A PHASE IB STUDY OF OLAPARIB WITH CONCOMITANT RADIOTHERAPY IN LOCALLY ADVANCED/UNRESECTABLE SOFT-TISSUE SARCOMA

Protocol *RADIOSARP*

VERSION N°13.0 DU |08|09|2021|- N° : IB 2015-05

Incorporating substantial amendment N°1 of 08.19.2016
Incorporating substantial amendment N°2 of 02.14.2017
Incorporating substantial amendment N°3 of 05.17.2017
Incorporating substantial amendment N°4 of 03.20.2018
Incorporating substantial amendment N°5 of 05.28.2018
Incorporating substantial amendment N°6 of 01.03.2019
Incorporating substantial amendment N°7 of 08.06.2019
Incorporating substantial amendment N°8 of 10.14.2019
Incorporating substantial amendment N°9 of 02.27.2020
Incorporating substantial amendment N°10 of 09.10.2020
Incorporating substantial amendment N°11 of 05.18.2021
Incorporating substantial amendment N°12 of 09.08.2021

EudraCT n° 2015-003722-13

This trial is supported by 'Institut National du Cancer'

Coordinating Investigator

Paul SARGOS, MD
Radiothérapy
Department of Radiotherapy
Institut Bergonié
229, cours de l'Argonne – 33076 BORDEAUX Cedex, France
Tél : 05.56.33.33.33 – Fax : 05.56.33.04.85 – E-mail : p.sargos@bordeaux.unicancer.fr

Clinical Research Unit

Simone MATHOULIN-PÉLISSIER, MD, PhD — Institut Bergonié, Bordeaux
Head of the Unit

Carine BELLERA, PhD — Institut Bergonié, Bordeaux
Biostatistician

Sabrina SELLAN-ALBERT, MSc — Institut Bergonié, Bordeaux
Clinical Research Manager

Pharmacovigilance

Ludivine POIGNIE, PharmD — Institut Bergonié, Bordeaux

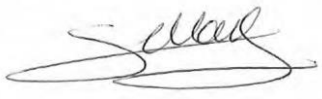
SPONSOR **INSTITUT BERGONIE**

TABLE OF CONTENT

APPROVAL AND SIGNATURES OF PROTOCOL

Titre du protocole : A phase Ib study of Olaparib with concomitant radiotherapy in locally advanced/unresectable soft-tissue sarcoma.

Competent authority	Name : ANSM	Date de l'autorisation initiale	07/01/2016
		Référence :	151479A-12
		Autorisation MSA1	28/10/2016
		Autorisation MSA2	20/04/2017
		Autorisation MSA3	08/08/2017
		Autorisation MSA4	14/05/2018
		Autorisation MSA5	06/07/2018
		Autorisation MSA6	11/02/2019
		Autorisation MSA7	26/09/2019
		Autorisation MSA8	28/10/2019
		Autorisation MSA9	04/05/2020
		Autorisation MSA10	06/11/2020
		Autorisation MSA11	28/07/2021
		Autorisation MSA12	
Ethic Committee	Name : CPP du Sud-Ouest et d'Outre-Mer III	Date de l'avis favorable initial	25/11/2015
		Référence :	2015/109
		Avis favorable – MSA1	28/09/2016
		Avis favorable – MSA2	29/03/2017
		Avis favorable – MSA3	26/07/2017
		Avis favorable– MSA4	25/04/2018
		Avis favorable– MSA5	25/07/2018
		Avis favorable– MSA6	19/03/2019
		Avis favorable– MSA7	25/09/2019
		Avis favorable– MSA8	27/11/2019
		Avis favorable– MSA9	18/05/2020
		Avis favorable– MSA10	03/12/2020
		Avis favorable – MSA11	19/07/2021
		Avis favorable – MSA12	

