TRABECTEDIN COMBINED WITH DURVALUMAB (MEDI4736) IN PATIENTS WITH ADVANCED PRETREATED SOFT-TISSUE SARCOMAS AND OVARIAN CARCINOMAS
A PHASE IB STUDY

Protocol *TRAMUNE*

Statistical Analysis Plan (SAP)
Version n°1.1 – 07/06/2019

Source documents:
Protocol V5.0 of 10/01/2019 & Annotate CRF 2.0 12/03/2019

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VERSIONS AND MODIFICATIONS

Version	Date	Modification(s)	Context
1.0	14/01/2018	-	-
1.1	07/06/2019	**Cover page :** Pharmacist, logo **2.2. Eligibility status :** CI n°9, CI n°12, CI n°13, CNI n°9, CNI n°14, CNI n°18 **2.4 Expansion cohort/Evaluable for efficacy**	New version of protocol and accuracy of definitions

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SYNOPSIS (V5.0 OF THE 10.01.2019)

Title of the study	**Trabectedin combined with durvalumab (MEDI4736) in patients with advanced pretreated soft-tissue sarcomas and ovarian carcinomas.** **A Phase Ib study**
Abbreviation of the trial	**TRAMUNE**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Doctor Maud TOULMONDE** **Department of Medical Oncology**
Scientific responsive	**Doctor Anne FLOQUET** **Department of Medical Oncology**
Number of investigational sites planned	**Phase I (dose escalation):** 2 centers - Institut Bergonié, Bordeaux, France (PI : Pr Antoine Italiano) - Centre Léon Bérard, Lyon, France (PI : Dr Mehdi Brahmi) **Phase I (expansion cohorts):** 3 centers - Institut Bergonié (PI : Pr Antoine Italiano) - Centre Léon Bérard (PI : Dr Mehdi Brahmi) - Institut Gustave Roussy, Villejuif, France (PI : Dr Olivier MIR)
Number of patients	**Phase I (Dose escalation):** 20 patients **Phase I (Expansion cohorts)**: 30 patients (15 patients STS/15 patients ovarian carcinomas)
Duration of the study	Planned enrollment period: 30 months Treatment duration: until progression Follow-up: 1 year Study period: 3 years
Medical conditions	Adult patients with: - locally advanced or metastatic soft-tissue sarcoma (STS) who have failed anthracycline-containing chemotherapy (CT), - or ovarian carcinoma, without known g/s BRCA mutation, and must have received at least one line of platinum-containing regimen.
Objectives	**<u>Primary objective</u>** To determine the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first 21 days (D1 to D21), the safety profile and the dose limiting toxicities (DLT) of trabectedin given in combination with durvalumab in patients with advanced pretreated soft-tissue sarcoma and ovarian carcinomas. **<u>Secondary objectives</u>** • To evaluate the toxicity profile of trabectedin in association with durvalumab (NCI-CTCAE v4.03) • To determine preliminary signs of anti-tumor activity of trabectedin given in combination with durvalumab in two expansion cohorts (STS and ovarian carcinomas) in terms of: o Best overall response as per RECIST v1.1, o Objective response under treatment as per RECIST v1.1, o 6-month objective response as per RECIST v1.1, o 6-month progression-free status defined as per RECIST v1.1, o 1-year progression-free survival (PFS), o 1-year overall survival (OS).

	• To explore the pharmacodynamics (PD) of trabectedin in association with durvalumab as well as potential predictive biomarkers of activity and efficacy (blood and tumor tissue samples).

Study design	**STUDY DESIGN**
	This is a multicenter, prospective open-labeled phase Ib trial based on a dose escalation study design (3+3 traditional design) assessing three dose levels of trabectedin when prescribed in combination with durvalumab followed by two expansion cohorts (STS and ovarian carcinomas) once the MTD is established.
	
	DEFINITIONS
	• **Dose-limiting toxicity (DLT):** A DLT is defined as an adverse event (AE) or laboratory abnormality that fulfills all the criteria below:
	  o Begins on the first 21 days 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 CTCAE v4.03 :
	  ▪ Any grade 4 toxicity (except for vomiting without maximal symptomatic/prophylactic treatment and if toxicity is transaminitis, but which have to be resolved at Day 21, i.e. return to Baseline or grade 1).
	  ▪ Grade 3 non-haematological toxicity lasting > 7 days (except for 1st episode of nausea and if toxicity is transaminitis, which have to be resolved at Day 21, i.e. return to Baseline or grade 1).
	  ▪ Grade 3 hematologic toxicity lasting for > 7days.
	  ▪ Grade 4 neutropenia with fever.
	  ▪ Grade > 2 thrombocytopenia with bleeding.
	• **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 21 days. Conclusions of the steering committee for the definition of the MTD will be sumbmitted for approval to an independent data monitoring committee (IDMC) before opening the expansion cohorts.
	• **Recommended phase II dose (RP2D):** The RP2D dose corresponds to the dose level to be recommended for further investigations in phase II trials. Following the expansion cohorts, the RP2D for Trabectedin will be identified by the steering committee based on safety data from patients included in the dose escalation part and the expansion cohorts, as well as PD data. Data from all patients (escalation + expansion cohorts) will be used to define the RP2D.
	
	DOSE ESCALATION PART
	• 3 doses of trabectedin given in combination with durvalumab (fixed dose) will be investigated:
	
	Level | **-1** | **1** | **2** | **3**
	Trabectedin (3h) | 0.8 mg/m² | 1 mg/m² | 1.2 mg/m² | 1.5 mg/m²
	
	• The starting dose of trabectedin is 1 mg/m^2.
	• The maximum dose of trabectedin administered (1.5 mg/m^2) will not be exceeded.
	• No skipping of the dose will be allowed.
	• For a given patient, dose will never be escalated.
	• Patients will be allocated to the 3 dose levels following a 3 + 3 design.
	• A minimum of 3 patients and a maximum of 6 patients will be entered on each dose level.
	• All 3 patients within a dose level will be observed during 21 days (the period of

observation of DLTs) before accrual to the next higher dose level may begin.

- Dose escalation will proceed according to the following scheme:

Number of patients with DLT at one dose level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared as the maximum administered dose (MAD). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, dose escalation will be stopped, and this dose is declared as the MAD. Three additional patients will be entered at the next lowest dose if only 3 patients were treated previously at that dose.
≤1 out of 6	This will be the maximum tolerated dose (MTD).

- As described above, the maximum administered dose (MAD) for Trabectedin is the dose in which ≥ 2/3 or ≥ 2/6 patients experience DLT.
- If the MAD for Trabectedin is seen at the starting dose level, then dose level "-1" will be the recommended dose.
- The MTD for Trabectedin is defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced a DLT during the period of observation of DLTs.
- The steering committee will meet before proceeding or not to each dose escalation. In addition, , the steering committee will be consulted to resolve any specific issue regarding the DLT status.
- Conclusions of the steering committee for the definition of MTD will be submitted for approval to an independent data monitoring committee (IDMC) before opening the expansion cohorts.

EXPANSION COHORT

Once the MTD has been defined, the expansion cohorts will be opened. All patients will be treated at the MTD of Trabectedin (as defined in the dose escalation trial) given in association with Durvalumab with the same schedule as in the dose escalation trial. Following the expansion cohorts, the RP2D for Trabectedin will be identified by the steering committee based on safety data from patients included in the dose escalation part and the expansion cohorts, as well as PD data. Data from all patients (escalation + expansion cohorts) will be used to define the RP2D.

