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

Protocol *TRAMUNE*

VERSION N°8.0 of |16|11|2021|- N° : IB 2016- 02

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APPROVAL AND SIGNATURES OF PROTOCOL

Title of protocole : Trabectedin combined with durvalumab (MEDI4736) in patients with advanced pretreated soft-tissue sarcomas and ovarian carcinomas**.** A phase Ib study

Competent authority	Name : ANSM	Date of initial authorization	05/05/2017
		Date of MSA 1 authorization	18/10/2017
		Date of MSA 2 authorization	09/02/2018
		Date of MSA 3 authorization	28/09/2018
		Date of MSA 4 authorization	08/02/2019
		Date of MSA 5 authorization	16/03/2020
		Date of MSA 6 authorization	NA
		Date of MSA 7 authorization	NA
		Date of MSA 8 authorization	07/06/2021
		Date of MSA 9 authorization	02/02/2022
		Référence :	160939A-12
Ethic Committee	Name : CPP du Sud-Ouest et d'Outre-Mer III	Date of initial approval	21/12/2016
		Date of MSA 1 approval	27/09/2017
		Date of MSA 2 approval	31/01/2018
		Date of MSA 3 approval	29/08/2018
		Date of MSA 4 approval	27/02/2019
		Date of MSA 5 approval	20/04/2020
		Date of MSA 6 approval	NA
		Date of MSA 7 approval	NA
		Date of MSA 8 approval	26/05/2021
		Date of MSA 9 approval	23/02/2022
		Référence :	2016/98

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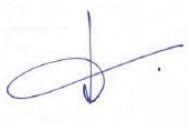
Managing Director	Pr François-Xavier MAHON Institut Bergonié – Bordeaux Phone:+335.56.33.33.33/Fax:+335.56.33.33.30 Mail : f.mahon@bordeaux.unicancer.fr	16/11/2021	
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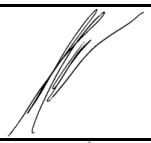
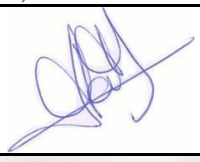
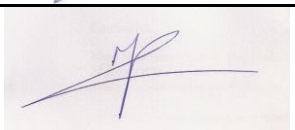
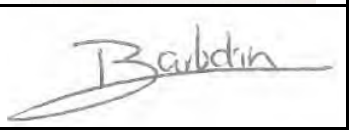
Scientific responsive	Dr Anne FLOQUET Institut Bergonié – Bordeaux Phone :+335.56.33.32.46/Fax :+335.56.33.04.85 Mail : a.floquet@bordeaux.unicancer.fr	16/11/2021	
Responsible of Unit Clinical Research	Pr Simone MATHOULIN-PÉLISSIER Institut Bergonié – Bordeaux Phone:+335.56.33.33.98 / Fax:+335.56.33.04.66 Mail : s.mathoulin@bordeaux.unicancer.fr	16/11/2021	
Biostatistician	Marina PULIDO Institut Bergonié – Bordeaux Phone: +335.24.07.19.29/Fax:+335.56.33.04.85 Mail : m.pulido@bordeaux.unicancer.fr	16/11/2021	
Data-Manager	Sandrine BARBOTIN Institut Bergonié – Bordeaux Phone: +335.56.33.33.33/Fax:+335.56.33.04.85 Mail : s.barbotin@bordeaux.unicancer.fr	16/11/2021	

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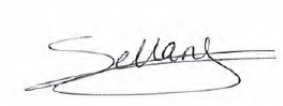
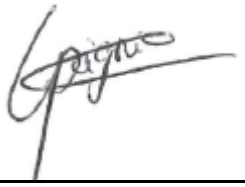
Clinical research Manager	Sabrina SELLAN-ALBERT Institut Bergonié – Bordeaux Phone:+335.56.33.78.05 Fax:+335.56.33.04.85 Mail : s.albert@bordeaux.unicancer.fr	16/11/2021	
Pharmacist	Ludivine POIGNIE Institut Bergonié – Bordeaux Phone:+335.56.33.33.94/Fax:+335. 56.33.04.85 Mail : l.poignie@bordeaux.unicancer.fr	16/11/2021	

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 :

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SYNOPSIS

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

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	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,

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	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),

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<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>Primary endpoint
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</td></tr>
</table>

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	response observed, will be centrally reviewed for all patients, by an independent expert radiologist. Reviewed data will be used for the efficacy analysis. **<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.**

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Phase I (Expansion cohorts):

- 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:
  - Cohort A: patients with advanced STS.
  - Cohort B: patients with advanced ovarian carcinomas
- For each cohort:
  - 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).
  - 14 eligible and assessable subjects are required.
  - 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.
  - 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.

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Schedule of assessments and procedures for treatment by the combination of trabectedin with durvalumab

	SCREENING	*CYCLE 1*			*CYCLE 2*			*CYCLE 3*			*CYCLE N*			*END OF TREATMENT*
		W1	W2	W3	W1	W2	W3	W1	W2	W3	W1	W2	W3	
Trabectedin (IV)		**D1**			**D1**			**D1**			**D1**			
Durvalumab (IV)		**D2**			**D2**			**D2**			**D2**			
Consultation	**X**		**D8**											**X**
24h-hospitalization		**D1-2**			**D1-2**			**D1-2**			**D1-2**			
Written Informed consent	X													
Demographics data	X													
Medical history/baseline condition	X													
Concomitant treatments	X	Throughout the treatment period												
Physical examination	X[d]	X	X		X			X			D1			X[j]
Assessment of signs and symptoms	X[d]	X	X		X			X			D1			X
Performance status (ECOG)	X[d]	X	X		X			X			D1			X
Vital signs (heart rate, blood pressure, temperature)	X[d]	X	X		X			X			D1			X
Height	X													
Weight	X[d]	X	X		X			X			D1			X
Hematology[a]	X[d]	X[e]	X	X	X	X	X	X	X		D1			X
Biochemistry[b]	X[d]	X[e]	X	X	X	X	X	X	X		D1			X
Urinalysis[i]	X[d]	X[e]			X			X			D1			X
Thyroid test: T3, T4 and TSH	X[d]	X[e]			X			X			D1[f]			X
CA 125 (ovarian only)	X[d]	X[e]						X			D1[f]			X
aPTT, INR	X[d]	To be repeated if clinically indicated												
Serology[h]	X[d]													
Serum pregnancy test (*if indicated*)	X[d]	If indicated, to be repeated within 72 hours before C1D1 (serum) and to be repeated on Day 1 of each cycle (urine)												
Adverse Events	X	Throughout the treatment period												X
Tumor measurement	X[c]	Repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease, and response must be confirmed ≥ 4 weeks												X[j]
Echocardiography	X[k]	To be repeated every 2-3 months												
Immunological biomarkers		**D1**			**D1**									
Circulating DNA		**D1**			**D1**			**D1**			**D1[g]**			
Biopsy	**Baseline**					**D8**								

a: NFS, platelets
b: Serum electrolytes (Na+, K+, Cl-,Mg++and Ca++), liver function tests (AST, ALT, total bilirubin, GGT and AP), LDH, creatinine, creatinine clearance , glucose, CPK, total proteins, urea, albumin, bicarbonates, uric acid. Amylase and lipase at screening and Day 1 of each cycle.
c: baseline tumor assessment should be performed within 28 days (+/- 1 week) before treatment initiation
d: to be done in the 7 days prior inclusion
e : to be done within 24 hours before Day 1 of Cycle 1
f : every 3 cycles (ie. C3, C6, etc…)
g : until progression
h : Hepatitis A antibody, Hepatitis B surface antigen, Hepatitis C antibody and HIV antibody
i: bilirubin, blood, glucose, ketones, pH, protein, specific gravity.
j : Clinical and radiological tumor assessment (CT-scan/MRI), except for patients with confirmed PD at discontinuation or who had started a new treatment since.
k: Within 14 days prior to Day 1 of cycle 1 (+1 day tolerance)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de sécurité du Médicament
AP	Alkalin Phosphatase
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BER	Base Excision Repair
βhCGs	Beta Human Chorionic Gonadotrophins
BP	Blood Pressure
CAEPR	Comprehensive Adverse Events and Potential Risks
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CI	Confidence Interval
CNS	Central Nervous System
CPK	Creatine PhosphoKinase
CPP	Ethic Committee
CR	Complete Response
CRA	Clinical Research Associate
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computerized Tomography
CT	Chemotherapy
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DSB	Double-Strand Break
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial Ovarian Cancer
ESMO	European Society for Medical Oncology
FFPE	Formalin-Fixed Paraffin-Embedded
FUP	Follow-up
GCP	Good Clinical Practice
G-SCF	Granulocyte Colony Stimulating Factor
GIST	Gastro-Intestinal Stromal Tumor
HCC	HepatoCellular Carcinoma
HCG	Chorionic Gonadotropin
HGSOC	High-Grade Serous Ovarian Cancer
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independant Data Monitoring Committee
IEC	Investigational Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous

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LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normality -
LVEF	Left Ventricular Ejection Fraction
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NER	Nucleotide Excision Repair
NSCLCC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamy
PD	Progressive Disease
PFR	Progression-free rate
PFS	Progression-free Survival
PK	Pharmacokinetics
PLD	Pegylated Liposomal Doxorubicine
PPC	Primary Peritoneal Cancer
PR	Partial Response
PRE TT	Pre-treatment
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RDI	Relative Dose Intensity
RP2D	Recommended Phase II Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analyses Plan
SBP	Systolic Blood Pressure
SCLC	Small Cell Lung Cancer
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SoC	Standard of Care
SPC	Summary of Product Characteristics
SSB	Single Strand Break
STS	Soft Tissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAM	Tumor-Associated Macrophages
TCGA	The Cancer Genome Atlas
TT	Treatment
ULN	Upper Limit of Normality
WBC	White Blood Cells

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1. RATIONALE OF THE TRIAL

1.1. MANAGEMENT OF SOFT-TISSUE SARCOMA IN ADVANCED SETTING

Soft tissue sarcomas (STS) are uncommon tumors (1% of all adult malignancies) arising from mesodermal precursors [1;2]. Their diversity in site, histological subtypes (>50 recognized) [3] and frequency make difficult to draw universal conclusions and to find commons guidelines.
Surgery remains the principal therapeutic modality: the usual first-line treatment is wide margin surgery plus radiotherapy [4,5]; nevertheless, despite improved local control rates, more than half of the patients still develop and die from unresectable, locally advanced and/or metastatic disease [1].
Chemotherapy is currently used for the treatment of advanced and/or metastatic sarcomas, but very few cytotoxic drugs have shown activity in this clinical setting. Doxorubicin is considered the most active first-line agent and the most frequently used in advanced sarcoma, followed by ifosfamide and dacarbazine [1,6,7]. No survival benefit has been demonstrated for patients receiving doxorubicin-based combination therapy for advanced or metastatic disease [8,9], and conventional-dose, single-agent chemotherapy is considered the standard treatment for metastatic disease [10]. Combination therapy may be considered in some specific cases in order to maximize chance for tumor response, such as in locally advanced STS, in potentially resectable lung oligometastases, especially in young patients with high grade sarcomas), or when patients are symptomatic of their advanced unresectable disease.
In the palliative setting, when confronted with primary resistance or subsequent progression to standard anthracycline- and ifosfamide-based chemotherapy, the number of active cytotoxic agents for the treatment of relapsed/recurrent disease is very limited [11].
The last decade has seen major advances in the development of therapeutic agents in the field of STS with approval of trabectedine [12-16] and pazopanib [17;18] for the treatment of patients with STS after failure of anthracycline- and ifosfamide-based chemotherapy. However, with low response rates and ultimate disease progression, this situation represents an unmet medical need.

1.2. MANAGEMENT OF PLATINUM-SENSITIVE RELAPSED OVARIAN CARCINOMA

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer [19,20]. The median age at presentation of epithelial ovarian cancer (EOC) is 60 years. Due to the non-specific nature of symptoms, many women present with advanced disease and therefore have a poor prognosis.
After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy [21]. However, relapse occurs in the majority of cases, and only 10−30% of women experience long-term survival [21]. Advanced stage disease is associated with a 5-year survival rate of only 30−40% [19].
Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade [21]. The site of origin of epithelial ovarian cancer remains unclear. Some studies suggest that serous epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium [21-25]. EOC, PPC and fallopian tube cancer behave very similarly and are therefore treated in the same way.
The standard approach to treatment of advanced high-grade serous ovarian cancer (HGSOC) is cytoreductive surgery, either at time of diagnosis or interval debulking, with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to eight cycles of platinum- and taxane-based chemotherapy [26;27] is the global standard of care. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with deoxyribonucleic acid (DNA) [21, 28].
The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. Platinum-based regimens dominate ovarian cancer therapy and define treatment groups [29]. In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease; and patients whose disease relapses more than 6

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months after the last platinum-based therapy was administered are considered to have platinum-sensitive disease.
However, these classifications are somewhat arbitrary and do not take into account the molecular characteristics of a patient's tumor such as BRCA mutations.
In later lines of therapy, treatment choice is often restricted according to individual patient situation (e.g. performance status, organ function, residual toxicities from prior treatment, other comorbidities, and patient choice).

The two major types of DNA damage are the formation of DNA single-strand breaks (SSBs) and double-strand breaks (DSBs). SSBs are normally quickly repaired by a process known as base excision repair (BER). An additional DNA repair process known as homologous recombination repair (HRR) can repair double-strand breaks (DSBs). HR is a complex, multistep process that involves notably 2 proteins encoded by the breast cancer susceptibility 1 and 2 genes (BRCA1 and BRCA2).
Germline mutations in BRCA1 and BRCA2 genes are the strongest known hereditary factors for breast and EOC, accounting for up to 5% of all breast cancers and 15% of all EOCs [30,31]. Moreover, approximately 6 – 8% of patients with HGSOC have somatic mutations in BRCA1 or BRCA2 [30,32].
However, defects in the HRR pathway are not limited solely to mutations of BRCA1/2. The Cancer Genome Atlas (TCGA), which completed an analysis of molecular changes in HGSOC, estimated that approximately 50% of patients with HGSOC have alterations in genes involved in the HRR DNA repair [33].