Name and responsability	Address	Date	Signature
Managing Director	Pr François Xavier MAHON Institut Bergonié – Bordeaux Tél:05.56.33.33.33/ Fax: 05.56.33.33.30 Mail: f.mahon@bordeaux.unicancer.fr	08/09/2021	
Coordinating Investigator	Dr Paul SARGOS Institut Bergonié – Bordeaux Tél:05.56.33.78.05/Fax:05.56.33.04.85 Mail: p.sargos@bordeaux.unicancer.fr	08/09/2021	
Head of the Clinical Research Unit	Pr Simone MATHOULIN-PÉLISSIER Institut Bergonié – Bordeaux Tél:05.56.33.33.98 /Fax: 05.56.33.04.66 Mail:s.mathoulin@bordeaux.unicancer.fr	08/09/2021	
Biostatistician	Carine BELLERA Institut Bergonié – Bordeaux Tél:05.56.33.04.95/Fax:05.56.33.04.85 Mail : c.bellera@bordeaux.unicancer.fr	08/09/2021	
Clinical Research Manager	Sabrina SELLAN-ALBERT Institut Bergonié – Bordeaux Tel : 05.56.33.78.05/Fax:05.56.33.04.85 s.albert@bordeaux.unicancer.fr	08/09/2021	

Pharmacist	Ludivine POIGNIE Institut Bergonié – Bordeaux Tél:05.47.30.33.94/Fax: 05.56.33.04.85 Mail: l.poignie@bordeaux.unicancer.fr	08/09/2021	

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 :

SYNOPSIS

Title of the study	**A phase Ib study of Olaparib with concomitant radiotherapy in locally advanced/unresectable soft-tissue sarcoma**
Abbreviation of the trial	**RADIOSARP**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Doctor Paul Sargos** **Department of Radiotherapy**
Number of investigational sites planned	5 centres: - Institut Bergonié, Bordeaux - Centre Léon Bérard, Lyon - IUCT Oncopôle, Toulouse - Institut du Cancer, Montpellier - Institut de Cancérologie de l'Ouest, Nantes
Number of patients	41 patients
Duration of the study	Planned enrollment period: 56 months Treatment duration: Radiotherapy over a period of 6.5 weeks. Olaparib will be started one week before the start of radiotherapy and will be continued until the last day of radiotherapy. Beyond this period, Olaparib could be continued at the investigator's discretion until progression. Follow-up: 1 year Study period: 68 months
Medical conditions	**Adult patients with locally advanced/unresectable soft-tissue sarcoma (with or without metastases)**
Objectives	**Primary objective** **PHASE 1 TRIAL** To establish the recommended phase II dose (RP2D), the maximum tolerated dose (MTD), the safety profile and the dose limiting toxicities (DLT) of Olaparib given with concomitant radiotherapy in patients with locally advanced/unresectable soft-tissue sarcoma. **EXPANSION COHORTS** To determine preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in patients with locally advanced/unresectable soft-tissue sarcoma in terms of 6-month non-progression (complete response, partial response, stable disease as per RECIST v1.1) after centralized radiological review. **Secondary objectives** **DOSE ESCALATION PART PHASE 1 TRIAL:** - Preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in terms of 6-month non-progression, 6-month objective response, objective response under treatment, best response under treatment, 1-year progression-free survival (PFS) and 1-year overall survival (OS). Subgroup analyses will be conducted for metastatic and non-metastatic patients. - Functional assessment before and after treatment. - Pharmacokinetics (PK) of Olaparib. **EXPANSION COHORT:** - Preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in terms of 6-month objective response, objective response under treatment, best response under treatment, 1-year progression-free survival (PFS) and 1-year overall survival (OS). Subgroup analyses will be conducted for metastatic and non-metastatic patients. - Toxicity profile of Olaparib given with concomitant radiotherapy. - Functional assessment before and after treatment. - Pharmacokinetics (PK) of Olaparib.