Inclusion criteria

1. Histology :
   - Soft-tissue sarcoma histologically confirmed. In care outside a center of the RRePS Network, a central review is necessary (Pr. Coindre team),
   - histologically confirmed ovarian carcinoma (carcinosarcoma included), without known g/s BRCA mutation
2. ovarian carcinoma must have received at least one line of platinum-containing regimen.
3. Metastatic or unresectable locally advanced disease, not ammenable to curative therapy,
4. Age ≥ 18 years,
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1,
6. Life expectancy > 3 months,

	7. Patients must have measurable disease (lesion in previously irradiated field can be considered as measurable if progressive at inclusion according to RECIST v1.1) defined as per RECIST v1.1 with at least one lesion that can be measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan. 8. Documented disease progression according to RECIST v1.1 before study entry, 9. Patient must comply with the collection of tumor biopsies, 10. At least 1 line of chemotherapy in the palliative setting with use of Anthracyclines (for STS), 11. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment for neoplastic disease and/or radiotherapy, 12. 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, and platelet count ≥ 100 x 10^9/l. b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) and alkaline phosphatase (AP) ≤ 2.5 x ULN. c. Total bilirubin ≤ ULN. d. Albumin ≥ 25 g/l. e. Calculated creatinine clearance (CrCl) > 60 ml/min (according to Cockroft Gault formula). f. Thyroid function within normal laboratory ranges (TSH, free T3, free T4) g. Creatine PhosphoKinase (CPK) ≤ 2.5 x ULN 13. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. Both women and men must agree to use a highly effective method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception are described in protocol section 7.6.1.1, 14. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, concomitant endometrial carcinoma stage IA grade 1, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 15. 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 4.03), 16. Voluntarily signed and dated written informed consent prior to any study specific procedure, 17. Patients with a social security in compliance with the French law.
Exclusion criteria	1. Previous treatment with Trabectedin or an anti-PD-1, anti-PD-L1, anti-PD-L2, including durvalumab 2. Current or prior use of immunosuppressive medication including any use of oral glucocorticoids, within 21 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses 3. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), 4. Has an active autoimmune disease requiring systemic treatment within the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment, 5. Has evidence of active non-infectious pneumonitis, 6. Has an active infection requiring systemic therapy, 7. Currently active bacterial or fungus infection (> grade 2 NCI-CTCAE] HIV1, HIV2, hepatitis A or hepatitis B or hepatitis C infections), 8. Known central nervous system malignancy (CNS),

<table>
<tr><td></td><td>9. 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,
10. Previous enrolment in the present study,
112. Patient unable to follow and comply with the study procedures because of any geographical, social or psychological reasons,
12. Has received a live vaccine within 30 days prior to the first dose of trial treatment,
Note: the killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
13. Known hypersensitivity to any involved study drug or any of its formulation components,
14. Tumors not accessible for biopsy,
15. Known history of active tuberculosis.
16. Person under judicial protection or deprived of liberty
17. Cardiac dysfunction :
- LVEF (Left Ventricular Ejection Fraction)< 40% at baseline;
- or clinically symptomatic cardiac dysfunction (any % of LVEF at baseline)
18. Concomitant use of strong inhibitors or inductors of cytochrome CYP3A4 taken within 21 days prior to the first dose of study drug</td></tr>
<tr><td>Route of administration</td><td>Durvalumab will be administered by intravenous infusion every 3 weeks.
Trabectedin will be administered by intravenous infusion every 3 weeks.</td></tr>
<tr><td>Treatment schedule</td><td>Phase I: Dose escalation part
<table>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th></tr>
<tr><td>Trabectedin</td><td>Doses as appropriate for assigned dose level</td><td>IV</td><td>Day 1</td><td rowspan="2">3 weeks</td></tr>
<tr><td>Durvalumab</td><td>Fixed doses of 1120 mg</td><td>IV</td><td>Day 2</td></tr>
</table>
A treatment cycle consists of 3 weeks (21 days). 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 3 dose levels of Trabectedin following a 3 + 3 design:
<table>
<tr><th>Level</th><th>-1</th><th>1</th><th>2</th><th>3</th></tr>
<tr><td>Trabectedin (3h)</td><td>0.8 mg/m²</td><td>1 mg/m²</td><td>1.2 mg/m²</td><td>1.5 mg/m²</td></tr>
</table>
Expansion cohorts: All patients will receive the same treatment administration modalities at the MTD defined in the dose escalation part of the study.</td></tr>
<tr><td>Safety and efficacy evaluations</td><td>Safety: Dose-limiting toxicities will be assessed for 3 weeks.
Toxicities will be assessed on Day 8, 15, 22 and every 3 weeks afterwards.
Efficacy will be assessed every 2 cycles (6 weeks).</td></tr>
<tr><td>Endpoints</td><td><u>Primary endpoint</u>
Phase I /Dose escalation part
• Toxicity graded using the common toxicity criteria from the NC-CTCAE v4.03
• Incidence rate of DLT at each dose level during the first 21 days.
Phase I /Expansion cohorts
Preliminary signs of the antitumor activity of trabectedin given in combination with durvalumab will be assessed in terms of objective response rate (ORR) under treatment defined as the proportion of patients with complete or partial response (CR, PR) as per RECIST v1.1 criteria. Disease status under treatment, whatever the response observed, will be centrally reviewed for all patients, by an independent expert radiologist. Reviewed data will be used for the efficacy analysis.</td></tr>
</table>

	<u>Secondary endpoints</u>
	Phase I / Dose escalation part
	• Preliminary signs of antitumor activity in terms of:
	  o Best overall response defined as the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation as per RECIST v1.1 criteria.
	  o Objective response rate (ORR) defined as the proportion of patients with complete response or partial response, as per RECIST 1.. ORR under treatment and 6-month ORR will be reported .
	  o Progression-free rate (PFR) at 6 months defined as the proportion of patients with complete response, partial response or stable disease more than 24 weeks as per RECIST v1.1 criteria.
	  o Progression-free survival (PFS) defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first. 1-year PFS rate will be reported.
	  o Overall Survival (OS) defined as the time from study treatment initiation to death (of any cause). 1-year OS rate will be reported.
	• Pharmacodynamic study:
	  o Blood samples:
	  ▪ Serum level of cytokines, kynurenine and immunophenotyping of circulating immune cells.
	  ▪ Analyses of circulating DNA for identification and monitoring of mutations observed at the level of the circulating tumor cells (liquid biopsies concept).
	  o Tumor samples: Fresh pre-treatment and on-treatment tumor biopsies will be performed. Samples will be formalin fixed and paraffin-embedded or fresh frozen, and will be analyzed for:
	  ▪ Hematoxylin and eosin staining (H&E).
	  ▪ Immunohistochemistry (IHC) assessments including, but not limited to, the following markers: SP263, SP28-8 (PDL1), CSF-1R, CD68/CD163, CD8, MHC class I/II, CD31 (microvessel density), Ki67 and other exploratory markers. The analysis will be prioritized based on the amount of material available.
	  ▪ Genomics and transcriptomics exploratory analysis for predictive signatures in responders and mechanisms of resistance in non-responders.
	
	Phase I / Expansion cohorts
	• Preliminary signs of antitumor activity will be assessed in terms of 6-month ORR, best overall response, 6-month PFR, 1-year OS and PFS rates defined as for the escalation part of the phase I trial.
	• Toxicity defined above as for the escalation part.
	  • Phamacodynamics study defined above as for the escalation part.