1.3. TRABECTEDIN

1.3.1. Chemical structure

Trabectedin [Ecteinascidin 743, Yondelis®, ET 743] is a potent cytotoxic alkaloid isolated from the Caribbean sea squirt Ecteinascidia turbinata. It is formed by a monobridged pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings (A and B), linked to a 10-member lactone bridge through a benzylic sulfide linkage, and attached through a spiro ring to an additional ring system made up of a tetrahydroisoquinoline (subunit C). The molecular formula is C39H43N3O11S [(1'R,6R,6aR,7R,13S,14S,16R)-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-19-oxo-3',4',6,7,12,13,14,16-octahydrospiro[6,16-(epithiopropano-oxymethano)-7,13-imino-6aH-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-5-yl acetate]] and the molecular mass 761.84 g/mol.
Unlike conventional alkylating agents which bind to the major groove of DNA and predominantly form crosslinks to the Guanine N7 or O6 position, trabectedin predominantly binds to the minor groove of DNA and binds to the Guanine N2 position, (18) through an iminium intermediate generated in situ by dehydration of the carbinolamine moiety present in the ring A. The carbinolamine moiety is imperative for the pharmacological activity of trabectedin; van der Waals interactions stabilize the adduct, through hydrogen bonds between rings A and B, with neighboring nucleotides in the same or opposite strand of the DNA double helix, thus creating the equivalent to a functional interstrand crosslink.

1.3.2. Preclinical and mechanism of action

Cytotoxic concentrations of trabectedin delay cell cycle as progression through the S phase and produce arrest at G2/M, ultimately resulting in p53-independent apoptosis [34-37].
Trabectedin-induced DNA damage is recognized by the nucleotide excision repair (NER) pathway, resulting in stalled DNA-protein repair complexes [38,39] and cell death. Therefore, in contrast to that expected for a DNA-damaging agent, sensitivity to trabectedin is correlated to a functional NER [39-41]. On the other hand, trabectedin also induces DNA DSBs, mainly during early S phase, and this damage is repaired by the HRR pathway [44]. Moreover, there is evidence suggesting that trabectedin is particularly effective in cells lacking functional HR repair mechanisms, such as those with BRCA gene mutation or BRCAness phenotype [36,42,43]. Overall, preclinical data indicate that a functional transcription-coupled nucleotide excision repair (TC-NER) machinery and a deficient homologous recombination repair (HRR) machinery are required for in vitro sensitivity to trabectedin [43].
Besides its role as an alkylating agent, trabectedin has also an impact on tumor microenvironment. Trabectedin affects not only the neoplastic compartment but also monocytes and macrophages [45]. These findings opened an important area of research for the implications of macrophage pro-tumoral functions in disease progression. The exquisite selectivity of trabectedin against mononuclear phagocytes (monocytes and macrophages) was recently related to the activation of caspase 8 by membrane signalling TRAIL receptors that are selectively expressed by monocytes/macrophages and

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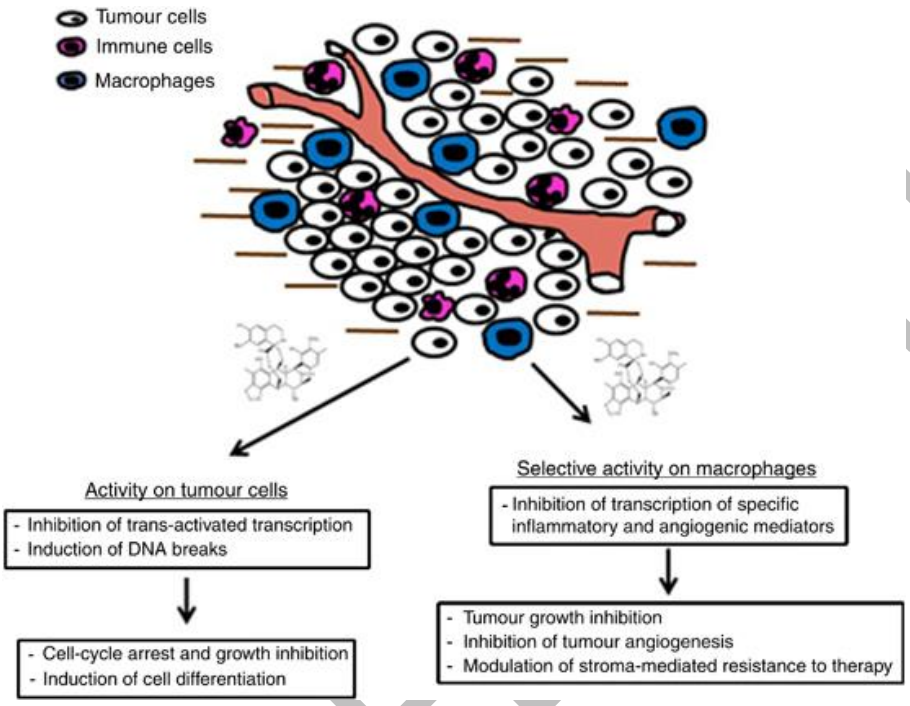
not neutrophils and lymphocytes [46]. Exposure to trabectedin also causes a strong decrease in the production of several cytokines and chemokines secreted by monocytes/macrophages and tumour cells such as IL-6, CCL2, CXCL8, Angiopoietin 2 or VEGF, but not of other biological stimulating mediators such as TNFα [47,48]. The importance of this anti-cancer activity was also demonstrated in vivo. The anti-inflammatory effects of trabectedin were indeed confirmed in different tumour xenografts and in human soft-tissue sarcoma samples from patients receiving trabectedin as neo-adjuvant therapy [46]. Interestingly, trabectedin still showed anti-tumour activity in xenograft with tumor cells resistant to trabectedin injected into mice indicating that the macrophage-targeted effect can be sufficient to significantly reduce neoplastic growth, under conditions where tumour cells are unresponsive to the drug [46]. Thus, trabectedin effects on the TME and on macrophages are—at least in part—important contributors of its anti-tumour and anti-metastatic activity. A summary of these effects are depicted in the figure below:



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1.3.3. Clinical data

Trabectedin is approved in Europe for the treatment of patients with advanced soft-tissue sarcoma (STS) after failure of anthracyclines and ifosfamide, or when they are not eligible to receive these agents. In this setting, the 6-month progression-free rate is about 35-40% [12-16].
Recently, Le Cesne et al [49] published a retrospective pooled analysis of trabectedin safety in 1132 patients with solid tumors enrolled in 19 worldwide phase II trials from 1998 to 2008, in order to summarize the safety experience of single agent trabectedin. Three schedules of administration were considered: 24-hour infusion every 3 weeks, 3-hour infusion every 3 weeks and 3-hour infusion for three consecutive weeks every 4 weeks. Tolerance was good in phase II development, with a rate of toxic death of 1.7%. Neutropenia (69.2%) and thrombocytopenia (36.3%) were the most frequent drug-related toxic events. The incidence and severity of neutropenia were higher with the q3wk 24-h schedule, grade 3 in 26.6% and grade 4 in 23.9% of patients. Of note, prophylactic use of granulocyte colony stimulating factor (G-CSF) was generally not permitted in the trabectedin trials and, therefore, only administered to 9.8% of the patients. Other common trabectedin-related adverse events reported in at least 20% of patients were nausea (64.7%), fatigue (58.3%), and vomiting (40.1%).
Transaminase increase was common with trabectedin, with a peak elevation at days 5–7 and a return to grade ≤1 at approximately day15 of each cycle. Dexamethasone was routinely administered to improve tolerance, including hepatic toxicity, and was given prior to infusion at the recommended dose of 20 mg 30 min before trabectedin in the majority of clinical studies. Rhabdomyolysis was uncommon (0.8%).
Extravasation-related AEs following injection were rare (6 out of 1132 patients, 0.5%), and only 3 of these events were serious or treatment limiting (grade 4). The use of a central-line was mandatory in the clinical trials.
No cumulative toxicities were apparent and trabectedin was able to be administered for prolonged periods (up to 59 cycles) to patients who exhibited sustained clinical benefit from stable disease or objective responses.

Trabectedin is also approved in recurrent platinum sensitive advanced ovarian cancer. In the study published by Monck et al. [50], trabectedin in combination with pegylated liposomal doxorubicine (PLD) provided a significant 21% risk reduction for progression or death compared with PLD monotherapy. Median PFS was 7.3 months for trabectedin/PLD and 5.8 months for PLD alone. Trabectedin/PLD also improved PFS compared with PLD alone by independent radiology analysis in platinum-sensitive patients (9.2 v 7.5 months, p = 0.0170). No significant difference in median PFS was observed in platinum-resistant patients (median, 4.0 and 3.7 months with combination and monotherapy, respectively).
Grade 3 or 4 neutropenia (28.8% and 33.9%) and grade 3 to 4 ALT elevations (28.5% and 8%) were more frequent with trabectedin/PLD. However, Grade 3 to 4 febrile neutropenia was uncommon (6,9%) and liver toxicity was never severe and rapidly resolved in all cases.

1.4. Durvalumab (MEDI4736)

1.4.1. Chemical structure

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1) Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.4.2. Preclinical data and mechanism of action

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, Durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays.
In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T-lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse (m)PD-L1 antibody demonstrated improved

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survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans (Investigator Brochure). Data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.4.3. Clinical data

As of the DCO dates (15Apr2015 to 18Sep2015), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies (Investigator Brochure).
Durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.
Of the 1,910 subjects, 1,279 received durvalumab monotherapy and 631 received durvalumab in combination with other anticancer agents. To date, no PK interaction has been observed between Durvalumab and these agents.

Of the 1,279 subjects who have received durvalumab monotherapy across the clinical development program, the majority of treatment related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. No studies have been completed or terminated prematurely due to toxicity. As of 07May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%).
Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each) and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects).

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.
Study CD-ON-MEDI4736-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response. In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-

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positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

1.4.4. Fixed dosing rationale

A population PK model was developed for MEDI4736 using monotherapy data from Study 1108 (Phase I study; N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors [66]). Population PK analysis indicated only a minor impact of body weight (WT) on the PK of MEDI4736 (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on a median body WT of approximately 75 kg). A total of 1000 patients were simulated using a body WT distribution of 40 to 120 kg. Simulation results demonstrated that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.
Similar findings have been reported by others [62-65]. Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [64]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters [65].
A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body WT of 75 kg, fixed doses of 1.12 g q3w (equivalent to 15 mg/kg q3w) of MEDI 4736 is included in the current study.

1.5. STUDY RATIONALE

Trabectedin is an agent approved for the treatment of STS and ovarian cancer. Recent data suggest that the antitumor activity of trabectedin is not only mediated by its interaction with DNA but also mediated by targeting tumor-associated macrophages (TAM) [51]. TAMs play a pivotal role in tumor growth and progression. They produce several molecules that sustain malignant cell survival, modify neoplastic extra-cellular matrix proteins, promote the development of a newly formed vessel, and assist tumor cells in their progression. Moreover, TAMs affect adaptive immune responses significantly by recruiting and stimulating Tregs and recruiting Th2 lymphocytes, which in turn inhibit Th1 cells, and by inducing anergy of naïve T cells.

Recent studies have shown that PDL1 is expressed in up to 58% of cases of STS, osteosarcomas and GIST [52-54]. This overexpression has been associated with prognosis. Besides, preliminary unpublished data from our lab corroborates the finding that a substantial proportion of STS express PDL1 on immune cells, notably type M2 macrophages (M.Toulmonde et al. JAMA ONCOL.2017 29), leading to speculate that drugs targeting this immune checkpoint would be of great interest in these tumors and particularly in sarcomas with complex genomics (including leiomyosarcomas and undifferentiated sarcomas).
PD-L1 is expressed in ovarian cancer and is a factor of poor prognosis [55]. Moreover a rapidly growing set of preclinical and clinical data promotes use of immunotherapy in ovarian cancer and numerous studies are ongoing [56,57].

TAM targeting has been associated with anti-tumor activity in sarcoma and ovarian cancer models [58-59]. Moreover, TAM targeting in combination with PD-1 checkpoint inhibitor has been shown to be effective in several tumor models, including a murine model of ovarian cancer [60-61].
We hypothesized that the combination of Durvalumab and Trabectedin could have a synergic immunomodulatory and antitumoral effect, in patients with relapsed unresectable or metastatic STS and ovarian carcinoma. Despite the existence of potential overlapping toxicities (transaminitis), the tolerance profile is also expected to be good.

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2. OBJECTIVES

2.1. 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.

2.2. 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).

3. STUDY DESIGN

3.1. OVERALL 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.

3.2. DEFINITIONS

Dose-limiting toxicity (DLT):

A DLT is defined as an AE or laboratory abnormality that fulfills all the criteria below:

- Begins on the first 21 days of treatment.
- Is considered to be at least possibly related to the study treatment.
- Meets one of the criteria below, graded as outlined or according to NCI-CTCAEv4.03 :
  - 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 > 7days (except for 1rst 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.

DLT status:

In addition, the steering committee will resolve any specific issue regarding the DLT status (see section 12.1.1).

Maximum tolerated dose (MTD):

The MTD is defined as the highest dose at which no more than 1 in 6 patients in the cohort experience a DLT in the first 21 days. The conclusions of the steering committee for the definition of

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of the MTD will be submitted 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. The RP2D dose for trabectedin when given in combination with Durvalumab, 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 (dose escalation trial and expansion cohorts) will be used to define the RP2D.

3.3. Dose escalation part

3.3.1. Treatment scheme

Trabectedin will be administered intraveinously, on day 1 of each cycle, every three weeks, as appropriate for assigned dose level.
Durvalumab will be administered intraveinously, at fixed doses of 1120 mg (equivalent to 15 mg/kg), on day 2 of each cycle, every three weeks.

A treatment cycle consists of 3 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.).

3.3.2. Dose levels

Dose escalation study assessing 3 doses level of Trabectedin given in combination with durvalumab (fixed dose).

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/m².
- The maximum dose of Trabectedin administered (1.5 mg/m²) will not be exceeded.
- Patients will be allocated to 3 doses 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.

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- 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 question regarding the DLT status (see section 12.1.1).
- 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.

3.4. EXPANSION cohorts

- Once the MTD has been defined based on the dose escalation study, the expansion cohorts will be opened. All patients will be treated at the MTD of Trabectedin (as defined in the escalation trial) given in association with durvalumab with the same schedule as in the phase I 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.