	- Pharmacodynamics (translational research)
Study design	**STUDY DESIGN** This is a multicenter, prospective phase Ib trial based on a dose escalation study design (TITE-CRM design) assessing four dose levels of Olaparib given with concomitant radiotherapy, followed by an expansion cohort. **DEFINITIONS** **Dose-limiting toxicity (DLT)** A DLT is defined as an adverse event (AE) or laboratory abnormality that fulfills all the criteria below: o Occurs during the period of observation of DLTs defined as the period between the first day of treatment administration and up to 6 weeks after the end of radiotherapy. o Is considered to be at least possibly related to the treatment strategy (radiotherapy or Olaparib). o Is unrelated to disease, disease progression, inter-current illness, or concomitant medications. o Meets one of the criteria below, graded as outlined or according to NCI CTCAEv4.0 : ▪ Any grade ≥ 3 musculoskeletal or cutaneous toxicity within the field of radiation: - Occurring at a radiotherapy dose < 30Gy - Occuring at a radiotherapy dose ≥ 30Gy and without regression to a grade ≤ 2 in a time limit of 4 weeks ▪ Any non-hematological toxicity ≥ grade 3 (except for nausea, vomiting, fatigue, alopecia and fever) ▪ Laboratory abnormality ≥ grade 3 lasting > 5 days (except for lymphopenia, hyperglycaemia and changes in serum electrolytes/enzymes without clinical impact) ▪ Febrile neutropenia (absolute neutrophil count [ANC] < 1.0 x109/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0 x 109/L ▪ Grade 4 neutropenia (absolute neutrophil count < 500) lasting ≥ 7 days ▪ Grade 4 thrombocytopenia or bleeding requiring a platelet transfusion ▪ Any other toxicity grade ≥ 4 ▪ Any other study drug related toxicity considered significant enough to be qualified as DLT in the opinion of the investigators after discussion with the sponsor. o In addition, the following events in case they are related to the toxicity of the treatments will also be considered as DLT: ▪ Interruption of radiotherapy for seven consecutive days or longer, ▪ Interruption of Olaparib for 14 days or longer, whether this interruption happens on consecutive days or not. A **DLT validation committee** will be consulted before the first escalation to a new dose level (see section 12.1.2). **Maximum tolerated dose (MTD)** The MTD for Olaparib is defined as the dose at which an unacceptable frequency of DLT is observed (33%). Conclusions of the steering committee for the definition of the MTD will be submitted to an independent committee (IDMC) before opening the expansion cohort. **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 Olaparib will be identified by the steering committee based on the MTD for Olaparib as defined following the dose escalation trial, as well as additional safety data, including acute and late toxicities, PK and PD data. Data from all patients (dose escalation trial and expansion cohort) will be used to define the RP2D.

DOSE ESCALATION PART

Regimen description:
Concomitant treatment by continuous Olaparib and radiotherapy.

- Olaparib will be given orally, continuously, twice a day, as appropriate for assigned dose level, from Day1 to the end of radiotherapy. Olaparib will be started one week before the start of radiotherapy and will be continued until the last day of radiotherapy. Beyond this period, Olaparib could be continued at the investigator's discretion and after sponsor authorization, until progression.
- Radiotherapy consists of fractionated focal irradiation at a dose of 1.8 Grays (Gy) per fraction given once daily five days per week (Monday through Friday), for a total dose of 59.4 Gy (ie. 33 fractions). Radiotherapy starts at D8.

Dose levels

- Dose escalation study assessing 4 doses level of Olaparib in association with concomitant radiotherapy.

Level	***-1***	**1**	**2**	**3**	**4**
Olaparib	*25 mg (daily)*	25 mg (b.i.d)	50 mg (b.i.d)	100 mg (b.i.d)	150 mg (b.i.d)

- The starting dose of Olaparib is 25 mg b.i.d.
- The maximum dose of Olaparib administered (150 mg x 2) will not be exceeded.
- No skipping of the dose will be allowed.
- For a given patient, dose will never be escalated.
- **As long as no DLT is observed** patients will be allocated to 4 dose levels following a 3+3 design with the following characteristics:
    - Inclusions of cohorts of 3 patients,
    - At dose levels 1 and 2, before accrual to next higher dose level, at least 2 patients with 6-week follow-up will be required,
    - At dose level 3, before accrual to dose level 4, at least 2 patients with 8-week follow-up will be required
- **As soon as the first DLT is observed,** patients will be allocated following a TITE-CRM design [Normolle et al. Statistics in Medicine 2003]. When a patient is eligible for enrollment, the probability of DLT is estimated for each dose level, based on the trial experience up to that time and the prior expectations for toxicity.
    - Each new patient is assigned to the currently estimated target dose, defined as the dose having an estimated probability of toxicity closest to but not greater than the target rate (33%), subject to the following restrictions :
        - A minimum of 2 patients will be entered on each dose level,
        - At dose levels 1 and 2, before accrual to next higher dose level, at least 2 patients with 6-week follow-up will be required,
        - At dose level 3, before accrual to next higher dose level, at least 2 patients with 8-week follow-up will be required,
        - In case of important accrual rate, to maintain operating characteristics of TITE-CRM design and patient safety, the Sponsors might decide to suspend the inclusions,
    - The prior distribution of the dose-toxicity model will be chosen to control the expected number of toxicities in the trial under a variety of scenarios about the true relationship between dose and toxicity.
    - In the TITE-CRM paradigm, patients who have been enrolled in the trial but have not experienced DLT are included in the probability calculation with a weight equal to the proportion of the 13.5-week DLT observation period they have completed; patients who experience toxicity or completed the observation period without toxicity are assigned full weight.
    - Stopping rule: inclusions will stop in the dose escalation trial as soon 24 eligible and assessable patients will be enrolled.
- For the dose escalation part, a DLT validation committee will be consulted before the first escalation to a new dose level (see section 12.1.2).