Statistical considerations	**SAMPLE SIZE CONSIDERATIONS** **<u>Phase I (Dose escalation part)</u>:** • 3 dose levels • A minimum of 3 patients and a maximum of 6 patients per dose level • Therefore, the maximum number of patients is estimated to be 18 patients assessable for safety. To account for patients not assessable, we anticipate accruing a maximum of **20 patients for the dose escalation part of the phase I trial.** **<u>Phase I (Expansion cohorts):</u>** • The primary objective is to determine preliminary signs of anti-tumor activity of trabectedin given in combination with Durvalumab among two selected cohorts of patients (STS and ovarian carcinomas) in terms of objective response rate

	(ORR) under treatment as per RECIST v1.1 criteria.
	• Once the MTD is established for trabectedin, 2 distinct cohorts will be treated at the MTD:
	  o Cohort A: patients with advanced STS.
	  o Cohort B: patients with advanced ovarian carcinomas
	• For each cohort:
	  o Sample size is calculated based on the first stage of a 2-stage Gehan design assuming a 20% efficacy rate, 5% false positive rate and 10% precision (Gehan 1961).
	  o 14 eligible and assessable subjects are required.
	  o If at least one objective response (CR or PR as per RECIST v1.1) is observed under treatment, the study drug association will be considered worthy of further testing in this indication.
	  o Assuming, 10% are not eligible or cannot be assessed for the primary endpoint, **15 patients will be recruited for each of the 2 cohorts**, i.e. a total of 30 patients will be included in the expansion cohorts.
	
	STATISTICAL ANALYSIS
	• All analyses for the dose escalation part trial and the expansion cohorts will be descriptive; no p-values will be calculated.
	• For the dose escalation part:
	  - Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate.
	  - Toxicity observed at each dose level, graded according to the common toxicity criteria from the NCI-CTCAE v4.03, will be recorded in terms of event type, severity, dates of beginning and end, reversibility and evolution. Data will be gathered in tables summarizing toxicities and side effects for each dose level and cycle.
	  - DLT will be described in terms of number and incidence rates at each dose level. The number and percentage of patients who will have developed a DLT in each dose level will also be reported.
	  - Categorical endpoints (e.g. response) will be reported in terms of counts by dose level.
	• For the expansion cohorts:
	  - Categorical endpoints will be reported in terms of counts and proportions. Objective response rate under treatment, best response rate, 6-month PFR and 6-month ORR rates will be estimated using binomial estimates and reported with their 95% confidence interval (CI).
	• Continuous endpoints will be reported in terms of summary statistics that will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
	• Survival endpoints (PFS and OS) will be analyzed 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. We will describe also the observed median follow-up.

1 Study protocol (summary)

1.1 Objectives

1.1.1 Primary objective

To determine the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first 21 days (D1 to D21), the safety profile and the dose limiting toxicities (DLT) of trabectedin given in combination with durvalumab in patients with advanced pretreated soft-tissue sarcoma and ovarian carcinoma.

1.1.2 Secondary objectives

- To evaluate the toxicity profile of trabectedin in association with durvalumab (NCI-CTCAE v4.03),
- To determine preliminary signs of anti-tumor activity of trabectedin given in combination with durvalumab in two expansion cohorts (STS and ovarian carcinomas) in terms of :
  - Best overall response as per RECIST v1.1,
  - objective response under treatment as per RECIST v1.1,
  - 6-month objective response as per RECIST v1.1,
  - 6-month progression-free status defined as per RECIST v1.1,
  - 1-year progression-free survival (PFS),
  - 1-year overall survival (OS).
- To explore the pharmacodynamics (PD) of Trabectedin in association with Durvalumab as well as potential predictive biomarkers of activity and efficacy (blood and tumor tissue samples).

1.2 Study design

This is a multicenter, prospective open-labeled phase Ib trial based on a dose escalation study design (3+3 traditional design) assessing three dose levels of trabectedin given in combination with durvalumab, followed by two expansion cohorts (STS and ovarian carcinomas) once the MTD has been established.

2 Definition of the study population

2.1 Definitions

2.1.1 Dose escalation part

The following patients will not be included in the population assessable for safety (primary analysis) and thus will be replaced:

- Patients who received ≤ 75% RDI (Relative Dose Intensity) for trabectedin OR ≤ 75% RDI for durvalumab over cycle 1, due to drug-related AE not considered as DLT.
- Patients who goes off treatment over cycle 1 for reasons unrelated to toxicity (DLT or any other AE), e.g. progression, lost to follow-up, will be replaced Population assessable for safety (primary analysis): all patients who completed the DLT assessment period or who developed DLT are included in the analysis.

2.1.2 Expansion cohorts

- Eligible population: All patients included without major violation of eligibility criteria.
- Population assessable for efficacy: All patients eligible and for whom the following conditions are statisfied:
  - Received at least one complete or two incomplete treatment cycles,

- At least one disease measurement recorded not less than six weeks after treatment onset.

- The following patients will also be included in the population assessable for efficacy; they will be considered as “inevaluable for response” for the primary endpoint as per RECIST v1.1 criteria (i.e. objective response under treatment) and not be replaced in the primary efficacy analysis:
  - Any eligible patients who received at least one treatment cycle or two incomplete treatment cycles and experience disease progression or die due to disease progression prior to response evaluation (will be considered as “inevaluable for response” due to early, progression).
  - Patients withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment (will be considered as “inevaluable for response” due to toxicity).
  - 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 (will be considered as “inevaluable for response" due to significant clinical deterioration).
- Safety population: all patients having received at least one (any) 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.

2.2 Eligibility status

2.2.1 Screening failure

Inclusion and non-inclusion criteria will not be verified for the screen failures (variable SCR_PT=1).

2.2.2 Inclusion criteria

Criteria	eFORM Variable	Control WHERE SCR_PT=0 (Screening failures exclusion)
1. Histology : - Soft-tissue sarcoma histologically confirmed. In care outside a center of the RRePS Network, a central review is necessary (Pr. Coindre team), - histologically confirmed ovarian carcinoma (carcinosarcoma included), without known g/s BRCA mutation	INCLUSION CRITERIA **C1I** DISEASE HISTORY **HIST_REV** **DIAGNOSIS** **OVARIAN** **STS**	**OK if: (C1I = 1 and (HIST_REV = 1 and DIAGNOSIS= 1 and STS=1) or (C1I = 1 and HIST_REV = 1 and DIAGNOSIS= 2 and OVARIAN=0)**
2. ovarian carcinoma must have received atleast one line of platinum-containing regimen.	INCLUSION CRITERIA **C2I** DISEASE HISTORY **DIAGNOSIS** PREVIOUS TREATMENT OF THE TUMOR **CHEMOTH** **PLATINIUM**	**OK if: C2I = 1 and (CHEMOTH =1 and PLATINIUM =1 where DIAGNOSIS = 2)**
3. Metastatic or unresectable locally advanced disease, not ammenable to curative therapy,	INCLUSION CRITERIA **C3I** DISEASE STATUS AT INCLUSION **LA_DIS** **META_DIS**	**OK if: C3I = 1 and (LA_DIS = 1 or META_DIS = 1)**
4. Age ≥ 18 years,	INCLUSION CRITERIA **C4I** ASSESSMENT OF INCLUSION **DT_BIRTH** **DT_CONS** **DT_INC**	**OK if: C4I = 1 and D_BIRTH GE 18** Where D_BIRTH is a new variable : **Format DT_BIRTHBIS ddmmyy10.;** **DT_ BIRTHBIS =MDY(substr (DT_BIRTH,1,2), 15, substr (DT_BIRTH,4,4));** **D_BIRTH=round((DT_INC-DT_BIRTHBIS)/365.25,0.1); Label D_BIRTH =’DELAY’**
5. Eastern Cooperative Oncology	INCLUSION CRITERIA	**OK if: C5I = 1 and**