3.5. Patient's replacement

See section 10.2.

4. SELECTION OF PATIENTS

4.1. 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 palliatve 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).

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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 7.5,
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.

4.2. 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),
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,
11. 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

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STUDY PLAN

4.3. Duration of Study (Whole Population)

The total duration of the study will be approximately 36 months, including about 18 months of active enrolment.
Planned start date (first patient on study): February 2017.
Follow-up: 12 months

4.3.1. Dose escalation part

Follow-up: 6 months
End of study occurs when all of the following criteria have been satisfied:

- The trial is closed to recruitment

AND

- All patients have disease progression or are no longer on study medication

AND

- The last included patient has been followed for 6 months or is deceased

4.3.2. Expansion cohort

Follow-up: 12 months
End of study occurs when all of the following criteria have been satisfied:

- The trial is closed to recruitment

AND

- All patients have disease progression or are no longer on study medication

AND

- The last included patient has been followed for 12 months or is deceased

4.4. Definitions of duration of Study and Treatment (Per Patient)

Patients will receive study treatment as long as it is considered to be in their best interest. Patients will be evaluated at scheduled visits in up to three study periods:

- **Pre-treatment (PRE TT):** from signature of informed consent to the first administration of study drugs.
- **Treatment (TT):** from the first administration of study drugs to treatment discontinuation.
- **Follow-up (FUP):** after treatment discontinuation, patients will be followed up four weeks later for toxicities, and beyond if grade 3 or 4 toxicity, until resolution.

Patients who discontinue treatment *without progression* will be **followed every 12 weeks** until:

1. Disease progression,
2. Initiation of other antitumor therapy,
3. Death, or
4. The date of study termination, whichever occurs first.

After documented progression or start of a new antitumor therapy, patients will be **followed every 6 months until**:

1. Death, or
2. The date of study termination, whichever occurs first.

Patients will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period.

Patients will be considered to be **on-treatment** for the duration of their treatment until 30 days (4 weeks) after the last treatment administration, except if the patient starts a new antitumor therapy before this period.

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Patients may withdraw their consent at any time; no further study activities will be conducted on them.

Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication or starts a new antitumor therapy, regardless of the circumstances, and is defined as 30 days after the day of the last treatment administration, unless the patient starts a new antitumor therapy, in which case the date of administration of this new antitumor therapy will be considered the date of treatment discontinuation. The primary reason for any discontinuation will be recorded on the patient's case report form (CRF). If a patient discontinues treatment, every effort should be made to complete the scheduled assessments. Administration of the study treatments should be permanently discontinued if this is considered to be in the best interest of the patient. More specifically, treatment will be discontinued due to any of the following reasons:

- Withdrawal of consent or lost to follow-up,
- Disease progression,
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing,
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk,
- Pregnancy or intent to become pregnant,
- Grade ≥ 3 infusion reaction,
- Initiation of alternative anticancer therapy including another investigational agent,
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study,
- Patient refusal and/or non compliance with study requirements,
- Protocol deviation with an effect on the risk/benefit ratio of the clinical trial

Patients still experiencing a non-progression after 6 cycles will then be able to continue treatment off-study at the discretion of the investigator.

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 3.2.8). Patients have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.
The date and reason for study discontinuation will be clearly documented on the patient's CRF.

4.5. PROTOCOL DEVIATION

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the investigator, etc.).
Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the investigational medicinal product due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting serious adverse events (SAEs), etc.

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The investigators may suggest to the Sponsor the authorization of certain protocol deviations, especially if they are related to the inclusion/exclusion criteria or if they may have an effect on the evaluability of the patients. As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. Protocol deviations considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

4.6. SCREENING EVALUATION

During the pre-treatment period, and once the patient has signed the informed consent form, the Investigator will confirm the patient's eligibility for the study by conducting the assessments detailed below.

Screening assessments.

	ASSESSMENT	**TIME**
1. History and clinical examination	◆ Signed by the patient/legal representative Informed Consent Form	Prior to any specific study procedures
	◆ Medical history and baseline condition ◆ Complete physical examination ◆ Performance status (ECOG PS; see Appendix 1) ◆ Assessment of baseline signs and symptoms ◆ Concomitant treatments	Within two weeks prior to Day 1 of cycle 1 (+1 week tolerance) D-14 to D-1
	◆ Vital signs: heart rate, blood pressure, body temperature, weight and height	Within 7 days prior to Day 1 of cycle 1 (+3 day tolerance) D-7 to D-1
	◆ Demographic data ◆ Primary diagnostic and prior treatment/s data: • Date of diagnosis of the primary disease • Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), specifying the date of best response and the time to progression	Within four weeks prior to Day 1 of cycle 1 D-28 to D-1
2. Pathology	◆ Central review to confirm soft-tissue sarcoma diagnosis, except in case of diagnosis confirmed by the RRePS Network ◆ Histologically confirmed ovarian carcinomas	Material sent within 7 days after signed informed consent
3. Laboratory tests	◆ **Hematology**: neutrophils, lymphocytes, basophils, eosinophils, monocytes, haemoglobin, haematocrit, platelet count, red blood cell count, total white cell count, VGM, CCMH, TCMH. ◆ **Biochemistry**: Serum electrolytes (Na^+, K^+, Cl^- ,$Mg^{++}$and Ca^{++}), liver function tests (AST, ALT, total bilirubin†, GGT and AP), LDH, creatinine, glucose, CPK, total proteins, urea, creatinine clearance albumin, lipase, amylase, bicarbonates, uric acide. ◆ **Thyroid function**: TSH, T3 and T4 ◆ **CA 125** for ovarian carcinoma only ◆ **Coagulation:** aPTT, INR ◆ **Serology**: Hepatitis A antibody, Hepatitis B surface antigen, Hepatitis C antibody, and HIV antibody ◆ **Urinalysis**: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance	Within 7 days prior to inclusion (+3 days tolerance). D-7 to D-1

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	ASSESSMENT	TIME
4. Creatinine clearance	◆ Calculated using the Cockroft formula (see Appendix 2)	Within 7 days prior to inclusion (+3 days tolerance) D-7 to D-1
5. Pregnancy test, if applicable	**Measurement** of serum human chorionic gonadotropin (HCG)	Within 7 days prior to Day 1 of cycle 1 (+1 day tolerance) D-7 to D-1
6. Tumor assessment	◆ CT-scan or MRI of all measurable sites, as per RECIST 1.1 (Appendix 3)	Within four weeks prior to Day 1 of cycle 1 (+1 week tolerance) D-28 to D-1
7. Other tests	◆ Intercurrent events, concomitant diseases and treatments.	Within two weeks prior to Day 1 of cycle 1. D-14 to D-1
8. LVEF	◆ Echocardiography	Within 14 days prior to Day 1 of cycle 1 (+1 day tolerance) D-14 to D-1

ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CCMH: Mean corpuscular hemoglobin concentration ; CPK, creatine phosphokinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT: gamma-glutamyltransferase ; INR: international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; RECIST v1.1, Response Evaluation Criteria In Solid Tumors; TCMH: mean corpuscular haemoglobin; TSH, thyroid stimulating hormone; VGM, Mean corpuscular volume.

(†):If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

4.7. EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment.

Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination ◆ Performance status (ECOG PS; see Appendix 1) ◆ Vital signs: heart rate, blood pressure, body temperature and weight	Day 1 of cycle 1 Repeat on Day 8 of Cycle 1 Repeat on Day 1 of each subsequent cycle
	◆ Assessment of signs and symptoms	Throughout the treatment period
	◆ Concomitant diseases and treatments	Throughout the treatment period
2. Laboratory tests*	◆ **Hematology**: neutrophils, lymphocytes, basophils, eosinophils, monocytes, haemoglobin, haematocrit, platelet count, red blood cell count, total white cell count, VGM, CCMH, TCMH. ◆ **Biochemistry**: Serum electrolytes (Na^+, K^+, Cl^- ,$Mg^{++}$and Ca^{++}), liver function tests (AST, ALT, total bilirubin†, GGT and AP), LDH, creatinine, glucose, CPK, total proteins, urea, albumin, bicarbonates, uric acide. Lipase and amylase (*). ◆ **Coagulation:** aPTT and INR if clinically indicated ◆ **Urinalysis**(*): bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance	Within 24 hours before Day 1 of cycle 1 (except coagulation) Repeat on Days 8 and 15 of Cycle 1* Repeat on Days 1, 8 and 15 of Cycle 2* Repeat on Days 1 and 8 of Cycle 3* Repeat on Day 1 of each subsequent cycle* (*): at day 1 of each cycle only
	◆ **Thyroid function**: TSH. If TSH is abnormal, free T3 and free T4	Within 24 hours before Day 1 of cycle 1 Repeat on day 1 of cycle 2* Repeat on day 1 of subsequent cycles (ie. C3, C6, C9, etc.)*

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	ASSESSMENT	TIME
	◆ **CA 125** for ovarian carcinoma only	Repeat on day 1 Cycle 3 and every 3 subsequent cycle*
3. Creatinine clearance	◆ Calculated using the Cockroft formula (see Appendix 2)	Within 24 hours before Day 1 of cycle 1 Repeat on Days 8 and 15 of Cycle 1* Repeat on Days 8 and 15 of Cycle 2* Repeat on Days 8 of Cycle 3* Repeat on Day 1 of each subsequent cycle*
4. Pregnancy test, if applicable	◆ **Measurement** of human chorionic gonadotropin (HCG)	Within 72 hours prior to Day 1 of cycle 1 (serum) Will be repeated on day 1 of each cycle, in women with childbearing potential (urine)
5. Tumor assessment	◆ CT-scan or MRI of all measurable sites, as per RECIST (see Appendix 3)	Tumor assessment must be repeated every six weeks (±7 days) and at least four weeks after first documentation of objective response even if there are treatment delays
6. PD study – immunological biomarkers	◆ Blood samples : 1 EDTA x 4ml ; 1 EDTA x6 ml and 1 heparin x 6 ml	At cycle 1 day 1 and at cycle 2 day 1 For more details; see section 15.1.1
7. Circulating DNA	◆ Blood samples : 2 EDTA x 10 ml	At D1 of each cycle, until progression
8. Biopsy	◆ Tumor biopsy	At baseline and at cycle 2 day 8 (+/- 2 days) For more details; see section 15.1.1
9. Adverse events	As per NCI-CTCAE, v4.03.	Throughout the treatment period
10. LVEF	Echocardiography	Every 2-3 months throughout the treatment period

*For all laboratory tests a window of 72 hours will be allowed.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CCMH: Mean corpuscular hemoglobin concentration; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT: gamma-glutamyltransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD: pharmacodynamics assessment; RECIST, Response Evaluation Criteria In Solid Tumors TCMH: mean corpuscular haemoglobin; VGM, Mean corpuscular volume.

(†):If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

4.8. EVALUATION AT the END OF TREATMENT

The end-of-treatment visit will be scheduled 30 days (4 weeks) after the last treatment administration (a window of ±1 week is allowed).
Regardless of the reason for discontinuation, the complete workup has to be done at the end-of-treatment visit. This will include the following assessments:

- Assessment of signs and symptoms.
- Complete physical examination.
- ECOG performance status.
- Vital signs [heart rate, blood pressure, weight and temperature].
- Hematology.
- Biochemistry.
- Urinalysis
- Calculated CrCl.
- Thyroid function

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- CA 125 measurement
- Clinical and radiological tumor assessment (CT-scan/MRI) (except for patients with confirmed PD at discontinuation or who had started a new treatment).
- Intercurrent events and concomitant disease and treatments.
- Safety assessment (AEs).

Adverse events must be reported for 30 days after the last treatment administration or until the start of a new antitumor therapy, whichever occurs first. All SAEs occurring within 90 days of the last treatment administration or until the start of a new antitumor therapy, whichever occurs first, will be reported. Beyond this period of time, only those SAEs suspected to be treatment-related will be reported (see Section 11).

4.9. FOLLOW-UP AFTER the END-OF-TREATMENT VISIT

- The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2).
- After treatment discontinuation, patients will be followed for four weeks after until resolution of toxicities, if any.
- Patients who discontinue treatment without PD will be followed every 12 weeks until disease progression, other antitumor therapy or death or until the date of study termination, whichever occurs first.
- After disease progression, patients will be followed every 6 months until death or until the date of study termination, whichever occurs first.
- Patients who withdraw consent will not be followed with any study procedures.

All AEs (including SAEs) suspected to be treatment-related (trabectedin and/or durvalumab) or research-related will be followed-up until the events or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor.

5. REGISTRATION PROCEDURES

5.1. Screening

Upon signature of consent, screened patient will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator.

See procedure of study

5.2. Inclusion

Upon signature of consent, eligible patient will be entered in the study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator.

See procedure of study

6. STUDY TREATMENT

Sponsor will provide Trabectedin and Durvalumab, with identifying labels that will include all the information required by local regulations.
Investigational medicinal products (IMPs) will have to be requested to Institut Bergonié using appropriate forms provided by the Sponsor.
The study sites will have to ensure drug traceability at all times.

6.1. Description of treatment

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For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the IMP Investigator's Brochure and/or the more updated Summary of Product Characteristics (SPC), all provided as separate documents.

6.2. Pharmaceutical Informations

Product description	Galenic	Dosage	Route of administration	Storage	Supply
Trabectedin	Infusion	0.05 mg/ml	Intravenous	2°C ≤ temp ≤ 8°C	Yes
Durvalumab	Infusion	50 mg/ml	Intravenous	2°C ≤ temp ≤ 8°C	Yes

6.3. Administration of treatment

Treatment will be administered on an inpatient/outpatient basis.

In a first time, on Day 1, Trabectedin should be administered as a 3-hour intravenous (IV) infusion. All patients must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to Trabectedin administration; not only as anti-emetic prophylaxis but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

Durvalumab should be administered on Day 2 as a 1-hour intravenous (IV) infusion.

Regimen description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Trabectedin	Doses as appropriate for assigned dose level	IV	Day 1	3 weeks
Durvalumab	Fixed doses of 1120 mg	IV	Day 2	

6.4. Durvalumab

6.4.1. Formulation/packaging/storage

Durvalumab will be supplied as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

6.4.2. Study drug preparation

For patients, a fixed doses of 1120 mg should be prepared.