	▪ Conclusions of the steering committee for the definition of the MTD and the RP2D will be submitted to an independent committee (IDMC) before opening the expansion cohort. **EXPANSION COHORT** Once the MTD and the RP2D has been defined based on the dose escalation study, the expansion cohort will be opened. All patients will be treated at the RP2D of Olaparib (as defined in the escalation trial) given in association with concomitant radiotherapy with the same schedule as in the phase I trial. Following the expansion cohort, the RP2D for Olaparib may be refined by the steering committee based on the MTD and RP2D (as defined at the end of the dose escalation trial), as well as additional safety data including safety data from the expansion cohort, PK and PD data. Data from all patients (escalation + expansion) will be used to refine the RP2D.
Translational research	For consented patients, a tumor tissue biopsy sample is required to be collected at inclusion, at Day 8 of Cycle 1 before the start of the radiotherapy and one month after the end of the radiotherapy (ie. week 12). Patients must provide additional consent for these optional tumor tissue biopsy samples. o Analysis of the tumor tissue samples may include, but not be limited to: o DNA extraction and sequencing in order to identify: ▪ If the patient has a mutation in BRCA1, BRCA2, or another gene in the HR repair pathway ▪ If a patient has a BRCA reversion or other mutation(s) that may be associated with response or resistance to olaparib plus radiotherapy o DNA extraction and sequencing of single nucleotide polymorphisms (SNPs) to identify genomic scars and to determine whether genomic scarring can be used as a predictor of olapraib + radiotherapy response o Immunohistochemistry analysis to assess NHEJ pathway integrity, cleaved Caspase-3 and γ-H2AX staining pre- and on treatment (week 4) o Gene expression profiling on extracted RNA to potentially identify a signature associated with response to olaparib + radiotherapy • For all patients who have undergone surgery after initial treatment, surgical sample (block FFPE) will be collected to perform, but not limited to, immunohistochemistry analysis to assess γ-H2AX and CD3/CD8/CD20/CD23 staining.
Inclusion criteria	1. Histology: patients with soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network, 2. Upper/Lower limb or trunk wall soft-tissue sarcoma, 3. Age ≥ 18 years, 4. Locally advanced or locally recurrent primitive tumor, outside any previously irradiated field.Patients presenting operable locally advanced or locally recurrent tumor can be included. Patients with metastases can be included in the protocol, 5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, 6. Life expectancy ≥ 6 months, 7. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements, 8. Adequate hematological, renal, metabolic and hepatic function: - Haemoglobin ≥ 9 g/dL and no blood transfusions in the 14 days prior to study entry - Absolute neutrophil count (ANc) ≥ 1.5 x 10^9/L - Platelets ≥ 100 x 10^9/L - Total bilirubin ≤ 1.5 x upper limit of normality (ULN), - Alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) ≤ 2.5 x ULN, - Serum creatinine ≤ 150 µmol/L or creatinine clearance ≥ 50 mL/min (according to local institution) in case of serum creatinine > 150 µmol/L, - TP, INR ≤ 1.5 x ULN