Group (ECOG) performance status (PS) ≤ 1,	**C5I** BASELINE CONDITION AND M. HIST. **ECOG_PTR** C1D1-CLINICAL EXAMINATION **ECOG_CYC** **DT_VISIT** C1D1-D2 TREATMENT **DT_TRA**(Trabectidin administration date)	**ECOG_PTR in (0 1)** **OR IF** **C5I = 1 and (ECOG_PTR in (-2 -9)) and (ECOG_CYC in (0 1)) and ((DT_TRA - DT_VISIT) > 0)**
6. Life expectancy > 3 months,	INCLUSION CRITERIA **C6I**	**OK if: C6I = 1** **Investigator decision**
7. Patients must have measurable disease (lesion in previously irradiated filed can be considered as measurable if progressive at inclusion according to RECIST v1.1) defined as per RECIST v1.1 with at least one lesion that can be measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan,	INCLUSION CRITERIA **C7I** TUMOR ASSESSMENT BASELINE **NUM_LESI** **MEA1INC – MEA5INC**	**OK if: C7I = 1 and** **NUM_LESI GT 0** **and ((MEA1INC or MEA2INC or MEA3INC or MEA4INC or MEA5INC) GE 10)**
8. Documented disease progression according to RECIST v1.1 before study entry,	INCLUSION CRITERIA **C8I** DISEASE STATUS AT INCLUSION **DT_LPROG**	**OK if: C8I = 1 and DT_LPROG completed**
9. Patient must comply with the collection of tumor biopsies,	INCLUSION CRITERIA **C9I** ASSESSMENT OF IINCLUSION **DT_INC** BIOPSY **BIOPS** C1D1 - BIOPSY **BIOP_PHAR**C1D1–CLINICAL EXAMINATION **DT_VISIT**	**OK if: C9I = 1 and ((BIOPS=1) or (BIOPS=2 and BIOP_PHAR=1 and (DT_VISIT - DT_INC LE 0)))**
10. At least 1 line of chemotherapy in the palliative setting with use of Anthracyclines (for STS),	INCLUSION CRITERIA **C10I** DISEASE HISTORY **DIAGNOSIS** PREVIOUS TREATMENT OF THE TUMOR **CHEMOTH** **ANTHRA**	**For STS (DIAGNOSIS= 1) , OK if:** **C10I = 1 and** **CHEMOTH = 1 and** **ANTHRA =1**
11. At least three weeks since	INCLUSION CRITERIA	Find the last treatment:

last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy,	**C11I** ASSESSMENT OF INCLUSION **DT_INC** DISEASE HISTORY **CHEMOTH** (chemotherapy) **T_CHEIMM** (targeted chemo /immunotherapy) **DT_CHEME** (date of last line of chemo) **RADIO** (radiotherapy) **DT_LSEQ** (last sequence)	For radiotherapy (RADIO=1): **If (RADIO=1) then DT_LTRT=DT_LSEQ** For chemotherapy (CHEMTH=1)/targeted chemotherapy/immunotherapy (T_CHEIMN): **If (CHEMOTH =1 or T_CHEIMM=1) then Do ; DT_LTRT=DT_CHEME End;** **OK If : C7I = 1 and (DT_INC– DL_LTRT GE 21 days)**
12. 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, and platelet count ≥ 100 x 10^9/l. b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) and alkaline phosphatase (AP) ≤ 2.5 x ULN. c. Total bilirubin ≤ ULN. d. Albumin ≥ 25 g/l. e. Calculated creatinine clearance (CrCl) > 60 ml/min (according to Cockroft Gault formula). f. Thyroid function within normal laboratory ranges (TSH, free T3, free T4) g. Creatine PhosphoKinase (CPK) ≤ 2.5 x ULN	INCLUSION CRITERIA **C12I** LABORATORY TEST **HEMO** **NEUT** **PLAT** **ALT** **AST** **ALKA** **BILI** **ALBU** **CREAC** **TSH** **FREE T3** **FREE T4** **CPK**	**C12I = 1 and HEMO GE 9 and NEUT GE 1.5 and PLAT GE 100 and ALBU GE 25 and CREAC GT 60 and AST completed and ALT completed and ALKA completed and BILI completed and TSH completed and T3 completed and T4 completed and CPK completed** **Investigator decision for the value of the following laboratory tests: ASAT/ALAT/Alka/Total Bilirubin/TSH/free T3/free T4/CPK** **10^9/l = G/L**
13. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. Both women and men must agree to use a	INCLUSION CRITERIA **C13I** ASSESSMENT OF INCLUSION **SEX** **REPROD** BASELINE COND. AND M. HIST.	**OK if: C13I=1 AND ((SEX=2 and REPROD=2) or (SEX=2 and REPROD=1 and PREG_PTR = 1 and DT_PREG completed and R_PREG = 0 and DT_TRA - DT_PREG>=0 and DT_TRA -**

highly effective method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception are described in protocol section 7.6.1.1,	**PREG_PTR** **DT_PREG** **R_PREG** **CONT_PTR** C1D1 **DT_TRA**	**DT_PREG<=3 and CONT_PR=1)** **OR** **(SEX=1 and CONT_PR=1)**
14. 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,	INCLUSION CRITERIA **C14I**	**C14I = 1** **Investigator decision**
15. 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 4.03),	INCLUSION CRITERIA **C15I**	**C15I = 1** **Investigator decision**
16. Voluntarily signed and dated written informed consent prior to any study specific procedure,	INCLUSION CRITERIA **C16I** ASSESSMENT OF INCLUSION **DT_CONS**	**C16I = 1 and** **DT_CONS completed (or filled)**
17. Patients with a social security in compliance with the French law relating to biomedical research (Article 1121-11 of French Public Health Code).	INCLUSION CRITERIA **C17I**	**C17I = 1** **Investigator decision**

2.2.3 Non-inclusion criteria

Criteria	eFORM Variable	Control WHERE SCR_PT=0 (Screen failures exclusion)
1. Previous treatment with Trabectedin or an anti-PD-1, anti-PD-L1, anti-PD-L2, including Durvalumab,	ELIGIBILITY FORM **C1NI**	**C1NI = 0** **Investigator decision**
2. Current or prior use of immunosuppressive medication including any use of oral glucocorticoids, within 21 days before the first dose of	ELIGIBILITY FORM **C2NI**	**C2NI = 0** **Investigator decision**

durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses		
3. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis),	ELIGIBILITY FORM **C3NI**	**C3NI = 0** **Investigator decision**
4. Has an active autoimmune disease requiring systemic treatment within the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment,	ELIGIBILITY FORM **C4NI**	**C4NI = 0** **Investigator decision**
5. Has evidence of active non-infectious pneumonitis,	ELIGIBILITY FORM **C5NI**	**C5NI = 0** **Investigator decision**
6. Has an active infection requiring systemic therapy,	ELIGIBILITY FORM **C6NI**	**C6NI = 0** **Investigator decision**
7. Currently active bacterial or fungus infection (> grade 2 NCI-CTCAE] HIV1, HIV2, hepatitis A or hepatitis B or hepatitis C infections),	ELIGIBILITY FORM **C7NI** LABORATORY TEST **HEP_A** **HEP_B** **HEP_C** **HIV**	**C7NI = 0 and HEP_A NE 1 and HEP_B NE 1 and HEP_C NE 1 and HIV NE 1** **Investigator decision**
8. Known central nervous system malignancy (CNS),	ELIGIBILITY FORM **C8NI**	**C8NI = 0** **Investigator decision**
9. 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,	ELIGIBILITY FORM **C9NI** ASSESSMENT OF INCLUSION **SEX** **REPROD** BASLINE COND. AND M. HIST. **PREG_PTR** **DT_PREG** **R_PREG** **CONT_PTR**	**C9NI = 0 and ((SEX=2 and REPROD=2) OR (SEX=2 and REPROD=1 and PREG_PTR = 1 and DT_PREG completed and R_PREG = 0 and CONT_PR=1) OR (SEX=1 and CONT_PR=1)** **Investigator decision**
10. Previous enrolment in the present study,	ELIGIBILITY FORM **C10NI**	**C10NI = 0** **Investigator decision**