Preparation of durvalumab doses for administration with an IV bag.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

24 hours at 2°C to 8°C

4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours (that is, the individual storage time limits are not additive). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Fixed doses of 1120 mg of Durvalumab for patients will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

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Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab is added to the IV bag volume 250 mL (possibility of use IV bag volumes 100 to 1000 mL such that final concentration is within 1 to 20 mg/mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.4.3. Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

6.5. Trabectedin

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the more updated Summary of Product Characteristics (SPC), provided as separate documents.

No lock of the BSA is required.

6.6. General Concomitant Medication and supportive care guidelines

6.6.1. Acceptable concomitant medication

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs only.

6.6.2. Prohibited concomitant medication

Subjects are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Trabectedin and Durvalumab
- Radiation therapy
  - o Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella zoster, yellow fever, intranasal influenza, rabies, BCG and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Other medications that are prohibited in this trial are described in the exclusion criteria section.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.6.3. Restrictions during study

6.6.3.1. CONTRACEPTION

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

- **Female patient of child-bearing potential:**

  Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (table below) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of study treatment. Non-sterilised male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

- **Male patients with a female partner of childbearing potential:**

  - Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of study treatment. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
  - Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table below).

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N.B Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in table below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 1. Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

6.6.3.2. BLOOD DONATION

Subjects should not donate blood while participating in this study and for 90 days after receipt of the final dose of investigational products.

6.6.4. Potential drug interaction

6.6.4.1. DURVALUMAB

No formal drug-drug interaction studies have been conducted with durvalumab.

There are no known clinically significant interactions of durvalumab with other medicinal products.

6.6.4.2. TRABECTEDIN

Since Trabectedin is metabolised mainly by CYP3A4:

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- Co-administration of trabectedin with potent inhibitors of the isoenzyme CYP3A4 (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) is prohibited.
- Co-administration of trabectedin with potent inductors of the isoenzyme CYP3A4 (e.g. rifampicin, phenobarbital, Saint John's Wort) is prohibited as it would decrease the exposure to trabectedin.

The following website may be referenced for a more extensive list of P450 inhibitors and inducers: http://medicine.iupui.edu/clinpharm/ddis/main.

Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product. Caution should be taken if **medicinal products associated with hepatotoxicity** are administred concomitantly with trabectedin, since the risk of hepatotoxicity may be increased.

Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. **statins**) are administred concomitantly with trabectedin, since the risk of rhabdomylolysis may be increased.

Concomitant use of trabectedin with **phenytoin** may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended and with yellow fever vaccine is specifically contraindicated.

Concomitant administration of **inhibitors of P-gp**, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such situations.

6.7. Dosing delays/dose modifications and adverse event management

No changes in durvalumab dose are allowed. If immune related adverse events occur, the durvalumab administration will be adjusted (delayed doses) as per the toxicity management guidelines (Appendix 4).

Dose escalation: Toxicities that would lead to dose modification should be discussed with the sponsor.

Expansion cohorts: Doses will be reduced for haematological and other adverse events. Dose adjustments are to be made according to the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.03 (NI-CTCAE).

6.7.1. General rules for dose modification

6.7.1.1. DURVALUMAB

Management of toxicity is **described in appendix 4**.

Reactions may occur during or after the infusion of study medication. The reaction may cause fever or chills and a change in blood pressure or difficulty in breathing.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.

If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.

The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

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6.7.1.2. TRABECTEDIN

Prior to re-treatment, patients must fulfil the baseline criteria defined previously (see Inclusion criteria section). If any of the following events occur at any time between cycles, the dose must be reduced to the lower level according to table below, for subsequent cycles:
- Neutropenia < 500/mm3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia < 25,000/mm3
- Increase of bilirubin >ULN and/or AP >2.5 xULN
- Increase of AST or ALT > 5xULN which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

For more information, please see trabectedin's SPC.

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not allowed.

Dose level	Trabectedin dose (mg/m^2)
-1	0.8
1	1
2	1.2
3	1.5

Capillary Leak Syndrome cases (CLS) have been reported with trabectedin (frequency uncommon). If symptoms of possible CLS develop, such as unexplained edema with or without hypotension, reassess albumin level. A rapid decline in albumin level may be indicative of CLS. If a diagnosis of CLS is confirmed after exclusion of other causes, discontinue trabectedin and promptly initiate CLS treatment according to institutional guidelines.

Recommendation for management of LVEF results from baseline cardiac echography:
- Patients with a LVEF >50% and asymptomatic will be regularly clinically monitored for cardiac symptoms, and cardiac echography will be performed if clinically indicated.
- Patients with LVEF between 40% and <50% but asymptomatic will be regularly clinically monitored for cardiac symptoms, and cardiac echography will be performed at 6 weeks and 12 weeks and every 12 weeks thereafter.
- Patients with LVEF <40% or with clinically symptomatic cardiac dysfunction (any % of LVEF at baseline) **will be excluded** from the trial and specialised cardiac management will be advised.

Recommandation for dose adaptation in case of LVEF drop during treatment with trabectedin :
- For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥15% or <LLN with an absolute decrease of ≥5%), trabectedin should be discontinued.
- In case of cardiac symptoms, no matter the LVEF, trabectedin will be stopped and specialised cardiac management will be advised.

6.7.2. Events of clinical interest and immune mediated adverse event (imeics)

Events of clinical interest of a potential immunologic etiology (imECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. imAEs may be predicted based on the nature of the durvalumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential imAEs. An imAE can occur shortly after the first dose or several months after the last dose of treatment.
If an imAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an imAE.

All imAE should be reported to sponsor (see section 11.7).

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imAE will be managed according to the toxicity management guidelines (appendix 4).Durvalumab will be delayed until if the adverse reaction remains at Grade 1 or less.
If another episode of a severe adverse reaction occurs, only Durvalumab will be permanently discontinued.
Patient requiring 2 delays of Durvalumab injection should go off protocol therapy.

Ir-AE are described in this section, but not limited to the items outlined below. For management, refer to the appendix 4 and to most updated Investigator Brochure.

6.7.2.1. PNEUMONITIS

Pneumonitis has been reported in patients receiving Durvalumab.
Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia. Early consideration of pneumonitis should be realised when patients present with new onset or worsening of respiratory symptoms such as dyspnoea or cough. Prompt treatment with steroids is important as per current established toxicity management guidelines.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, the Dosing Modification and Toxicity Management Guidelines will be applied (appendix 4). The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation
The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination: Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2: Saturation of peripheral oxygen (SpO2)

When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible: ILD Markers (KL-6, SP-D) and β-D-glucan; Tumour markers: Particular tumour markers which are related to disease progression; Additional Clinical chemistry: CRP, LDHFor recurrente moderate (Grade 2) pneumonitis: permanently discontinue Durvalumab.

6.7.2.2. COLITIS

Colitis has been reported in subjects receiving Durvalumab.
Patients should be monitored for signs and symptoms of colitis or diarrhoea. Investigators are instructed to begin diarrhoea management early to minimise the risk of colitis.

6.7.2.3. HEPATITIS

Hepatitis has been reported in subjects receiving Durvalumab.
Immune-mediated hepatitis/hepatic toxicity is the inflammation of the liver. Hepatic AEs induced by PD-1/PD-L1 inhibitors commonly present as asymptomatic increase of AST and ALT, rarely total bilirubin. A proportion of patients may be presenting with fatigue, fever and radiologic appearances including hepatomegaly, periportal lymphadenopathy and periportal oedema.

6.7.2.4. NEPHRITIS

Nephritis has been reported in subjects receiving Durvalumab.
The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure.
Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral oedema, haematuria, loss of appetite

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6.7.2.5. ENDOCRINOPATHIES

The clinical presentation of immune-mediated endocrinopathies include hypothyroidism, hyperthyroidism, type 1 diabetes mellitus and nonspecific symptoms of headache and fatigue, but may also include myalgias, visual field defects, behavioural changes, electrolyte disturbances, loss of appetite and hypotension. Patients will generally have abnormal endocrine laboratory test results that include thyroid-stimulating hormone, free T4, total and free T3, cortisol, adrenocorticotrophic hormone, luteinising hormone, folliclestimulating hormone, and testosterone.

6.7.2.6. SEVERE SKIN REACTIONS (RASH, DERMATITIS)

Immune-mediated severe skin reactions has been reported in patients treated with Durvalumab.

Immune-mediated dermatitis is generally mild and presents as mild local or diffuse maculopapular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes.

For rash and dermatitis: prompt treatment with steroids (topical or systemic based on severity) is important.

In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or haemorrhagic manifestations. In such cases, withhold Durvalumab and refer the patient for specialized care for assessment and treatment.
If diagnosis is confirmed, permanently discontinue Durvalumab.

6.7.2.7. IMMUNE-MEDIATED MYOCARDITIS

Investigators should exercise clinical judgment in managing actual patients alongside the guidelines presented in the protocol(s). An event that exhibits rapid progression and/or the likelihood for high morbidity/mortality requires that clinical judgment be exercised above and beyond toxicity management guidelines to ensure that treatment is optimally tailored to any given patient's specific case.
For example, the general principles outlined in the toxicity management guidelines describe prompt initiation of corticosteroids for both Grade 2 events (that have persisted for 4-5 days) and Grade 3-4 events; clinical judgment applied to this baseline guidance for an event that exhibits rapid progression and/or the likelihood for high morbidity/mortality – such as myocarditis – would warrant prompt initiation of high-dose corticosteroids without delay even for grade 2 cases. Similarly, clinical judgment for patients with suspected myocarditis should lead investigators to obtain a cardiology consult and institute a thorough diagnostic work-up (that includes exclusion of other alternate causes such as infection), and the appropriate management that includes discontinuing drug (permanently if biopsy-proven immune-mediated myocarditis) and, as already noted, the prompt use of steroids or other immunosuppressives.

6.8. Packaging and Labeling

The following information will appear on the labels:

- Name of the Sponsor.
- Study number/Patient number.
- Dosage and route of administration.
- Quantity or contents of container.
- Batch number/packaging number.
- Expiration date and storage conditions.
- Local legal information, as appropriate.

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6.9. Supplies and Drug Accountability

Trabectedin and Durvalumab will be supplied to investigators.
For ordering study drugs, please confer process of this study and pharmaceutical procedure.
Proper drug accountability will be done by the clinical trial monitor. Each study site will keep records to allow a comparison of quantities of drug received and used at each site. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.
All unused drug supplied by the Sponsor will be properly destroyed at the study site, at the end of the study. The documentation of this procedure must be provided to the clinical trial monitor.

6.10. Treatment Compliance

The Investigator is responsible for supervising compliance with the instructions described in this study protocol.

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7. STUDY EVALUATIONS

Study evaluations aim to assess:

- Diagnosis
- Efficacy
- Safety

7.1. Central review for diagnosis of soft-tissue sarcoma

7.1.1. Diagnosis of soft-tissue sarcoma

If diagnosis of sarcoma was not confirmed by the RRePS Network, pathological central review will be performed to confirm histological diagnosis of soft-tissue sarcoma by Pr Coindre and collaborators, Department of Pathology, Institut Bergonié, Bordeaux, France. The reviewer will assess the pathological diagnosis, document the results on the 'Pathological request form' response completed and sign this form.

Every discrepancy will be discussed between referral investigator, Pr Coindre or collaborators and the Sponsor, until a final decision is reached. Patients with diagnosis different from soft-tissue sarcoma will be considered ineligible and will not be included in the study.

7.1.2. Pathological specimen sampling necessary for central review

For a gross description and diagnostic information concerning pathological specimens, reference to "Recommendations for reporting soft-tissue sarcomas" is strongly advised (Recommendations, 1999). Available tumor samples obtained at diagnosis or at relapse, as unstained slides (10), and/or preferable paraffin-embedded tumor blocks (one or two) are mandatory for central review.

7.1.3. Pathological process schedule and implementation (not applicable if diagnosis reviewed in the RRePS Network)

Each site will send to Institut Bergonié within 7 days after the signature of informed consent:

- A completed pathology request form
- 10 unstained slides and/or preferable FFPE (Formalin-Fixed Paraffin-Embedded) block of specimen tumor sampling, obtained anytime during disease development
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology if any.

All material must be sent to:

Institut Bergonie - Service Pathologie
Technicienne Anapath Recherche Clinique
Protocole TRAMUNE
229 cours de l'Argonne - 33076 Bordeaux Cedex, France
Tél: +33 5.56.33.78.53

7.2. Efficacy – Expansion cohort only

The antitumor activity of trabectedin given in combination with durvalumab will be evaluated as per RECIST v1.1, in terms of objective response under treatment, best overall response, 6-month objective response, 6-month progression-free status, , 1-year PFS and OS.

7.2.1. Assessing Objective Tumor Response (RECIST v1.1)

- A comprehensive workup will be performed at baseline and every six weeks.
- Whenever the response criteria are met, the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response.
- The same method will be used to evaluate each identified lesion both at baseline and throughout the study.
- Treatment will be administered as long as no disease progression or unacceptable toxicity is found, or as long as no other reasons for treatment discontinuation are met.
- Assessment of efficacy will be essentially based on a set of measurable lesions identified at baseline as target lesions and followed until disease progression and following the RECIST v1.1 criteria (Einsenhauer, 2009).

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7.2.2. Centralized Radiological Review (Institut Bergonié)

7.2.2.1. GENERAL PROCEDURE

Centralized radiological review will be performed to confirm disease status in comparison with baseline, Week#6, Week#12, Week#18, etc…. For patients included in the reference center, CT scan will be initially read by a radiologist who differs from the expert.
Review process will be centralized at Institut Bergonié and will be performed by a radiologist expert in soft tissue sarcomas.The judgment provided by the expert reviewer will be retained and used in statistical analyses.

7.2.2.2. REVIEW PROCESS SCHEDULE

All tumor evaluations will be sent as soon as they become available.
Patient's information must be recorded on a provided imaging CD.

7.2.2.3. PRACTICAL IMPLEMENTATION

For each shipment, each media should be accompanied by the Radiological Forms provided by the Sponsor.

All CDs must be sent to the sponsor CRA as described in guidelines provided as a separate document.