	9. Women of childbearing potential must have a negative serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1. Female patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug. Males patients, who are sexually active, and their partners of child bearing potential must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 3 month after last dose of study drug. Acceptable birth control methods are described in appendix 6. Subjects of non-childbearing potential are those who have: ・Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments, ・LH and FSH levels in the post menopausal range for women under 50, ・radiation-induced oophorectomy with last menses >1 year ago, ・chemotherapy-induced menopause with >1 year interval since last menses, ・or surgical sterilisation (bilateral oophorectomy or hysterectomy). 10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up, 11. Voluntary signed and dated written informed consent prior to any specific procedure, 12. Patients with a social security in compliance with the French law
Non Inclusion criteria	1. Any previous treatment with a PARP inhibitor, including Olaparib, 2. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication, 3. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy, 4. Patients with known active hepatic disease (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids, 5. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), superior vena cava syndrome, extensive bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent, 6. Patients with uncontrolled seizures, 7. Men or women of childbearing potential who are not using an effective method of contraception as previously describes; women who are pregnant or breast feeding, 8. Prior or concurrent malignant disease diagnosed or treated in the last 2 years, except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 9. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used), 10. Concomitant use of known strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, boosted protease inhibitors, indinavir, saquinavir, telithromycin, clarithromycin, nelfinavir, boceprevir and telaprevir), moderate CYP3A4 inhibitors (such as ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil), strong CYP3A4 inducers (such as phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) and moderate CYP3A4 inducers (such as bosentan, efavirenz, modafinil), 11. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome, 12. Blood transfusions within 14 days prior to study start,

<table>
<tr><td></td><td>13. Patients with myelodysplastic syndrome/acute myeloid leukaemia,
14. Major surgery within 14 days of starting study treatment,
15. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
16. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
17. Previous enrollment in the present study,
18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product,
19. Patients who not have recovered from any effects of any major surgery,
20. Individuals deprived of liberty or placed under legal guardianship.
21. Patients who have tumor in contact with, invading or encasing for more than 50% any major blood vessels and/or patients requiring vascular reconstruction.</td></tr>
<tr><td>Route of administration</td><td>Olaparib will be administered per os bi-daily, as appropriate assigned dose level, during 7.5 weeks (D1 to D52). Olaparib should be started one week before the start of radiotherapy and will be continued until the last day of radiotherapy. Beyond this period, Olaparib could be continued at the investigator’s discretion and after sponsor authorization, until progression.

Radiotherapy consists of fractionated focal irradiation:
During Dose escalation:
At a dose of 1.8 Grays (Gy) per fraction given once daily five days per week (Monday through Friday) over a period of 6.5 weeks, for a total dose of 59.4 Gy. Radiotherapy starts at D8.

During expansion cohort:
Resecable tumors: At a dose of 2 Grays (Gy) per fraction given once daily five days per week (Monday through Friday) over a period of 5 weeks, for a total dose up to 50 Gy. Radiotherapy starts at D8.
Unresecable tumors: At a dose of 1.8 Grays (Gy) per fraction given once daily five days per week (Monday through Friday) over a period of 6.5 weeks, for a total dose of 59.4 Gy. Radiotherapy starts at D8.</td></tr>
<tr><td>Treatment schedule</td><td>Dose escalation
<table>
<tr><th colspan="4">Regimen Description</th></tr>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th></tr>
<tr><td>Olaparib</td><td>as appropriate for assigned dose level</td><td>Per os</td><td>Twice daily, continuously during 7.5 weeks</td></tr>
<tr><td>Radiotherapy</td><td>59.4 Gy</td><td>NA</td><td>1.8 Gy per fraction given once daily five days per week (Monday to Friday) over a period of 6.5 weeks.</td></tr>
</table>
Treatment consists of 7.5 weeks unless evidence of disease progression or study discontinuation (withdrawal of consent, intercurrent illness, unacceptable adverse event or any other changes rendering further treatment unacceptable, etc. see section 5.2)

4 dose levels :
<table>
<tr><th>Level</th><th>-1</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Olaparib</td><td>25 mg (daily)</td><td>25 mg (b.i.d)</td><td>50 mg (b.i.d)</td><td>100 mg (b.i.d)</td><td>150 mg (b.i.d)</td></tr>
</table>
Expansion cohort: All patients will receive the same regimen with Olaparib given in association with concomitant radiotherapy at the recommended dose defined in the dose escalation cohort.
Total radiotherapy dose will be adapted with patient condition</td></tr>
</table>

<table>
<tr><td></td><td>(resectable/unresecable)
<table>
<tr><th></th><th>Total radiotherapy dose</th><th>Schedule</th></tr>
<tr><td>Resectable tumors</td><td>Up to 50 Gy</td><td>2 Gy per fraction given once daily five days per week (Monday to Friday) over a period of 5 weeks</td></tr>
<tr><td>Unresectable tumors</td><td>Up to 59.4 Gy</td><td>1.8 Gy per fraction given once daily five days per week (Monday to Friday) over a period of 6.5 weeks.</td></tr>
</table></td></tr>
<tr><td>Endpoints</td><td>
PHASE I TRIAL: DOSE ESCALATION PART

<u>Primary endpoint:</u>
▪ Toxicity graded using the common toxicity criteria from the NCI v4.0.
▪ Incidence rate of DLT at each dose level during treatment period up to six weeks after end of radiotherapy.