11. Patient unable to follow and comply with the study procedures because of any geographical, social or psychological reasons,	ELIGIBILITY FORM **C11NI**	**C11NI = 0** **Investigator decision**
12. Has received a live vaccine within 30 days prior to the first dose of trial treatment, Note: the killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.	ELIGIBILITY FORM **C12NI**	**C12NI = 0** **Investigator decision**
13. Known hypersensitivity to any involved study drug or any of its formulation components,	ELIGIBILITY FORM **C13NI**	**C13NI = 0** **Investigator decision**
14. Tumors not accessible for biopsy,	ELIGIBILITY FORM **C14NI** BIOPSY **BIOPS** ASSESSMENT OF IINCLUSION **DT_INC** C1D1 - BIOPSY **BIOP_PHAR** **DT_BIOPH** C1D1–CLINICAL EXAMINATION **DT_VISIT**	**C14NI = 0** **and BIOPS = 1 or (BIOPS=2 and BIOP_PHAR=1 and (DT_BIOPH - DT_INC LE 0)))** **Investigator decision**
15. Known history of active tuberculosis,	ELIGIBILITY FORM **C15NI**	**C15NI = 0** **Investigator decision**
16. Person under judicial protection or deprived of liberty.	ELIGIBILITY FORM **C16NI**	**C16NI = 0** **Investigator decision**
17. Cardiac dysfunction : - LVEF (Left Ventricular Ejection Fraction)< 40% at baseline; - or clinically symptomatic cardiac dysfunction (any % of LVEF at baseline),	ELIGIBILITY FORM **C17NI** BASELINE COND. AND M. HIST. **LVEF**	**C17NI = 0 and LVEF >=40** **Investigator decision**
18. Concomitant use of strong inhibitors or inductors of cytochrome CYP3A4 taken within 21 days prior to the first dose of study drug	ELIGIBILITY FORM **C18NI**	**C18NI = 0** **Investigator decision**

2.2.4 Eligible population

- Eligible population: All patients included without major violation of eligibility criteria.

Criteria	eFORM variable	Program (SAS)
Eligible Population	**ELIGIBILTY FORM** **C1I C2I C3I C4I C5I C6I C7I C8I C9I C10I C11I C12I C13I C14I C15I C16I C17I C1NI C2NI C3NI C4NI C5NI C6NI C7NI C8NI C9NI C10NI C11NI C12NI C13NI C14NI C15NI C16NI C17NI**	**ELI=1** **If (C1I = 0 or C2I = 0 or C3I = 0 or C4I = 0 or C5I = 0 or C6I = 0 or C7I = 0 or C8I = 0 or C9I = 0 or C10I = 0 or C11I = 0 or** **C12I = 0 or C13I = 0 or C14I = 0 or C15I = 0 or C16I = 0 or C17I = 0 or C1NI = 1 or C2NI = 1 or C3NI = 1 or C4NI = 1 or C5NI = 1 or C6NI = 1 or C7NI = 1 or C8NI = 1 or C9NI = 1 or C10NI = 1 or C11NI = 1 or C12NI = 1 or C13NI = 1 or C14NI = 1 or C15NI = 1 or C16NI = 1 or C17NI = 1)** **then ELI=0**

CREATION OF A NEW INDICATOR VARIABLE

Patients fulfilling inclusion and non-inclusion criteria will be considered as ELIGIBLE (ELI= 1).

New binary variable ELI
Label: « Eligibility based on CRF»
ELI= 1 if the patient is eligible
ELI =0 if the patient is not eligible

2.3 Dose escalation part/ Assessable for safety

The following patients will not be included in the population assessable for safety (primary analysis) and thus will be replaced:

- Patients who received ≤ 75% RDI (Relative Dose Intensity) for trabectedin OR ≤ 75% RDI for durvalumab over cycle 1, due to drug-related AE not considered as DLT.
- Patients who goes off treatment over cycle 1 for reasons unrelated to toxicity (DLT or any other AE), e.g. progression, lost to follow-up, will be replaced.

Population assessable for safety (primary analysis): all patients who completed the DLT assessment period or who developed DLT are included in the analysis.

CREATION OF A NEW INDICATOR VARIABLE
New binary variable TOL
Label: « Assessable for Safety»
TOL = 1 if the patient is assessable for safety (primary analysis)
TOL = 0 if the patient is not assessable for safety (primary analysis)

Criteria	eFORM variable	Control / program
Patient received ≤75% RDI (Relative Dose Intensity) for trabectedin OR ≤ 75% RDI for durvalumab over cycle 1, due to drug-related AE not considered as DLT	CYCLE 1 – DAY 1 AND DAY 2 (WEEK1) TREATMENT ***Trabectedin*** **DOSE_TRA** (dose) **VPRE_TRA** (volume of preparation) **VOL_TRA** (administered volume) **WHY_TRA** (2=AE related to treatment) ***Durvalumab*** **DOSE_DU** **VPRE_DU** **VOL_DU** **WHY_DU** DOSE-LIMITING TOXICITY FORM **DLT_CYC** **OCC_CYC** **REL_ST**	**IF** ***Trabectedin*** ((**Dose effectivement reçue VPRE_TRA and VOL_TRA**/ DOSE_TRA) ≤75% **AND** INT_TRA =1 AND WHY_TRA=2 AND DLT_CYC=0) **OR** ***Durvalumab*** (**Dose effectivement reçue VPRE_DU and VOL_DU** / 1120 mg) ≤75% **AND** INTER_D=1 AND WHY_DU=2 AND DLT_CYC=0) **THEN TOL = 0**
Patient goes off treatment over cycle 1 for reasons unrelated to toxicity (DLT or any other AE), e.g. progression, lost to follow-up	DISCONTINUATION VISIT END OF TREATMENT / end of treatment form **DT_SOT** **DT_EOT** **EOTREASO** DISCONTINUATION VISIT END OF TREATMENT / visit **DIS_TRT** **TRA_EOT** **DUR_EOT** DOSE-LIMITING TOXICITY FORM **DLT_CYC** AE FORM **NUMAE** **AEVENT** **DT_AE** **MAX_INT** **TRA_MOD** **DUR_MOD**	DT_EOT-DT_SOT<=21 days **AND** EOTREASO NOT IN (4 12) **AND** DLT_CYC=0 Additional control if DT_EOT-DT_SOT<=21 days - Listing Other reason - Listing visit of end of treatment: DIS_TRT / TRA_EOT / DUR_EOT - Listing AE with TRA_MOD IN=3 OR DUR_MOD=3 **THEN TOL=0**
Population assessable for SAFETY	**TOL** (new variable)	**TOL =1**

2.4 Expansion cohort/ Evaluable for efficacy

- Population assessable for efficacy: All patients eligible and for whom the following conditions are statisfied:
  - Received at least one complete or two incomplete treatment cycles,
  - At least one disease measurement recorded not less than six weeks after treatment onset.
- The following patients will also be included in the population assessable for efficacy; they will be considered as "inevaluable for response" for the primary endpoint as per RECIST v1.1 criteria (i.e. objective response under treatment) and not be replaced in the primary efficacy analysis:
  - Any eligible patients who received at least one treatment cycle or two incomplete treatment cycles and experience disease progression or die due to disease progression prior to response evaluation (will be considered as "inevaluable for response" due to early, progression).
  - Patients withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment (will be considered as "inevaluable for response" due to toxicity).
  - 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 (will be considered as "inevaluable for response" due to significant clinical deterioration).
- Safety population: all patients having received at least one (any) treatment administration.