7.3. Safety

Patients will be evaluable for safety if they have received at least one treatment administration. Safety will be evaluated using clinical examinations, which will comprise vital signs analysis, clinical assessment of AEs, changes in laboratory parameters (hematological and biochemical, including liver function tests) and any other analyses that may be considered necessary. Safety profile will be continuously followed during treatment up to 30 days after the last treatment administration or until the start of a new antitumor therapy, whichever occurs first. All AEs will be classified according to the NCI-CTCAE, v4.03.

8. STUDY ENDPOINTS

8.1. Primary endpoint

Phase I / Dose escalation part

Primary objective of the phase I trial is to establish the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D21), the safety profile, and the Dose Limiting Toxicities (DLT) of trabectedin given in combination with durvalumab.

Definition:

Dose-limiting toxicity (DLT):

A DLT is defined as an AE or laboratory abnormality that fulfills all the criteria below:

- Begins on the first 21 days of treatment.
- Is considered to be at least possibly related to the study treatment.
- Meets one of the criteria below, graded as outlined or according to NCI-CTCAEv4.03 :
  - 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 > 7days (except for 1rst episode of nausea without maximal symptomatic/ prophylactic treatment 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.

Endpoints:

- Toxicity graded using the common toxicity criteria from the NCI-CTCAE v4.03.
- Incidence rate of DLT at each dose level during the first 21 days.

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Phase I /Expansion cohorts

Primary objective of the expansion cohorts is to evaluate preliminary signs of the antitumor activity of trabectedin given in combination with durvalumab in terms of objective response under treatment. Following RECIST v1.1 recommendations (appendix 3):

- Objective response rate (ORR) is defined as the proportion of patients with complete or partial response (CR, PR) as per RECIST v1.1 criteria.
- Objective response under treatment is recorded from study treatment initiation until the end of treatment and determined once all the data for the patient is known.
- Claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
- **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.**

8.2. Secondary endpoints

Phase I / Dose escalation part

- Preliminary signs of antitumor activity in terms of:
  - Best overall response is 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 (appendix 3):
    Following RECIST v1.1 recommendations:
    - The best overall response is determined once all the data for the patient is known.
    - Claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
  - Objective response rate (ORR) is defined as the proportion of patients with complete response or partial response according to RECIST v1.1 criteria (appendix 3). ORR under treatment and 6-month ORR will be reported ORR under treatment is recorded from study treatment initiation until the end of treatment. Following RECIST v1.1 recommendations:
    - ORR under treatment is determined once all the data for the patient is known.
    - Claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
  - Progression-free rate (PFR) is defined as the proportion of patients with complete response, partial response or stable disease more than 24 weeks as defined as per RECIST v1.1 criteria (appendix 3). 6-month PFR will be reported. . Following RECIST v1.1 recommendations, claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
  - Progression-free survival (PFS) is 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.
  - Overall Survival (OS) is defined as the time from study treatment initiation to death (of any cause). 1-year OS rate will be reported.
- Pharmacodynamic study:
  - 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).
  - 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) assessmentsincluding, 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.

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- 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 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.

9. STATISTICAL CONSIDERATIONS

9.1. Hypotheses and number of subjects needed

9.1.1. Phase I (Dose escalation part)

- 3 dose levels
- A minimum of 3 patients will be entered in each dose level
- A maximum of 6 patients will be entered in each 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.**

9.1.1. Phase I (Expansion cohorts)

- 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 under treatment as per RECIST v1.1 criteria.
- Once the Maximum Tolerated Dose (MTD) is established for trabectedin, 2 distinct cohorts will be treated at the MTD:
  - Cohort A: patients with advanced STS.
  - Cohort B: patients with advanced ovarian carcinomas
- For each cohort:
  - 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).
  - 14 eligible and assessable subjects are required.
  - 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.

Assuming 10% patients not eligible or that 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**.

9.2. Definition of study populations

9.2.1. Phase I (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

9.2.2. Phase I (Expansion cohorts)

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

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- 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.

9.3. Statistical analysis

A statistical analyse plan (SAP) will be produced by the statistician and validated by the steering committee before the first statistical analysis. At the end of the dose escalation part of the phase I trial and before opening the expansion cohorts, an IDMC (see section 12.1.2) will be requested to assess safety data and validate MTD based on the statistical report produced by the statistician of the study.

9.3.1. 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.

9.3.2. Endpoint analyses

9.3.2.1. PHASE I TRIAL (DOSE ESCALATION PART)

- All analyses will be descriptive; no p-values will be calculated.
- 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.

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- 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.

9.3.2.2. EXPANSION COHORTS

- All analyses will be descriptive; no p-values will be calculated.
- Analyses will be conducted separately for sarcoma and ovarian cancer patients.
- Primary efficacy endpoint will be analysed based on the eligible and assessable population (see chapter 10.2 for definition):
  - 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 (section 10.2) 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 (section 10.2).
  - 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 (section 10.2).
  - 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 (section 10.2).
  - 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.

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10. ADVERSE EVENTS

10.1. Description of safety evaluation criteria

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG Appendix 1), a physical examination, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the NCI-CTCAE v4.03 scale available on the world wide web at http://ctep.info.nih.gov. All appropriate treatment areas should have access to a copy of the NCI-CTCAE v4.03.
In an emergency situation, the patient, his/her friends/family or treating physician will contact the investigator to report an event and/or to discuss the treatments to be implemented.

10.2. Definition

10.2.1. Adverse event

An adverse event is defined as any untoward medical occurrence which occurs in a patient, a clinical investigation subject. Adverse events include, but are not limited to:

- Abnormal test findings,
- Clinical symptoms and signs,
- Changes in physical examination findings,
- Hypersensitivity,
- Drug abuse,
- Drug dependency,
- Any suspected transmission of an infectious agent via a medicinal product.

As well as signs and symptoms resulting from:

- Drug overdose,
- Drug withdrawal,
- Drug misuse,
- Drug interactions,
- Extravasation,
- Exposure during pregnancy,
- Exposure during breastfeeding,
- Medication error,
- Occupational exposure.

10.2.2. Serious adverse event

A Serious Adverse Event (SAE) is defined as an adverse event regardless of the dose and that:

- results in death (fatal) and/or,
- is life-threatening and/or,
- requires inpatient hospitalization or prolongation of existing hospitalization and/or,
- results in persistent or significant disability/incapacity and/or,
- results in congenital anomaly/birth defect and/or,
- is medically significant.

Medical and scientific judgment is exercized in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent, pathogenic or non-pathogenic, is assessed as a serious adverse event with the seriousness criterion important medical event. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. The terms "suspected transmission" and "transmission" are considered synonymous.

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Any abnormal laboratory's result resulting as a grade 4 in the CTCAE v4.03 will be considered a serious adverse event even if this event is not clinically relevant.
Whether or not corresponding to the above-mentioned criteria, any other adverse event considered a serious by any IMP, any healthcare professional or any investigator should be handled as a serious adverse event.

10.2.2.1. DEATH

Death as such is the outcome of a SAE or the seriousness criteria and should not be used as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

10.2.2.2. LIFE-THREATENING EVENT

Any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2.2.3. HOSPITALIZATION OR PROLONGATION OF HOSPITALIZATION

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.
Hospitalizations that do not meet criteria for SAE reporting are:

- Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
- Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE. However, these circumstances will be collected in the CRF.
- Pre-planned hospitalizations: Any pre-planned surgery or procedure must be documented in the source documentation and collected in the CRF. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

10.2.3. Non serious adverse event

A non-serious adverse event is an adverse event whose characteristics do not meet the criteria of a serious adverse event.

10.2.4. Adverse effect

An adverse effect is any untoward and unintended responses to an experimental drug regardless of the dose.

10.2.5. Expected/Unexpected character

An unexpected adverse event is an event whose nature, severity/intensity/frequency or outcome does not correspond to the information shown within the reference document for the study. The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the most updated Investigator's Brochure (IB) and/or Summary Product Characteristic (SmPC) for the studied IMP.
In practice, the term "new effect" is sometimes used as a synonymous of "unexpected adverse effect".

10.2.6. Intensity criterion

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Event (CTCAE) will be utilized for AE reporting.
The intensity of adverse events not listed in this classification will be assessed using the following descriptors:
Mild (grade 1): does not affect the patient's usual daily activities,
Moderate (grade 2): disturbs the patient's usual daily activities,
Severe (grade 3): prevents the patient's usual daily activities,
Very severe (grade 4): requires critical care/life-threatening,
Death (grade 5).

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10.2.7. New information

A new information is any new safety data that could lead to reevaluate the ratio between the benefits and risks of the research or the investigational product, to modify the use of the investigational product, the conduct of the research or the research documents or to suspend or interrupt or modify the protocol of research or similar research.
For trials of first administration or use of a health product in persons without any conditions: any serious adverse reactions. The study TRAMUNE is not concerned by this situation.

10.2.8. Special considerations

Certain product safety monitoring reports should be forwarded even if there is no associated adverse event. These reports involve circumstances that may increase the patient/consumer's risk of developing adverse events.
These circumstances include:

- medication errors,
- exposure during pregnancy,
- exposure during breastfeeding,
- overdose,
- misuse,
- extravasation,
- occupational exposure.

Some of these special circumstances are considered in more details below.
Medications errors: a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.
A medication error does not necessarily involve the administration of the product (e.g. the error may have been corrected prior to administration of the product).
Potential medication errors or "near-misses," which are individual reports of information or complaints about product name, labeling, or packaging similarities that do not involve a patient, are also reportable.

* Exposure during pregnancy: exposure during pregnancy refers to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at a given time during pregnancy to a medicinal product (or a blinded treatment). Even if there is no associated adverse event, exposure during pregnancy must always be reported. It can indeed provide the opportunity to obtain pregnancy outcome important information where appropriate.

Exposure during pregnancy may occur either:

- Through maternal exposure
  - A female becomes, or is found to be, pregnant either:
    - While receiving a medicinal product
    - After discontinuing a medicinal product
    - During or following environmental exposure to a medicinal product (eg, a nurse reports she is pregnant and that she was exposed to chemotherapy drugs via inhalation or after accidentally overturning a bottle)

or

-Through paternal exposure

- A male has been exposed to a medicinal product (either due to treatment or environmental circumstances) prior to or around the time of conception and/or is exposed during the partner pregnancy.

* Exposure during breastfeeding: exposure during breastfeeding occurs where an infant or child may have been exposed through breast milk to a medicinal product during breastfeeding by a female taking the product.

All drug exposure during breastfeeding cases are reported, whether or not there is an associated adverse event.

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10.3. Serious adverse event and new information notification (responsibility of the investigator)

Serious adverse events, regardless of relationship to the study drugs, will be reported by the investigator in the patient's CRF.

The investigator will notify to the Vigilance Unit without delay about any serious adverse events or new events occurring:

- From the date of the informed consent is signed,
- During the whole patient treatment period as defined by the research,
- Until 90 days after the last dose of the IMP/studied treatments or until the start of a new antitumor therapy, whichever occurs first,
- Beyond this period of time, only those SAEs suspected to be related to the IMP or the research (other treatments used, diagnostic procedures, examinations carried out during the research) will be collected without any limitation in terms of deadline. Nonetheless, the Sponsor will evaluate any safety information related to the clinical trial that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

- Whenever possible the investigator will record the main diagnosis instead of the signs and symptoms.

Type of Event	Reporting procedure	Deadline for reporting to the sponsor
SAE	SAE Notification form + written report form if necessary	To be reported immediately to the sponsor
New information	Written report form	To be reported immediately to the sponsor
Pregnancy	Pregnancy Notification form + Written report form if necessary	As soon as pregnancy is confirmed

The investigator must complete the "Serious Adverse Event Notification Form" (Appendix 5) immediately, in English, and assess the relationship with the study treatment. The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) – R&D UNICANCER
Fax: +33 1 44 23 55 70
Or contact : R&D Unicancer – Mail : pv-R&D@unicancer.fr

For each event, the investigator will record:

- A description of the event that is as clearly as possible, using medical terminology,
- Date AE met criteria for serious AE, the date the event ended
- Date of the serious adverse event notification form report - The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- The patient's relevant medical history
- Concomitant medications / therapies
- The causal link between this event and the trial treatment, disease treated or an intercurrent disease or treatment, or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.) :
  - ✓ Causality assessment in relation to all study medications
  - ✓ Causality assessment in relation to Study procedure(s)
  - ✓ Causality assessment in relation to Additional Study Drug

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- ✓ In addition, when applicable, the investigator must also indicate if this event is related to disease progression.

- Clinical course. If the event was not fatal, it should be monitored until recovery, until the patient has returned to his/her previous condition, or until any sequelae have stabilized,

- Whenever possible, the investigator must also attach the following with the serious adverse event report:
  - A copy of the hospitalization or extended hospitalization report,
  - A copy of the autopsy report, if required,
  - A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
  - Any other document he or she considers useful and relevant.

All these documents must be anonymized. Additional information may be requested (by fax, by telephone or during a visit) by the CRA and/or by the Vigilance Unit using a follow-up request form.

The investigator is responsible for providing appropriate medical follow-up for patients until resolution or stabilization of the adverse event or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

The investigator keeps the documents about the presumed adverse effect so that the information previously sent can be added to if necessary.

The investigator responds to requests for additional information from the Vigilance Unit in order to document the original observation.

New cancers : the development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

10.4. Reporting pregnancy cases occurred within the clinical trial

Pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within 90 days from the patient's discontinuation visit, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP is suspected,
- Possible exposure of a pregnant woman (this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP),
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Vigilance Unit immediately by facsimile using the Pregnancy Report form (appendix 7). In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her consent to provide the information in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify the Vigilance Unit the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the Vigilance Unit by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 90 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also be reported to the Vigilance Unit by facsimile within 24 hours of the Investigators' knowledge of the event.

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Whenever possible, the investigator must also attach the following with the serious adverse event report:

- A copy of the hospitalization or extended hospitalization report,
- A copy of the autopsy report, if required,
- A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
- Any other document he or she considers useful and relevant.

All these documents must be anonymized.

Additional information may be requested (by fax, by telephone or during a visit) by the Vigilance Unit.