<u>Secondary endpoints</u>
▪ 6-month non-progression is defined as CR, PR or stable disease (SD, more than 24 weeks) at 6 months according to RECIST 1.1.
▪ 6-month objective response is defined as CR or PR at 6 months according to RECIST 1.1.
▪ Best objective response under treatment is defined as complete (CR) and partial response (PR) recorded from the start of study treatment until the treatment with confirmation ≥ 4 weeks after initial documentation, as per RECIST 1.1. Objective response under treatment is determined once all the data for the patient is known.
▪ Best response under treatment is defined as the best response (CR, PR, SD) as per RECIST 1.1 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. It is determined once all the data for the patient is known.
▪ 1-year Progression-free survival (PFS): 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 Overall Survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
Functional assessment graded using the Muskuloskeletal Tumour Society Rating Scale (Enneking, 1987).
▪ Pharmacokinetics (PK): PK measurements expressed as the AUC, the half-life of Olaparib and concentration peak.
▪ Pharmacodynamics (translational research): Predictive biomarkers analysis on available archived tumor tissue and mechanisms of action/pharmacodynamic activity on fresh biopsy (pre-treatment and week 4 of treatment).

EXPANSION COHORT

<u>Primary Endpoint</u>
▪ 6-month non-progression is defined as CR, PR or stable disease (SD, more than 24 weeks) at 6 months according to RECIST 1.1.Disease status under treatment will be reviewed centrally by an expert radiologist.
▪ Reviewed data will be used for this primary endpoint analysis.
</td></tr>
</table>

	Secondary Endpoints Toxicity, 6-month objective response, objective response under treatment, best response under treatment, PK, PFS and OS as defined above for the phase I escalation study. Predictive biomarkers analysis on available archived tumor tissue and mechanisms of action/pharmacodynamic activity on fresh biopsy (pre-treatment, day 8 and week 12).
Statistical considerations	**NUMBER OF SUBJECTS NEEDED** **Dose escalation part** ▪ 4 dose levels ▪ A minimum of 2 patients per dose level ▪ Rule of thumb is to set the sample size to be six times the number of dose levels. Therefore, the maximum number of patients is estimated to be about 24 eligible and assessable patients. To account for patients not eligible/assessable, we anticipate accruing a maximum of **26 patients for the dose escalation part of the phase I trial.** **Expansion 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 non-progression (CR, PR or SD) 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 in the expansion cohort.** **STATISTICAL ANALYSIS** ▪ All analyses for the dose escalation part trial and the expansion cohorts will be descriptive; no p-values will be calculated. Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and standard errors. Missing data will not be imputed. • Objective response rate under treatment, best objective response rate under treatment, 6-month non-progression and 6-month objective response rates will be calculated using binomial estimates and reported with their 95% confidence interval (CI). Subgroup analyses will be conducted for metastatic and non-metastatic patients. • 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. Subgroup analyses will be conducted for metastatic and non-metastatic patients.

Schedule of assessments and procedures

	SCREENING	*W 1*	*W 2*	*W 3*	*W 4*	*W 5*	*W 6*	*W 7*	*W 8*	*W10*	*W12*	*W14*	*WN[i]*	*W 24*	*EOT*	*Surgery [l]*	*FOLLOW-UP*
		D1	D8	D15	D22	D29	D36	D43	D50	D64	D78	D92					
Olaparib (per os)		**D1 to the end of radiotherapy**								**……Xf…….**							
Radiotherapy			**D8 up toD52 (until 33 fractions)**														
Consultation oncologist	**X**	**X**			**X**				**D52**		**X**		**X[i]**	**X**	**X**	to be performed at D30, D60 and D90 after surgery	**X[d]**
Consultation radiotherapist			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**					
Written Informed consent	X																
Demographics data	X																
Medical history/baseline condition	X																
Concomitant treatments	X	Throughout the study															
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X[d]
Assessment of signs and symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X[d]
Performance status (ECOG)	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X[d]
Vital signs (heart rate, blood pressure, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X[d]
Height	X																
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X[d]
Hematology	X	X[a]		X		X		X	X	X	X	X	X[i]	X	X		
Biochemistry[b]	X	X[a]		X		X		X	X	X	X	X	X[i]	X	X		
ECG (QTc)	X[c]								X	In case of Olaparib is continued, to be performed every 2 months					X		
Serum pregnancy test (*if indicated*)	X[h]	X	Repeat if indicated														
Urinary dipstick	X	Repeat if indicated															
Adverse event(s)		Throughout the study															
Tumor measurement by RMI	X[h]										X			X			X[d]
Tumor measurement by CT Scan, in case of metastatic disease	X[h]								X[k]				X[k]				
PK		X	X			X[e]											
Tumor biopsy (optional)[g]		X	D8								X						
Functional assessment MSTS [j]			X							X							