CREATION OF A NEW INDICATOR VARIABLE

New binary variable ELI_EFF
Label: « Evaluable for Efficacy»
ELI_EFF= 1 if the patient is evaluable for the efficacy analysis
ELI_EFF =0 if the patient is not evaluable for the efficacy analysis

Criteria	eFORM variable	Control
Population evaluable for EFFICACY	**ELI_EFF** (new variable)	**ELI_EFF = 1 IF**
• Received one complete or two incomplete treatment cycles	**CYCLE 1 – DAY 1 AND DAY 2 (WEEK1)** **CYCLE 2 – DAY 1 AND DAY 2 (WEEK1)** **ADMI_TRA** (1=Done) **ADMI_DUR** (1=Done) **VPRE_TRA** **VOL_TRA** **VPRE_DUR** **VOL_DUR** **INT_TRA** **INTER_D**	**Cycle 1 completed** (C1_ADMI_TRA = 1 **and** C1_ADMI_DUR = 1 **and** (C1_VPRE_TRA = C1_VOL_TRA) **and** (C1_VPRE_dur= C1_VOL_dur)) **Or** **Cycle 1 incomplete and Cycle 2 done** **(**C1_ADMI_TRA = 1 **and** C1_ADMI_DUR = 1 **and** ((C1_VPRE_TRA NE C1_VOL_TRA) **or** (C1_VPRE_dur NE C1_VOL_dur))**) and**

		((C2_ADMI_TRA = 1 **or** C2_ADMI_DUR = 1) **and** (C2_VOL_TRA >0 or C2_VOL_TRA >0)**)** Additional control: Date of start cycle Total dose given during cycle Therapy changes during cycle **AND**
• one disease measurement recorded not less than six weeks after treatment onset	**TUMOR ASSESSMENT (TUM_CYC)** **DIS_EVA** (1=week 6) **DT_MEAC**	**DIS_EVA =1 and** Information on tumor assessment completed and date of tumor assessment
		OR IF
❖ Received at least one treatment cycle and experience disease progression or die due to disease progression prior to response evaluation after the start of study treatment	**CYCLE 1 – DAY 1 AND DAY 2 (WEEK1)** **ADMI_TRA** (1=Done) **ADMI_DUR** (1=Done) **TREATMENT (EOTRT)** **EOTREASO** (1=Disease progression and 12=Disease progression and Adverse event(s)) **END OF STUDY (EOS)** **REA_STUD** (3=Death) **DT_DEATH** **CA_DEATH** (1= Progression of disease) **TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement)	**(C1_ADMI_TRA = 1 and C1_ADMI_DUR = 1)** Additional control: Date of start cycle Total dose given during cycle Therapy changes during cycle **AND ((EOTREASO in (1 12) or (CA_DEATH=1 and EOS_REA = 3)) and DT_MEAC is blank)** **OR IF**
❖ withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment	**DISCONTINUATION VISIT** **TRA_EOT** (0=toxicity) **DUR_EOT** (0=toxicity) **TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement)	**DT_MEAC** is blank **AND** **TRA_EOT =0 or DUR_EOT=0** **OR IF**
❖ 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	**TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement) **DISCONTINUATION VISIT END OF TREATMENT (EOTRT)** **DT_SOT, DT_EOT** (start and end of treatment) **EOTREASO** (8= General or specific changes in patient's condition) **ADVERSE EVENT FORM (AEV)** **DT_AE, DTENDAE** (start and end date) **TRA_MOD** (**3=** Definitively stopped) **DUR_MOD** (**3=** Definitively stopped) **TRA_REL** (2= Unrelated) **DUR_REL** (2= Unrelated)	**DT_MEAC** is blank **EOTREASO = 8**

- Safety population: all patients having received at least one (any) treatment administration

CREATION OF A NEW INDICATOR VARIABLE

Patients will be evaluable for safety if they have received at least one treatment administration. (SAF=1).

New binary variable ELI_DLT
Label: « Safety population»
SAF= 1 if the patient is assessable for safety
SAF =0 if the patient is not assessable for safety

Criteria	eFORM variable	Control
Safety population	**CYCLE 1 – TREATMENT** **VOL_TRA** (Administered volume) **VOL_DUR** (Administered volume)	**SAF = 1** **IF (VOL_TRA LE 0) AND (VOL_DUR LE 0) then SAF= 0**

3 Statistical methods

3.1 Descriptive analysis

All analyses 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.

3.2 Endpoint analysis

3.2.1 Dose escalation part

- Primary endpoint will be analyzed on the population assessable for safety of the phase I trial (escalation part).
- Toxicity observed at each dose level, graded according to the Common Terminology Criteria for Adverse Events v4.0 from the NCI, will be recorded in terms of event type, severity, dates of beginning and end, reversibility and evolution. Data will be gathered in tables summarizing toxicities and side effects for each dose level and cycle.
- DLT will be described in terms of number and incidence rates at each dose level. The number and percentage of patients who will have developed a DLT in each dose level will also be reported.
- Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate.
- Categorical endpoints: best overall response, ORR under treatment and at 6 months, 6-month ORR and 6-month PFR, will be reported in terms of counts by dose level.
- Continuous endpoints will be reported in terms of summary statistics that will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
- Survival endpoints (PFS and OS) will be analyzed 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.

- Missing data will not be imputed.

3.2.2 Expansion cohorts

- Analyses will be conducted separately for sarcoma and ovarian cancer patients.
- Primary efficacy endpoint will be analysed based on the eligible and assessable population:
  - Each patient will be assigned one of the following categories:
    - Complete response
    - Partial response
    - Stable disease
    - Progression
    - Inevaluable for response
  - The rate of objective response (complete or partial response) under treatment will be reported:
    - All eligible and assessable patients will be included in the denominator for the calculation of the objective response rate (ORR).
    - The 95% two-sided confidence limits will be provided for the ORR (binomial law).
    - First endpoint conclusions will be based on the objective response rate ORR for all eligible and assessable patients (section 10.2) after centralized radiological review of the data.
- As regards to the other efficacy endpoints, the analyses will be carried out in the eligible and assessable population:
  - Each patient will be assigned one of the following categories:
    - Complete response
    - Partial response
    - Stable disease
    - Progression
    - Inevaluable for response
  - The rate of best overall response will be calculated as the number of patients alive with the best response (recorded from the start of the treatment) divided by the number of patients eligible and assessable.
  - The 6-month progression-free rate will be calculated as the number of patients remaining alive and progression-free at 6 months from the start of the treatment divided by the number of patients eligible and assessable.
  - The 6-month objective response rate will be calculated as the number of patients alive with complete or partial response at 6 months divided by the number of patients eligible and assessable.
  - The 95% two-sided confidence limits will be provided for the calculated rates (binomial law)
- 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).
- 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.