10.5. Report of Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab and/or trabectedin, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.6. Report of Hepatic function abnormality

Hepatic function abnormality (as defined by cases where a subject shows an AST or ALT ≥3xULN and total bilirubin ≥ 2xULN in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor using the SAE form unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

Hy's Law: Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 4, the Toxicity Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

10.7. Reporting events of clinical interest and immune-mediated adverse events

Information on how to identify and evaluate imAE/imAEs has been developed and is included in appendix 4. . All imAE imAEs should be reported to sponsor.

ImAE observed with durvalumab include:

- Colitis, Intestinal perforation
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity

Increase of AST and ALT should be reported as event of clinical interest if it meets the criteria of seriousness such as hospitalization and especially if treatment was given because of the event.

- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

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- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism, type I diabetes mellitus)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Rash / dermatitis (including Stevens-Johnson syndrome, toxic epidermal necrolysis, rashes complicated by dermal ulceration or necrotic, bullous or haemorragic manifestations)
- Myositis/Polymyositis
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis

o Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, uveitis, haematological events, sarcoidosis and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

The investigator will notify the Vigilance Unit without delay about any events of clinical interest.

The investigator must complete the specific form (Appendix 6) immediately, in English The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) – R&D UNICANCER
Fax: +33 1 44 23 55 70
Or contact : R&D Unicancer – Mail : pv-R&D@unicancer.fr

Adverse events that are both an SAE and an imAEimAEs should be reported one time as an SAE only, however the event should be appropriately identified as an imAEimAEs too in the database.

10.8. report of Non serious adverse event

TYPE OF EVENT	REPORTING PROCEDURES	DEADLINE FOR REPORTING TO THE SPONSOR
Non-serious AE	Case report/record form	Does not need to be reported immediately

Non-serious adverse events will be reported by the investigator in the patient's CRF and will be followed up until complete resolution.

If an adverse event becomes serious, it should be reported and followed-up as mentioned in the previous reporting procedures.

If the investigator wishes to decrease the trial treatment dose or temporarily stop the study management without respecting protocol procedures, he/she should previously discuss it with the coordinator.

However, symptomatic treatment can be prescribed to manage the adverse event.

Any definitive interruption of the procedure has to be immediately notified to the sponsor. The patient remains in the study and is followed-up according to the procedures described in the protocol.

10.9. Responsibility of Vigilance Unit

The Vigilance Unit will analyze each SAE to define:

- The relationship with the study treatment,
- The listedness/expectedness according to the most updated reference safety information of the studied IMP:
  - Investigator's Brochure (IB) for the Durvalumab (MEDI4736)
  - and Summary Product Characteristic (SmPC) for the Trabectedine (Yondelis®).

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10.10. Notification and registration of unexpected serious adverse events and new information (responsibility of the sponsor)

The sponsor notifies unexpected serious adverse events and new information to the Regulatory Authorities (in person, or through an organization which has received allowances for this task) according to the usual notification procedures.

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11. QUALITY ASSURANCE AND TRIAL MONITORING

11.1. Monitoring of the trial

11.1.1. Steering Committee

The study will be supervised and monitored by a steering committee comprising members participating in the study:

- Dr. M. Toulmonde, Coordinating Investigator and Chairman of the committee.
- Dr. A. Floquet, Scientific responsive, medical oncologist.
- A representative of the sponsor (Pr S. Mathoulin-Pélissier or a substitute).
- The biostatistician of the trial (Ms. M. Pulido, or a substitute).
- The pharmacist of the trial (Ms. L. Poignie, or a substitute).

This committee must ensure the following:

- Implementation and regular follow-up of the study
- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

For the dose escalation part, the steering committee will be consulted before proceeding or not to the next dose level.
In addition, the steering committee will resolve any specific issue regarding the DLT status. Note however, that medical oncologists of the steering committee cannot comment on the DLT status of patients they have been in charge of. In such case, the opinion of another medical oncologist who has not treated the patient will be sought.

The steering committee decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

11.1.2. Independent Data Monitoring Committee

- An independent data monitoring committee (IDMC) will be created at the request of the relevant Authority, the sponsor or the steering committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC.
- Conclusions of the steering committee for the MTD definition based on the dose escalation trial will be submitted for approval to the IDMC before opening the expansion cohorts. If necessary, a second IDMC may be set up at the end of the expansion cohorts.
- Implementation of the IDMC committee will be performed according to the internal procedures at Institut bergonié.

Composition of the IDMC

- This Committee must comprise at least one qualified oncologist, one pharmacologist and one statistican:
    - Qualified oncologist (Pr Jean Emmanuel KURTZ)
    - Pharmacologist (Dr Berdaï)
    - Statistician (Thomas Filleron)
- All of whom will have experience in the monitoring and analysis of clinical trials. One of these members will be appointed as the Trial Rapporteur.
- Each of these members must be unconnected with the trial and cannot, therefore, be one of the trial investigators.
- These members are appointed by the Sponsor in consultation with the trial co-ordinator and the steering committee.

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Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data;
- Making recommendations on the continuation, early discontinuation (in the case of toxicity) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Any recommendation from the IDMC that can be made public will be announced by the Sponsor and not by the steering committee. The Sponsor is responsible for sending IDMC recommendations to the regulatory authorities [ANSM (French Agency for the Safety of Health Care Products) and EMEA (European Medicines Evaluation Agency)].

11.2. Quality assurance

11.2.1. Data collection

The data will be collected on an electronic case report form and directly input via the Internet. Only the investigators and the Investigator's Clinical Research Assistants (CRAs) appointed by the later and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by an online trial management software on the Internet (Macro v4, Infermed Company); it will be transferred and monitored remotely in real time.

The study CRA and/or any other person appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study CRA will contact the investigators regarding the study implementation visit.

All of the necessary data will be collected on an electronic case report form provided by the sponsor. The generic names of the concomitant medication will be given in French.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The case report form will be validated by the investigator or the CRA at the authorized center whenever data is entered.

Laboratory data exceeding normal limit values will be commented upon if they are considered clinically significant. Data other than that requested within the scope of the protocol can be collected as additional data; their interest will be specified.

11.2.2. Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the Institut Bergonié,
- the quality control of the research site data by the CRA whose role is to:
    - check compliance with the protocol, GCP and current legislation and regulations,
    - check the consent and eligibility of each patient taking part in the trial,
    - check the consistency and coherence of case report form date against the source documents.
    - check that each serious adverse event is reported,
    - monitor the traceability of the study medication (dispensation, storage and drug accountability),
    - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the patients have not participated in a trial for which an exclusion period currently applies.

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- The possible audit and inspection of study centers
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each patient (100% level): patient identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, adverse events, principal response variables. The personal data relating to each patient shall remain confidential. On the electronic case report form or any other form dispatched, the patients will be identified solely by their initials (1 /name – 1 /surname) and an inclusion number. However, the investigators must keep a list identifying the patients in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant data required strictly in accordance with this control procedure. The CRAs are subject to professional secrecy under the conditions defined by Articles 226-13 and 226-14 of the French penal code. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each patient in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

11.2.3. Handling of missing data

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

11.2.4. Audits/Inspections

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit.All the documents relating to this study must be available for such an inspection after prior notification.

11.2.5. Data management

The data are entered using an electronic case report form (e-CRF) created with Macro 4.2 (Infermed limited 2010). Data entry is performed by the CRA-I using login and password provided by the database administrator. It is carried out at the research unit of Bergonie Institute.
Each step of the data management is described in the data management plan (DMP) drafted by the data manager. This document is validated by the coordinating investigator, the statistician, the CRA-C and the database administrator and is performed according to the internal procedures of the research unit.
The process of data lock/unlock is performed according to our procedure and after validating a check list.
All data will be backed-up daily and kept for 30 days.

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12. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

Clinical Research Management Unit – Institut Bergonié
Contacts:
Lucie Bard – Tel.: +33 5 47 30 61 96, e-mail: l.bard@bordeaux.unicancer.fr
or Marie-Laure Marty – Tel.: +33 5 47 30 60 79, e-mail: m.marty@bordeaux.unicancer.fr

The study will be carried out in accordance with:

- Law no. 2012-300 dated 5 March 2012 (law "Jardé") relating to researchs involving the human person.
- The ethical principles of the current version of the "Declaration of Helsinki" (available on its full version on the site http://www.wma.net).(Appendix 4)
- Good Clinical Practice (GCP): I.C.H. version 4 of 9 November 2016 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementating decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 amended by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 amended by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The application of Circular DHOS/INCA/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.
- Law no. 2004-800 dated 6 August 2004, concerning bioethics, amended by law No. 2012-387, dated 22 March 2012.

12.1. Clinical Trial authorization

This trial is registered under Eudract N° 2016-004720-33.

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on |_2_|_1_|/|_1_|_2_|/|_2_|_0_|_1_|_6_|.

The Relevant Authority, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM - French Agency for the Safety of Health Care Products) authorized the clinical trial on |_0_|_5_|/|_0_|_5_|/|_2_|_0_|_1_|_7_|.

Any amendments to the protocol concerning study objectives, patient population and principal methods will require an amendment, which must be approved by the EC and l'ANSM. The sponsor will inform the EC and ANSM of expected and/or unexpected serious adverse events in accordance with current regulations and within 30 days after of completion of the trial.

The sponsor will send the summary of the final report to the relevant Authority within one year of completion of the trial.

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The sponsor has made a commitment to compliance the Reference methodology for the processing of personal data carried out in biomedical research: Référence methodology MR-001. This commitment of compliance is registred under No 118019 of the 07/11/2006.

12.2. Insurance policy

The Institut Bergonié has taken out an insurance policy (policy No 0100871914011 160002 10998) with société HDI-Gerling, Tour opus 12, 77, Esplanade de la Défense, 92914 PARIS LA DEFENSE through an insurance broker, namely Biomédic Insure (Parc d'Innovation Bretagne Sud, CP 142, 56038 Vannes Cedex, Tel. 02 97 69 19 19) in case compensation is payable to investigators or patients taking part in the study.

12.3. Informing and obtaining consent from patients

The investigator in charge of the patient will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The patient can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The patient's written consent will be obtained prior to entry into the study by using the Patient Information Leaflet and Informed Consent Form. These forms must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the investigator. The original will be given to the patient and the second, archived in the investigator's folder. Upon request, a copy will be sent to the sponsor in a sealed envelope.

12.4. Sponsor's responsibilities

The sponsor of the clinical trial, the Institut Bergonié, will take the initiative for this clinical trial. The Institute will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain the Eudract No. and register the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- Obtain clinical trial authorization for the initial project and any amendments from the EC and ANSM; approval by the EC and decision taken by ANSM.
- Notify the relevant authority any suspected unexpected serious adverse reaction (SUSAR),
- Give trial-related information to the site directors, pharmacists and investigators,
- Notify the relevant authority of the trial start and end dates,
- Draft the final trial report and sent the summary to ANSM,
- Send the trial results to the relevant authority, EC and investigators,
- Archive essential trial documents in the sponsor's folder for a minimum period of 15 years after the trial has ended.

12.5. Investigators' responsibilities

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee and the relevant authority (ANSM).

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the ethics committee and the relevant authority having authorized the proposed changes.

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It is the responsibility of the principal investigator is:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start patient recruitment after authorization has been obtained from the sponsor,
- to ensure that he/she is available for investigators's meeting anf for "monitoring".

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs or e-CRFs) for each of the patients enrolled in the trial and to allow the Clinical Research Assistant (CRA) duly authorised by the Sponsor a direct access to source documents so that the latter can validate the data on the CRF or e-CRF,
- to promptly notify the sponsor of any serious adverse event and/or new information occurring during the trial,
- to date, correct and validate corrections on the case report forms (CRFs or e-CRFs) and the Data Query Forms (DQFs),
- to accept regular visits CRA and eventually visits of auditors duly authorised by the Sponsor or inspectors of regulatory authorities,
- to inform trial participants of the overall results of the research on first demand.

12.6. Authority to execute the trial

The investigator shall certify that he/she is authorized to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other agreements that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

12.7. Regulations governing the collection of human biological samples

During the medical procedures to be carried out, samples will be collected for medical purposes. A fraction of these samples will be kept and used for scientific research purposes.

The patient will be informed of this research and provided that he/she approves by signing an informed consent, these samples intended for research will be:

- Initially prepared and stored using a specific technique to preserve them under excellent conditions.
- and secondly, used within the scope of this research.

The preparation, storage and use of these samples will not in any way affect current or future medical care administered to the patient for the purpose of diagnosis or treatment.

The results of this research may, in future, appear in scientific publications. All of the data shall remain anonymous.

Obtaining and using additional samples
This biomarker study is made up of exploratory research that is described in the section "Ancillary Study".

On completion of the trial, provided that the patient agrees and provided that not all of the samples have been used, the said samples can be used for subsequent scientific research purposes without the approval of the Ethics Committee (EC) and the signing of a new consent form by the patients included.

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12.8. Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient Committees for Clinical Research in Oncology)

The Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient Committees for Clinical Research in Oncology) was created on the initiative of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) (Federation of Anti-Cancer Centers) and the Ligue Nationale Contre le Cancer (National Anti-Cancer League) in order to review clinical trial protocols in oncology. This Federation of Patient Committees is co-ordinated by the Office for Clinical and Therapeutic Trials and groups together the League patient committees as well as other health care establishments. The Sponsor undertakes to transmit the protocol to the Federation for review. The Federation undertakes to propose improvements focusing primarily on the quality of the information leaflet, the availability of a treatment and monitoring plan and the suggestion of measures aimed at improving patient comfort.

12.9. Data processing

In accordance with the French Law on Data Protection and Civil Liberties of 06 August 2004 and its implementing decrees, the Sponsor shall follow the methodology of reference MR001 of the Commission Nationale de l'Informatique et des Libertés (French National Commission for Data Protection and Liberties).

Furthermore, if the biomedical research data is computer processed or managed by computerized systems, each Center:

- shall check and document the fact that the computerized systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation);
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems;
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail) ;
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access;
- shall update the list of persons authorized to amend the data;
- shall keep appropriate back-up copies of the data;
- shall maintain blind status, where applicable (e.g. during data entry and processing);
- shall ensure that personal data used within the scope of the trial is processed in accordance with the conditions defined by law No. 78-17 dated 6 January 1978 relating to data processing, files and liberties modified by law No. 2004-801 of 6 August 2004 and its implementing regulations.

