety analysis.

Statistical analysis
For the phase I trial, two documents will be produced by the statistician:
- A statistical analyse plan (SAP) before the first patient's inclusion,
- A statistical report.

For the phase II trial, four documents will be produced by the statistician:
- Two statistical analyse plans (SAP): one for the interim statistical analysis and one for the final statistical analysis.
- Two statistical reports: one for the interim statistical analysis and one for the final statistical analysis.

At the end of the phase I trial, an IDMC will be requested to assess safety data based on the statistical report produced by the statistician of the study. Similarly, an IDMC will be requested at the end of the first stage of the phase II trial to analyse preliminary safety and efficacy data.

Patient characteristics at baseline
The patients entered into the study will be described according to the following characteristics:
- Compliance with eligibility criteria,
- Epidemiological characteristics,
- Clinical and laboratory characteristics,
- Treatment characteristics.

Endpoint analysis PHASE I trial

- Primary endpoint will be analyzed on the population assessable for safety of the phase I trial.
- Toxicity will be graded using the common toxicity criteria from the NCI v4.0.
- Incidence rate of DLT will be reported at each dose level on cycle 1.
- All analyses for the phase I trial will be descriptive; no p-values will be calculated. Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and standard errors. Missing data will not be imputed.

Endpoint analysis PHASE II trials

- Efficacy endpoints will be analyzed on the population assessable for efficacy.
- The safety analysis will be performed on the safety population.
- Quantitative variables will be described using mean and standard deviations if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be reported.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).
- Objective response rate under treatement, 6-month non-progression rate will be calculated using binomial estimates and reported with their 95% confidence interval (CI).
- Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.

Interim statistical analysis (phase II ONLY)

An interim statistical analysis will be carried out after the inclusion of the first 13 eligible and assessable patients. The trial will be terminated if 3 or less responses are observed. Otherwise, the second group of 30 subjects will be recruited. At the end of this first stage, an Independent Data Monitoring Committee (IDMC) will be request to analyze preliminary efficacy and safety data based on the statistical report produced by the statistician of the study. Inclusion will not be suspended during this interim analysis.

Schedule of assessments and procedures – Phase I

		CYCLE 1				CYCLE 2				CYCLE 3				CYCLE N	END OF TREATMENT
	SCREENING	Wk1	Wk 2	Wk3	Wk 4	Wk 5	Wk 6	Wk7	Wk 8	Wk9	Wk 10	Wk11	Wk 12		
CP b.i.d		**X**		**X**		**X**		**X**		**X**		**X**		**D1 to D7 D15 to D21**	
Trabectedin i.v		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1, D8 and D15**	
24h-36h Hosp		**D1**		**D15**											
Ambulatory Hosp			**D8**			**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1, D8 and D15**	
Consultation	**X**														**X**
Informed consent	X														
Demographics	X														
Medical History	X														
Concomitant treatments	X	X……X													
Physical exam	X	X		X		X				X				D1	X
Vital signs	X	X		X		X				X				D1	X
Height	X														
Weight	X	X		X		X				X				D1	X
Performance status	X	X		X		X				X				D1	X
Hematology[a]	X	X	X	X		X	X	X		X	X	X		X[d]	X
Biochemistry[b]	X	X	X	X		X	X	X		X	X	X		X[d]	X
ECG	X	X													X
Toxicity		X……..X													
Tumor measurement	X	Repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease													X
B-HCG[c]	X	X													
PK		D1		D15											
Biomarkers		X				X									
Biopsy		X			D28										
Echocardiography	X	Repeated if indicated													
Serious and/ or non- serious adverse events collection	X	Throughout the study													X (until 30 days later last dose administered and beyond this period only SAEs related to research or IMP)

a: Hemoglobin, platelets, CBC w/diff
b: Albumin, Alkaline phosphatase, total bilirubin, bicarbonate, calcium, chloride, creatinine, CPK, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
c: if indicated and repeated if necessary
d: on weeks 1, 2 and 3 of each subsequent cycle

Schedule of assessments and procedures – Phase II

		CYCLE 1				CYCLE 2				CYCLE 3				CYCLE N	END OF TREATMENT
	SCREENING	Wk1	Wk 2	Wk3	Wk 4	Wk 5	Wk 6	Wk7	Wk 8	Wk9	Wk 10	Wk11	Wk 12		
CP b.i.d		**X**		**X**		**X**		**X**		**X**		**X**		**D1 to D7 D15 to D21**	
Trabectedin i.v		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1, D8 and D15**	
Ambulatory Hosp		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1, D8 and D15**	
Consultation	**X**														**X**
Informed consent	X														
Demographics	X														
Medical History	X														
Concomitant treatments	X	X…….…X													
Physical exam	X	X		X		X				X				D1	X
Vital signs	X	X		X		X				X				D1	X
Height	X														
Weight	X	X		X		X				X				D1	X
Performance status	X	X		X		X				X				D1	X
Hematology[a]	X	X	X	X		X	X	X		X	X	X		X[d]	X
Biochemistry[b]	X	X	X	X		X	X	X		X	X	X		X[d]	X
ECG	X														X
Toxicity		X…….…..X													
Tumor measurement	X	Repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease													X
B-HCG[c]	X	X													
Biomarkers (optional)		X				X									
Biopsy (optional)		X			D28										
Echocardiography	X	Repeated if indicated													
Serious and/ or non- serious adverse events collection	X	Throughout the study													X (until 30 days later last dose administered and beyond this period only SAEs related to research or IMP)

a: Hemoglobin, platelets, CBC w/diff
b: Albumin, Alkaline phosphatase, total bilirubin, bicarbonate, calcium, chloride, creatinine, CPK, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
c: if indicated and repeated if necessary
d: on weeks 1, 2 and 3 of each subsequent cycle