3.2.3 Primary endpoint

- **Dose escalation part**

Criteria	eFORM Variables	Control / program (TOL=1)
Toxicity will be graded using the common toxicity criteria from the NCI v4.0.	ADVERSE EVENT FORM **AEVENT** (adverse event) **AESAE** (is a serious adverse event) **AE_NUMAE** (Toxicity number) **DT_SAE , DT_AE** (date of beginning) **DTENDAE** (date of the end or death) **INIT_INT, MAX_INT** (intensity) **TRAB_REL** (relation to Trabectedin) **DURV_REL** (relation to Durvalumab) **AE_TRA_MOD** (Trabectedin modification) **AE_DUR_MOD** (Durvalumab modification) **AE_OUTC** (outcome)	**Listing of Adverse events** + descriptive statistics
Incidence rate of DLT will be reported at each dose level on cycle 1.	CYCLE 1 – TREATMENT **DOSE_TRA** DOSE-LIMITING TOXICITY FORM **DT_EVENT** **OCC_CYC (occurred for the first 21 days)** **GR4_TOX** **GR3_NHT** **GR3_HT** **GR3_NEU** **GR2_THR** **OTH_DLT**	**Listing Of DLT + rate of DLT (Number of DLT / TOL)** descriptive statistics

- **Expansion cohorts**

Criteria	eFORM Variables	Control (TOL=1)
Objective response rate, defined as the rate of complete or partial response according to RECIST v1.1	ASSE _CYC (TUMOR ASSESSMENT) **DT_MEASC** (date of measurement) **ME1RTLC-ME5 RTLC** (measures of lesions) **SUM_RTLC** (largest diameters) **EVA1RLNMC-EVA5 RLNMC** (non-measurable lesions eval) **RES_RTL, RES_RNTL** (target and non-target lesions) **OV_REV** (overall response) CR=1, PR=2, SD=3, PD=4,NE=5 New variables : **NB_BORR** (nb of objective response case) END OF STUDY (END_STU) **DT_EOS** (date of end of study)	**Status at each TUMOR ASSESSMENT**

3.2.4 Secondary endpoints

For dose escalation part: Only the patients assessable for safety (TOL = 1) will take part into this analysis.

For expansion cohorts: Only the patients evaluable for efficacy (ELI_EFF = 1) will take part into this analysis.

Criteria	eFORM variable	Control
Objective response rate, defined as the rate of complete or partial response according to RECIST v1.1	ASSE _CYC (TUMOR ASSESSMENT) **DT_MEASC** (date of measurement) **ME1RTLC-ME5 RTLC** (measures of lesions) **SUM_RTLC** (largest diameters) **EVA1RLNMC-EVA5 RLNMC** (non-measurable lesions eval) **RES_RTL, RES_RNTL** (target and non-target lesions) **OV_REV** (overall response) CR=1, PR=2, SD=3, PD=4,NE=5 New variables : **NB_BORR** (nb of objective response case) END OF STUDY (END_STU) **DT_EOS** (date of end of study)	**Status at each TUMOR ASSESSMENT**
6-month objective response rate , defined as the rate of complete or partial response at 6 months according to RECIST v1.1	ASSE _CYC (TUMOR ASSESSMENT) **DT_MEASC** (date of measurement) **ME1RTLC-ME5 RTLC** (measures of lesions) **SUM_RTLC** (largest diameters) **EVA1RLNMC-EVA5 RLNMC** (non-measurable lesions eval) **RES_RTL, RES_RNTL** (target and non-target lesions) **OV_REV** (overall response) CR=1, PR=2 TREATMENT **DT1_START** ((Day 1 of treatment) New variables : **NB_ORR** (nb of objective response case at 6months)	**DT_START** filled in **ME1RTLC-ME5 RTLC** (filled in if needed) **SUM_RTL** C filled in and check recist1.1 criteria **EVA1RLNMC-EVA5 RLNMC** (filled in if needed) **RES_RTL, RES_RNTL** (filled in) **Compute number of patients with OV_REV in (1 or 2) at 6 months**
6-month Non-progression rate (NPR) defined as the percentage of patients with CR, PR or stable disease (SD) according to RECIST v1.1, (CR, PR or SD more than 24 weeks)	ASSE_CYC (TUMOR ASSESSMENT) **DT_MEASC** (date of measurement) **ME1RTLC-ME5 RTLC** (measures of lesions) **SUM_RTLC** (largest diameters) **EVA1RLNMC_EVA5RLNMC** (non-	**DT_START** filled in **ME1RTLC-ME5 RTLC** (filled in if needed) **SUM_RTL** C filled in and check recist1.1 criteria **EVA1RLNMC-EVA5 RLNMC** (filled

	measurable lesions eval) **RES_RTL, RES_RNTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2, SD=3 **TREATMENT** **DT1_START** ((Day 1 of treatment) New variables : **NB_NPR** (nb of non-progression case at 6 months)	in if needed) **RES_RTL, RES_RNTL** (filled in) **Compute number of patients with OV_REV in (1 2 3) at 6 month for at least 24 weeks**

1 and 2-year Progression-Free Survival (PFS) defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.	**END OF TREATMENT FORM**
	DT_SOT (Date of start of treatment)
	EOTSTATU (Status)
	EOTREAO (Reason end)
	DT_PROG (Date of progression if occurred)
	Type of progression (if progression occurred)
	FOLLOW UP FORM
	DT_FUP (date of visit)
	STATUSP (Vital status)
	PRO_LAS, DT_FPROG (date of progression)
	END OF STUDY (END_STU)
	DT_EOS (date of end of study)
	REA_STUD (reason)
	DT_DEATH (date of death)
		Check if everything is filled in
		If (DT_PROG is blank) then
		Do;
		If (PRO_LAS=0) then {
		PFS= DT_EOS-DT_SOT ;
		If (REA_STUD='death') then
		IND_PFS=1
		Else IND_PFS=0
		}
		Else {
		PFS=DT_FPROG – DT_SOT;
		IND_PFS=1}
		End;
		Else {
		PFS= DT_PROG – DT_SOT;
		IND_PFS=1}

1 year Overall Survival (OS), OS is defined as the time from study treatment initiation to death (of any cause).	**END OF TREATMENT (EOTF)** **DT_SOT** (start date of treatment) **EOTSTAU** (Status) **EOTREAO** (Reason end) **FOLLOW UP FORM** **DT_FUP** (date of visit) **STATUSP** (Vital status) **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **REA_STUD** (reason) **DT_DEATH** (date of death) **DT_LFUP** (date of last follow_up)	Check if everything is filled in **If (STATUSP NE 'dead') then do;** **if (REA_STUD ='death') then {** **OS= DT_DEATH-DT_SOT;** **IND_OS=1;** **}** **Else {OS= DT_EOS-DT_SOT;** **IND_OS=0;** **}** **end;** **Else { OS= DT_LFUP -DT_SOT;** **IND_OS=1; }**
Pharmacodynamic (PD) and predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points).	**LABORATORY TEST** **BIOMARKERS AND CIRCULATING DNA**	

4 Annexes

4.1 Appendix 1: List of datalistings for each dose allocated report

4.1.1 Summary of patient treatment on cycle 1 (D1 – D21)

Datalisting 1. Demographic characteristics and treatment: Patient's center, number, age at inclusion, sex, Trabectidin start date, Trabectidin dose, Trabectidin perfusion interrupted, Trabectidin Relative Dose intensity, Durvalumab start date, Durvalumab dose, Durvalumab perfusion interrupted, Durvalumab Relative Dose intensity, C2D1 theorical date, C2D1 real date.