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify subjects taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these subjects to be identified whilst maintaining the confidentiality of the personal data, in accordance with law No. 78-17, duly amended.

The archiving data is performed according to the applicable regulations and under the responsibility of investigator. All data and the patient indentification codes will be kept for at least 15 years after the completion or discontinuation of the trial.

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13. CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained and the data and results generated by the trial legally belong to as their obtaining the Institut Bergonié, which can use this data at its own discretion.
According to article R 5121-13 of the French Public Health Code, investigators and people who will have to collaborate in the trial shall be bound by professional secrecy with regard to the particular nature of the products studied, trial, trial participants, and results. In particularly, all documentation relating to the trial sent to the investigator should be considered confidential information.
Without the consent of the sponsor, the investigator cannot,give information about trials at anyone, except the Minister in charge of Public Health, public health medical inspectors, public health pharmacists inspectors, the General Director and inspectors of ANSM.
The trial cannot be the subject of any written or verbal comments without the Sponsor's consent.

14. PUBLICATION AND VALORISATION

14.1. Scientific communication

All of the information arising from this study shall be considered confidential (cf. section 12).
All forms of publication must be submitted to the steering committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The steering committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities), and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required. In any case, the sponsor will control the first publication.
Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the Institut Bergonié, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial, and listing any organizations that have provided financial support.
For the principal publication, either in French or English, the authors are:

- the study coordinator
- the investigators will be listed on a pro rata basis according to the number of patients recruited
- a representative of the trial statistics unit (in the first 3 positions ot two last positions).

14.2. Information to patients

According to Article L.1122-1 of the Fench Code of Public Health Investigator undertakes to inform trial participants of the overall results of the research on first demand.

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16. BIOMARKER STUDIES

16.1. Blood sample for immunological biomarkers

16.1.1. Collection of available specimen

The main objective of this biomarker study is to explore pharmacodynamics and mechanisms of action of trabectedin + durvalumab as well as potential predictive biomarkers.
Blood biomarkers method guidelines will be provided by the sponsor as a separate document.

16.1.2. BM analysis

For each patient, blood samples will be collected at C1D1 and at C2D1.

- Immunophenotyping : 1x 4 ml sample of peripheral blood on EDTA (Purple cap tube).
- Kynurenine : 1x 6 ml sample of peripheral blood on EDTA (Purple cap tube).
- Cytokines : 1x6 ml sample of peripheral blood on Heparin (Green cap tube).

For more details, please refer to laboratory Guidelines.

16.1.3. Site performing BM study

- Immunophenotyping will be performed in **each investigating site** according to method guidelines provided by the sponsor as a separate document.

- Cytokines dosage and kynurenine dosage will be performed centrally

The samples will be stored in dedicated labeled boxes and containers labeled with coded numbers to ensure full compliance with privacy policy. Samples will be grouped in each institution and sent once and frozen for centralized processing as described in a specific SOP provided by the Sponsor.

16.2. Blood sample for circulating DNA

16.2.1. Collection of available specimen

The main objective of this study is to analyse circulating DNA and to identify mutations observed in tumor tissue in the blood (liquid biopsies concept).
Circulating DNA method guidelines regarding sample processing, storage conditions and shipment procedures will be provided by the sponsor as a separate document.

16.2.2. Collection – storage and shipping procedure

For ctDNA study, three 6 mL EDTA (Purple cap tube) samples of peripheral blood will be taken at D1 of each cycle, until progression. Samples will be grouped in each institution and sent once and frozen for centralized processing to:

Institut Bergonie – Laboratory bio pathology Protocol **TRAMUNE** 229 cours de l'Argonne - 33076 Bordeaux Cedex, France

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16.3. Tumor sample

16.3.1. Collection of specimen

For all patients, fresh pre-treatment and on-treatment (D8 cycle 2 with +/- 2 days) tumor biopsies will be performed (two core needle biopsy). One core needle biopsy will be formalin fixed and paraffin embedded [FFPE (Formalin-Fixed Paraffin-Embedded)] and one core needle biopsy will be fresh frozen at -80°C.
Note: if tissue of tumor lesion from < 3 months old archival tissue sample (both frozen and paraffin-embedded) obtained on locally advanced disease or metastasis with no subsequent treatment since; such tissue must be used as baseline tumor sample.

16.3.2. Handling and shipping of specimen

The samples will be labelled with coded numbers to ensure full compliance with privacy policies. Samples will be grouped in each institution and sent for centralized processing with the documents.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s).

16.3.3. Site performing analysis

All pathological specimens sampling with documents must be sent to:

Institut Bergonie – Pathology Unit
Protocol **TRAMUNE**
229 cours de l'Argonne
33076 Bordeaux Cedex, France

Tumor samples will be collected to explore the pharmacodynamics (PD) of trabectedin in association with durvalumab as well as potential predictive biomarkers of activity and efficacy. Tumor sample wille be analysed 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.

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APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

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

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APPENDIX 2: COCKROFT FORMULA

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \times G^{1}$$

[1]G (Gender) = 0.85 if Female; 1 if Male

Reference: *Cockcroft, DW, Gault, H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41 [84].*

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APPENDIX 3: EVALUATION OF RESPONSE. THE RECIST

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

DEFINITIONS

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with study drugs.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

DISEASE PARAMETERS

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

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Definition of the Best Response

The best response determination in trial where confirmation of complete or partial response is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (**generally 4 weeks later**). In this circumstance, the best overall response can be interpreted as in Table below.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR (complete response) may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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

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APPENDIX 4: DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION RELATED, AND NON IMMUNE-MEDIATED REACTIONS FOR DURVALUMAB

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of immune-mediated adverse events (imAEs) is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial lung disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution computed tomography (CT) scan – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modification required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies	**For Grade 1** – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤ 1 then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	**For Grade 2** – Monitor symptoms daily and consider hospitalization – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed – Promptly start systemic steroids (e.g., prednisone 1 to 2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated, consider Chest CT with contrast and repeat in 3-4 weeks – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4mg/kg/day started – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as tumor necrosis factor (TNF) inhibitors (e.g. infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Consider as necessary discussing with Clinical Study Lead
	Grade 3 or 4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consults; consider, as necessary, discussing with Clinical Study Lead. – Hospitalize the patient – Supportive Care (e.g. oxygen) – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5 mg/kgIV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines) started. Caution: rule out sepsis and refer to infliximab label for general guidance

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			before using infliximab

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Diarrhea/ Colitis **Large intestine perforation / Intestine perforation**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – When symptoms or evaluation indicate an intestinal perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay – Permanently discontinue study drug for any grade of intestinal perforation – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) including testing for clostridium difficile toxin, etc.) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event, including intestinal perforation – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	**For Grade 1 :** – Monitor closely for worsening symptoms – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤ 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤ 1, then study drug/study regimen can be resumedafter completion of steroid taper	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a gastrointestinal (GI) specialist for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, – If still no improvement within 2 to 3 days despite 1 to 2mg/kg IV methylprednisolone, promptly start immunosuppressant agent such as infliximab at 5mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤ 1 in 3 to 4 days

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	Grade 3 or 4	Grade 3: Hold study drug/study regimen until resolution to grade≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen if toxicity does not improve to Grade ≤1 within 14 days; Grade 4: Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – If still no improvement within 2 days, continue steroids and , promptly add further immunosuppressives (e.g. infliximab at 5mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Hepatitis (Elevated Liver function tests (LFTs)) **<u>Infliximab should not be used for management of Immune Related Hepatitis</u>** PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General guidance	**For Any Grade** – Monitor and evaluate LFTs: aspartate aminotransferase (AST), alanine Aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modification If it worsens, consider holding therapy	– Continue LFT monitoring per protocol
	Grade 2	**Hold Study drug/study regimen dose until resolution to Grade ≤ 1** • If toxicity worsens, then treat as Grade 3 or grade 4. • If toxicity improves to Grade ≤1 or baselin and there were no elevations in bilirubine, resume study drug / study regimen after completion of steroid taper (<10 mg prednisone or equivalent). Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Restart once resolved to **Grade ≤1 WITH DOSE REDUCTION FOR TRABECTEDIN** – Keep checking transaminitis twice weekly for the next cycle
	<u>Grade 3</u>:	• Hold study drug/study regimen For elevations in transaminases ≤8 × ULN (and no elevations in bilirubin), or elevations in bilirubin ≤5 × ULN until resolution to Grade <1 or baseline • Permanently discontinue study drug/study regimen for elevations in transaminases >8 × ULN or any elevations in bilirubin >5 × ULN	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressant therapy (i.e., mycophenolate mofetil 0.5-1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. Infliximab should NOT be used. – Perform Hepatology consult, abdominal workup and imaging as appropriate.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		- Dose modification for Trabectedin is mandatory if grade 3 If No decreasing of Transaminitis kinetic within the 4th week after previous infusion, permanently discontinue entire study regimen	
	Grade 4	Permanently discontinue study drug/study	

Hepatitis (elevated LFTs)	Any Elevations of AST, ALT, or TB as Described Below	General Guidance	For Any Elevations Described
Infliximab should not be used for management of immune-related **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** hepatitis. See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting			– Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For hepatitis B (HBV)+ patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV)+ patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but	

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Hepatitis (elevated LFTs)	Any Elevations of AST, ALT, or TB as Described Below	General Guidance	For Any Elevations Described
of either **increasing bilirubin or signs of DILI/liver decompensation**		(at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below.If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper. (<10 mg prednisone, or equivalent) Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. – If still no improvement within 2 to 3 days despite 1 to 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines).a Discuss with Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressant (e.g, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines)). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase riseFor example, manage dosing for second**			

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Hepatitis (elevated LFTs)	Any Elevations of AST, ALT, or TB as Described Below	General Guidance	For Any Elevations Described
			level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline) - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Consult Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression infections, recent IV contrast, medications, fluid status) – Consider using steroids in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event
	Grade 1	No dose modification	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 – Consider symptomatic treatment including hydration, electrolyte replacement and diuretics – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤ 1 or baseline then resume study drug/study regimen after completion of steroid taper	**For Grade 2:** – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol
	Grade 3 or 4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Carefully monitor serum creatinine – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Rash or dermatitis (including	**Any Grade** (refer to NCI CTCAE v 5 for definition of severity/grade depending on type of skin	General Guidance	**For Any Grade**: – Monitor for signs and symptoms of dermatitis (rash and pruritus) – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.**

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Pemphigoid)	rash)		– **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modification	**For Grade 1:** – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g.,emolient, lotion, or institutional standard)
	Grade 2	For persistent (> 1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤ 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent)	**For Grade 2 :** – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead as needed and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event persists for >1 week or recurs
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). • If toxicity worsens, then treat as Grade 4. **For Grade 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Consider, as necessary, discussing with Clinical Study Lead.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, hypopituitarism, adrenal insufficiency, type I diabete mellitus, hypophysitis;)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Consult Endocrinologist for endocrine events. – Consider, as necessary, discussing with Clinical Study Lead,. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c). – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modification	**For Grade 1:** – Monitor patient with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider consultating of an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5x LLN, or TSH >2x ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2, 3 or 4	For Grade 2-4 • endocrinopathies other than hypothyroidism and Type I Diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent) Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g. adrenal insufficiency) can be retreated with study drug/study regimen if patient	**For Grade 2, 3 or 4 :** – Consult endocrinologist to guide evaluation of endocrine function, and as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, corticosteroids (e.g., 1 to 2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones) – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – For patients with normal endocrine work up (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessment/MRI as clinically indicated.

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		is clinically stable as per Investigator or treating physician's clinical judgement, If toxicity worsens, then treat based on severity If toxicity worsens, then treat based on severity	

Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Amylase/Lipase Increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2,3 or 4	For Grade 2,3, or 4 In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade**		For Any Grade Consider Gastroenterology referral
	Grade 1	No dose modifications	For Grade 1 – IV hydration – Manage as per amylase/lipase increased (asymptomatic)

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	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity improves to Grade <1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	For Grade 2, 3, or 4 – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Neurotoxicity (to include but not limited to non-infection meningitis, non infectious encephalitis and . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE version 4.03 for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Perform symptomatic treatment with neurological consult as appropriate – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modification	**For Grade 1:** See "Any Grade" recommendations above. Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤ 1 For sensory neuropathy/ neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤ 1 Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. If toxicity worsens then treat as Grade 3 or Grade 4	**For Grade 2:** – Consider, as necessary, discussing with the Clinical Study Lead – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine) – Promptly start systemic steroids prednisone 1 to 2mg/kg/day PO or IV equivalent – If no improvement within 2 to 3 days despite 1 to 2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with an additional immunosuppressive therapy (e.g. IV IG or other immunosuppressant depending on the specific imAE).).
	Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Consider, as necessary, discussing with the Clinical Study Lead Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g. IV IG or other immunosuppressant depending on the specific imAE) – Once stable, gradually taper steroids over ≥28 days

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Peripheral neuromotor syndromes (such as Guillain-Barre and Myasthenia Gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG
	Grade 1	No dose modification	**For Grade 1:** – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Consult a neurologist
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤ 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	**For Grade 2:** – Consider discussing with the Clinical Study Lead, as needed. Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Consult a neurologist – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine) ***MYASTHENIA GRAVIS:*** ○ Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. ○ If Myasthenia Gravis-like neurotoxicity is present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis

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			○ Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). ***GUILLAIN-BARRE:*** ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability **For Grade 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4 :** – Consider discussing with Clinical Study Lead, as needed – Recommend hospitalization – Monitor symptoms and obtain neurological consult ***MYASTHENIA GRAVIS:*** ○ Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. ○ If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). ***GUILLAIN-BARRE:*** ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance Discontinue drug permanently if biopsy-proven immune-mediated myocarditis	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 :** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4	**If Grade 2** -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

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		drug/study regimen. **If Grade 3-4**, permanently discontinue study drug/study regimen.	- Infliximab is contraindicated for patients who have heart failure.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Myositis/ Polymyositis ("Poly/myositis")	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate Dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the Clinical Study Lead..
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead.. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant

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			– If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
	Grade 3 or 4 Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult – Consider, as necessary, discussing with the Clinical Study Lead. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after intial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis.

Other-Immune-Mediated reactions

General guidelines	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications Durvalumab	Toxicity Management
	Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, and vasculitis).	– The Clinical Study Leadmay be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.

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General guidelines	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications Durvalumab	Toxicity Management
	Grade 1	No dose modification.	Monitor as clinically indicated
	Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	For Grade 2, 3, or 4 Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
	Grade 3	Hold study drug/study regimen	
	Grade 4	Permanently discontinue study drug/study regimen	

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Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade:** – Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia)
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	**For Grade 1 or Grade 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards appropriate clinical practice guidelines, and society guidelines (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid)

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Non-immune Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard
Grade 1	No dose modifications	Treat accordingly, as per institutional standard
Grade 2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly, as per institutional standard
Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly, as per institutional standard
Grade 4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment and consultation with the Sponsor)	Treat accordingly, as per institutional standard

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAEimAE Immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia) ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

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APPENDIX 5: SERIOUS ADVERSE EVENT NOTIFICATION FORM

Serious Adverse Event Notification Form

TO BE FAXED TO THE UNICANCER VIGILANCE UNIT–N° + 33 (0)1.44.23.55.70

PROTOCOL :**TRAMUNE**	EUDRACT/ ID-RCB N°:**2016-004720-33**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__|__|__|__|__|__|__|__|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__| DATE OF BIRTH : |__|__|__|__|__|__|__|__| TREATMENT ARM: |__|

DOSE LEVEL (PHASE I STUDY): |__|

GENDER: F ☐ M ☐ WEIGHT (KG): |__|__| HEIGHT (CM): |__|__| BODY SURFACE AREA (M²): |__| . |__|

2. INFORMATION ON EVENT

DATE OF ONSET: |__|__|__|__|__|__|__|__| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS OR *MAIN SYMPTOM*: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH, DATE OF DEATH: .....|__|__|__|__|__|__|__|__|
☐ LIFE-THREATENING
☐ REQUIRING/PROLONGING HOSPITALIZATION
DATE OF ADMISSION: .....|__|__|__|__|__|__|__|__|
☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY
☐ CONGENITAL DISORDER/BIRTH DEFECT
☐ MEDICALLY RELEVANT

4. OUTCOME

☐ ONGOING EVENT ☐ UNKNOWN OUTCOME
☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE |__|__|__|__|__|__|__|__|
☐ RECOVERED WITH SEQUELAE, ☞ DATE |__|__|__|__|__|__|__|__|
SPECIFY SEQUELAE: .....
.....
☐ DEATH RELATED TO THIS EVENT, ☞ DATE |__|__|__|__|__|__|__|__|
☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE |__|__|__|__|__|__|__|__|
CAUSE OF DEATH: .....
.....
OR CAUSE UNKNOWN ☐
☐ AUTOPSY: YES ☐ NO ☐

IF PATIENT WAS HOSPITALIZED: DATE OF END OF HOSPITALIZATION: |__|__|__|__|__|__|__|__|
OR PATIENT STILL HOSPITALIZED AT TIME OF THIS REPORT ☐

FOR IMP TRIALS ☞ COMPLETE SECTION 5 FOR RADIOTHERAPY TRIALS ☞ COMPLETE SECTION 6 FOR OTHER NON IMP TRIALS ☞ COMPLETE SECTION 7

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S), including combined RADIOTHERAPY / SURGERY...) ..... TICK IF NA ☐

INVESTIGATIONAL PROCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP & OTHER COMBINED	ROUTE	SAE CYCLE NUMBER	DATES		DOSE & UNIT			
			DATE OF FIRST ADMINISTRATION/USE (1ST DAY OF 1ST CYCLE)	DATE OF LAST ADMINISTRATION/USE BEFORE SAE	LAST DOSE ADMINISTERED BEFORE SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION	
					DOSE	UNIT	DOSE	UNIT
1.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
2.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
3.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
4.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
5.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
6			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				
7.			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|				

UNBLINDING : YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?
☐ YES N°__ N°__ N°__ N°__ N°__ N°__ N°__ ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) IS STOPPED?
☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN REINTRODUCED?
☐ YES N°__ N°__ N°__ N°__ N°__ N°__ N°__ ☐ NO ☐ NA
DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCTION?
☐ YES ☐ NO ☐ NA

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Serious Adverse Event Notification Form

TO BE FAXED TO THE UNICANCER VIGILANCE UNIT–N° + 33 (0)1.44.23.55.70

PROTOCOL :TRAMUNE	EUDRACT/ ID-RCB N°:2016-004720-33	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__|__|____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐
INCLUSION N°: |_____| SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__| DATE OF BIRTH : |__|__|____|		

6. RADIOTHERAPY ..... TICK IF NA ☐

TECHNIQUE	FIELD(S)	DATES		DOSE (GY)	
		DATE OF FIRST ADMINISTRATION	DATE OF LAST ADMINISTRATION	LAST DOSE ADMINISTERED BEFORE SAE (GY)	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION (GY)
		|__|__|____|	|__|__|____|		
		|__|__|____|	|__|__|____|		
		|__|__|____|	|__|__|____|		
		|__|__|____|	|__|__|____|		

MACHINE (SPECIFY IF POSSIBLE TRADE NAME / MODEL/SERIAL NUMBER): .....

.....

HAS RADIOTHERAPY BEEN STOPPED?	HAS RADIOTHERAPY BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER RADIOTHERAPY IS STOPPED?	DID THE EVENT REAPPEAR AFTER RADIOTHERAPY REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER: .....

7. MEDICAL DEVICE or NON MEDICINAL PRODUCT, METHOD or ACTION ..... TICK IF NA ☐

DEVICE / Non Medicinal Product, Method or Action	DATES OF USE
COMMON DENOMINATION :	START DATE: |__|__|____|
TRADE NAME (IF EC MARKING) :	STOP DATE: |__|__|____|
MODEL :	VERSION (INCLUDED SOFTWARE) :
SERIAL NUMBER :	AND/OR BATCH NUMBER :
INDICATION OF USE FOR THE PATIENT :	

HAS DEVICE OR ONE (OR SEVERAL) PRODUCTS(S), METHOD(S) OR ACTION(S) BEEN STOPPED?	HAS DEVICE OR ONE (OR SEVERAL) PRODUCT(S), METHOD(S) OR ACTION(S) BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER STOP?	DID THE EVENT REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER, SPECIFY: .....

Serious Adverse Event Notification Form

TO BE FAXED TO THE UNICANCER VIGILANCE UNIT–N° + 33 (0)1.44.23.55.70

PROTOCOL :TRAMUNE	EUDRACT/ ID-RCB N°:2016-004720-33	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__|____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐
INCLUSION N°: |_____|	SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__|	DATE OF BIRTH : |__|__|____|

8. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USED TO TREAT REACTION)

CONCOMITANT DRUG	ROUTE	START DATE	STOP DATE	ONGOING	INDICATION
1.		FROM |__|__|__|	TO |__|__|__|	☐	
2.		FROM |__|__|__|	TO |__|__|__|	☐	
3.		FROM |__|__|__|	TO |__|__|__|	☐	
4.		FROM |__|__|__|	TO |__|__|__|	☐	

9. OTHER RELEVANT HISTORY (E.G. DIAGNOSTICS, ALLERGIES, PREGNANCY WITH LAST MONTH OF PERIOD, ETC…)

.....

.....

.....

10. ASSESSMENT: IN YOUR OPINION (INVESTIGATOR), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\|
☐ INVESTIGATIONAL RADIOTHERAPY,
☐ INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, **PLEASE SPECIFY** (TICK ONLY ONE BOX)

☐ PROTOCOL
☐ CONCOMITANT TREATMENT(S), SPECIFY: .....
☐ CONCOMITANT DISEASE(S), SPECIFY: .....
☐ OTHER, SPECIFY: .....

11. SAE NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE \|__\|/\|__\|/\|____\|

SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

DATE \|__\|/\|__\|/\|____\|

SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER: .....
DATE OF RECEIPT: \|__\|/\|__\|/\|____\| DATE OF THIS REPORT: \|__\|/\|__\|/\|____\|

ASSESSMENT (Tick only one box):

1 ☐ INVESTIGATIONAL **MP** (INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE NUMBER(S)° N° \|_\| N° \|_\| N° \|_\| N° \|_\| N°\|_\| N°\|_\| N°\|_\|
2 ☐ INVESTIGATIONAL **RADIOTHERAPY**,
3 ☐ INVESTIGATIONAL **MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (**SUSAR**)?
YES ☐ NO ☐

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)

4 ☐ PROTOCOL
5 ☐ CONCOMITANT TREATMENT(S)
6 ☐ CONCOMITANT DISEASE(S), SPECIFY .....
7 ☐ OTHER, SPECIFY .....

DATE \|__\|/\|__\|/\|____\| NAME ..... SIGNATURE : .....

APPENDIX 6 : EVENT OF CLINICAL INTEREST NOTIFICATION FORM

Event of Clinical Interest Notification Form

TO BE FAXED TO THE UNICANCER VIGILANCE UNIT–N° + 33 (0)1.44.23.55.70

PROTOCOL :**TRAMUNE**	EUDRACT/ ID-RCB N°:**2016-004720-33**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__||__|__||__|__|__|		

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__| DATE OF BIRTH: |__|__|\|__|__|__|__|

GENDER: F ☐ M ☐ WEIGHT (KG): |__|__| HEIGHT (CM): |__|__|

2. INFORMATION ON EVENT OF CLINICAL INTEREST

DATE OF ONSET: |__|__|\|__|__|\|__|__|__|__| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS OR MAIN SYMPTOM: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

.....

3. OUTCOME

☐ ONGOING EVENT ☐ UNKNOWN OUTCOME

☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE |__|__|\|__|__|\|__|__|__|__|

☐ RECOVERED WITH SEQUELAE, ☞ DATE |__|__|\|__|__|\|__|__|__|__|

SPECIFY SEQUELAE: .....

.....

☐ DEATH RELATED TO THIS EVENT, ☞ DATE |__|__|\|__|__|\|__|__|__|__| (Please complete a Notification of Serious Adverse Event)

☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE |__|__|\|__|__|\|__|__|__|__|

CAUSE OF DEATH: .....

..... (Please complete a Notification of Serious Adverse Event)

OR CAUSE UNKNOWN ☐

☐ AUTOPSY: YES ☐ NO ☐

3. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMP	Route	Cycle number	Date of first administration	Date of last administration before ECI	Last dose administered before ECI		Cumulative dose since the 1st administration	
					Dose	Unit	Dose	Unit
1.			|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|				
2.			|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|				

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?

☐ YES N°|_| N°|_| N°|_| N°|_| N°|_| N°|_| N°|_| ☐ NO ☐ NA

4. ASSESSMENT: IN YOUR OPINION (INVESTIGATOR), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°|_| N°|_| N°|_| N°|_| N°|_| N°|_| N°|_|

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, **PLEASE SPECIFY** (TICK ONLY ONE BOX)

☐ PROTOCOL
☐ CONCOMITANT TREATMENT(S), SPECIFY: .....
☐ CONCOMITANT DISEASE(S), SPECIFY: .....
☐ OTHER, SPECIFY: .....

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Event of Clinical Interest Notification Form

TO BE FAXED TO THE UNICANCER VIGILANCE UNIT–N° + 33 (0)1.44.23.55.70

5. ECI NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE|__|__|/|__|__|/|__|__|__|__|

SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

DATE|__|__|/|__|__|/|__|__|__|__|

SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER: .....
DATE OF RECEIPT: |__|__|/|__|__|/|__|__|__|__| DATE OF THIS REPORT: |__|__|/|__|__|/|__|__|__|__|

ASSESSMENT (Tick only one box):
☐ INVESTIGATIONAL **MP** SPECIFY THE NUMBER(S) N° |__| N° |__|

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)
☐ PROTOCOL ☐ CONCOMITANT TREATMENT(S) ☐ CONCOMITANT DISEASE(S), SPECIFY .....
☐ OTHER, SPECIFY .....

DATE |__|__|/|__|__|/|__|__|__|__| NAME ..... SIGNATURE : .....

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APPENDIX 7 : PREGNANCY NOTIFICATION FORM

Pregnancy Notification Form

To be faxed to the UNICANCER vigilance unit–n° + 33 (0)1.44.23.55.70

PROTOCOL :**TRAMUNE**	EUDRACT/ ID-RCB N°:**2016-004720-33**		COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :		SITE N°:
DATE OF THIS REPORT: |__|__|__|____|	INITIAL REPORT ☐	FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____|

SURNAME (1 LETTER): |__| 1ST NAME (LETTER): |__| DATE OF BIRTH (MM/AAAA):|___|_____| TREATMENT ARM: |__| DOSE LEVEL (ONLY FOR PHASE I STUDIES): |__|

GENDER: FEMALE ☐

MALE ☐

2. INFORMATION ON PREGNANT

THE PREGNANT IS: THE PATIENT ☐

A PATIENT PARTNER ☐ ☞ SPECIFY INITIALS: |___| DATE OF BIRTH (MM/AAAA) |___|_____|

DATE OF LAST MENSTRUAL PERIOD (DD/MM/AAAA): |___|___|_____|

ESTIMATED DATE OF DELIVERY (DD/MM/AAAA): |___|___|_____|

WAS THE PATIENT USING CONTRACEPTION? YES ☐ NO ☐

DESCRIBE ALL RELEVANT TREATMENTS ADMINISTERED TO THE PREGNANT AND HER PARTNER IF APPLICABLE (DATE AND DOSE OF INVESTIGATIONAL DRUGS AND CONCOMITANT TREATMENTS): .....

.....

.....

.....

.....

PARENTS RELEVANT MEDICAL HISTORY:

MOTHER: .....

.....

.....

FATHER: .....

.....

.....

3. FOLLOW-UP INFORMATION

FOLLOW-UP INFORMATION CAN BE OBTAINED FROM:

DOCTOR: .....

INSTITUTION: .....

ADDRESS: .....

E-MAIL: .....

PHONE: ..... FAX: .....

4. INVESTIGATOR

NAME: .....

DEPARTMENT: .....

PHONE: .....

FAX: .....

E-MAIL: .....

DATE (DD/MM/AAAA): |__|/|__|/|____|: SIGNATURE: .....

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APPENDIX 8 : DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1.The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

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12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

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Research Ethics Committees

23.The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25.Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26.In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances

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the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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