4.1.2 Listing of adverse events for each patient cycle 1 and after

Datalisting 2. Adverse event: : Patient's center, number, date of event, Event number, DLT, serious adverse event, adverse event, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death.

4.1.3 Listing of adverse events with any changes in grade

Datalisting 3. Adverse event with changes : Patient's center, number, date of event, serious adverse event, adverse event, initial intensity, maximum intensity, Date of change, New grade, outcome.

4.1.4 Listing of serious adverse events (SAE) for each patient

Datalisting 4. Serious adverse events: Patient's center, number, sae start date,, adverse event, serious adverse event, SOC, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death.

4.2 Appendix 2: List of datalistings at the end of the escalation part and at the end of the expansion part

Each datalisting will be described according to the phase of the study (escalation part OR expansion part).

4.2.1 Inclusion form

Datalisting 1.1. Demographic characteristics: patient's number, center, birth date, histology, date of inclusion, sex, signed and dated written informed consent
Datalisting 1.2. Inclusion and non-inclusion criteria.

4.2.2 Tumor assessment: Baseline

Datalisting 2.1. Measurable lesions: Date of measurement, number of lesions, site, localisation description, measure, method, centralized review
Datalisting 2.2. Non-measurable lesions: Date of measurement, number of lesions, site, localisation description, evaluation, method, centralized review

4.2.3 Drug delivery

Datalisting 3.1. Durvalumab: start and end date, dose, therapy change, main reason for change, pills returned at pharmacy, total dose received during each cycle
Datalisting 3.2. Trabectedine: start and end date, dose, therapy change, main reason for change, pills returned at pharmacy, total dose received during each cycle

4.2.4 Tumor assessment

Datalisting 4. Tumor response: Date of measurement, Disease evaluation, sum of the largest diameters, new lesions, target lesions, non-target lesions, overall response, treatment continuation, centralized review

4.2.5 End of treatment

Datalisting 5. End of treatment: stard and end dates of treatment, status (complete response,…), reason for the end of the treatment, date of progression, type of progression

4.2.6 Adverse event

Datalisting 6.1. Adverse event: Event number, adverse event, serious adverse event, sae start date, soc, date of event, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death
Datalisting 6.2. Serious adverse events: SAE number, adverse event, serious adverse event, sae start date, soc, date of event, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death

4.3 Appendix 2 : List of Tables and Figures

4.3.1 Study populations

Table 1.1. Description of center
Table 1.2. First and last consent date, date of last end study.
Table 1.3. Number of patients registered, treated, eligible, eligible and assessable for efficacy, assessable for safety

4.3.2 Patient characteristics at baseline

Table 2. Demographic characteristics and general medical conditions at baseline for each study populations: age, sex, weight, height, Heart rate, blood pressure, body temperature, performance status

4.3.3 Tumor characteristics at baseline

Table 3. For each study population: description of disease diagnosis, histological diagnosis, anatomic location, grade, type of event (initial / relapse), metastasis (Y/N), sites of Metastasis and prior treatment (surgery, radiotherapy, chemotherapy)

4.3.4 Drug delivery

Table 4.1. For all patients registered: Frequency of delivered cycle of Durvalumab.
Table 4.2. For all patients registered: Frequency of delivered cycle of Trabectedine.
Table 4.3. For each study population: number of reduction, delay and discontinuation (temporary stop and definitive stop) and reasons

4.3.5 End of treatment

Table 5.1. For each patient registered: Dates of start and end of treatment, number of cycle received, status at end of treatment, reason for end of treatment
Table 5.2. For each patient eligible: Dates of start and end of treatment, number of cycle received, status at end of treatment, reason for end of treatment
Table 5.3. For each patient eligible and assessable for efficacy: Dates of start and end of treatment,

number of cycle received, status at end of treatment, reason for end of treatment
Table 5.4. For each patient assessable for safety: Dates of start and end of treatment, number of cycle received, status at end of treatment, reason for end of treatment

4.3.6 Objective response

Table 6.1. For each patient eligible and assessable for efficacy: Dates of start and end of treatment, date, new lesions and response at each tumor evaluation (week 6, week 12, week 18, week 24 and end of treatment), status at the end of treatment, date and type of progression
Table 6.2. For all patients eligible and assessable for efficacy: Frequency and rate with 95% confidence interval (binomial law) of objective responses observed at the 6-month evaluation
Table 6.3. For each arm of treatment: Frequency and rate with 95% confidence interval (binomial law) of each category observed as objective response
Table 6.4. For all patients eligible and assessable for efficacy: Frequency and rate with 95% confidence interval (binomial law) of objective responses observed during the first 6 months (whatever the evaluation time)
Table 6.5. For each arm of treatment: Frequency and rate with 95% confidence interval (binomial law) of each category observed as objective response (whatever the evaluation time)

4.3.7 Best response

Table 7.1. For all patients eligible and assessable for efficacy: Frequency and rate with 95% confidence interval (binomial law) of each category observed as best response
Table 7.2. For each arm of treatment: Frequency and rate with 95% confidence interval (binomial law) of each category observed as best response

4.3.8 6-month non-progression

Table 8.1. For each patient eligible and assessable for efficacy: Dates of start and end of treatment, date, new lesions and response at each tumor evaluation (week 6, week 12, week 18, week 24 and end of treatment), status at the end of treatment, date and type of progression
Table 8.2. For all patients eligible and assessable for efficacy: Frequency and rate with 95% confidence interval (binomial law) of non-progression observed at the 6-month evaluation
Table 8.3. For each arm of treatment : Frequency and rate with 95% confidence interval (binomial law) of non-projection observed at the 6-month evaluation
Table 8.4. For all patients eligible and assessable for efficacy: Frequency and rate with 95% confidence interval (binomial law) of non-projection observed during the first 6 months (whatever the evaluation time)
Table 8.5. For each arm of treatment : Frequency and rate with 95% confidence interval (binomial law) of non-projection observed during the first 6 months (whatever the evaluation time)

4.3.9 Progression-free survival

Table 9.1. For all patients eligible and assessable for efficacy: Median PFS, 6-month PFS rate and 1-year PFS rate
Table 9.2. For each arm of treatment: Median PFS, 6-month PFS rate and 1-year PFS rate
Figure 1: Kaplan-Meier – PFS curves – Patients eligible and assessable for efficacy

4.3.10 Overall survival

Table 10.1 For all patients eligible and assessable for efficacy: Median OS, 6-month OS rate and 1-year OS rate
Table 10.2. For each arm of treatment: Median OS, 6-month OS rate and 1-year OS rate
Figure 2: Kaplan-Meier – OS curves – Patients eligible and assessable for efficacy

4.3.11 Safety: Adverse events (AE)

Table 11.1. For all patients assessable for efficacy: Number and percentage of AE observed by SOC and type of event
Table 11.2. For each patient assessable for safety: Event number, adverse event, serious adverse event (Y/N), SOC, date of event, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death

4.3.12 Safety: Serious adverse events (SAE)

Table 12.1. For all patients assessable for efficacy: Number and percentage of SAE observed by SOC and type of event
Table 12.2. For each patient assessable for safety: Event number, adverse event, SOC, date of event, initial intensity, maximum intensity, treatment modification, imputability, outcome, date of the end or death