[a] biology < 7 days must be available, screening tests may be used if < 7 days ; [h]must be < 4 weeks
[b] NFS, MCV, MCHC, MCH, Albumin, alkalin phosphatase , total bilirubin, urea, calcium, creatinine, fasting glucose, LDH, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT],GGT, sodium.TP, INR, CPK
[c] repeated within 24 hours if > 470msec
[d] Every 3 months until death or study termination.
[e]: to be done on Day 28
[f] could be continued until progression at the investigator's discretion and sponsor authorization
[g] at baseline, at D8 before radiotherapy initiation and week 12

[h] within 28 days prior to the start of study treatment
[i] If Olaparib is continued, visit each month: Week 16 and 20, etc
[j] Completed by the radiotherapist at baseline and at the end of radiotherapy treatment
[k] : Every 8 weeks
[l]: if applicable

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADP	Adenosine Diphosphate
AE (s)	Adverse Event (s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de sécurité du Médicament
AP	Alkaline Phosphatase
aPTT	Activate Partial Prothrombin Time
AST	Aspartate Aminotransferase
CI	Confidence Interval
CPP	Ethic Committee
CR	Complete Response
CRA	Clinical Research Assistant
CrCL	Creatinine Clearance
CRF	Case Report Form
CT	Computerized Tomography
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DQF	Data Query Form
DSB	Double-Stranded Binding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
FFPE	Formalin-Fixed Paraffin-Embedded
FUP	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma Glutyl-transferase
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Homologous Recombinaison repair
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medical Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IrEICS	Events of Clinical Interest Immune-related
IUD	IntraUterine Device
LDH	Lactate Dehydrogenase
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHEJ	Non-Homologous End Joining
NPR	Non Progression Rate
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRE TT	Pre-Treatment
PS	Performance Status

PT	Prothrombin
PTT	Prothrombin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RRePS	Réseau de Référence en Pathologie des Sarcomes des Tissus mous et des Viscères
SAE	Serious Adverse Event
SD	Stable Disease
SmPC	Summary Product Characteristic
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSB	Single-Stranded Binding
STS	Soft Tissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normality
US	United States
TT	Treatment

1. RATIONALE OF THE TRIAL

1.1. SOFT-TISSUE SARCOMAS

Soft tissue sarcoma (STS) is a rare malignant tumour arising in connective tissue of the extremities, the truncal wall or the retroperitoneal space. In France, its incidence is 3,6 cases per 100000 population per year (approximately, 4000 new cases are diagnosed each year in France) [1].
Surgery is the cornerstone of the management with radical resection or conservative resection followed by external beam radiotherapy. For locally advanced STS, when surgical resection is impossible, radiotherapy alone may be offered but local control and outcome are poor. Slater et al., reported in 72 patients with unresectable sarcomas treated with radiotherapy alone (44-88Gy) a 5-year local control of only 29% [2]. In another cohort of 112 patients, 5-year local control, disease free survival and overall survival were 45%, 24% and 35% respectively [3]. Slater's and Kepka's series seem showing a dose response relationship with longer tumour control in patients who received 65Gy or more but without statistical significance. Moreover, an increase of the delivered dose is difficult in practice with more complications. In Slater's series, 26% of patients treated with a dose above 65Gy had major complications. New directions must be also explored to improve radiotherapy efficacy in locally advanced STS.

1.2. OLAPARIB

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.
PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR).
The pre-clinical experience is fully described in the current version of the olaparib IB.
Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.
The toxicology studies indicate that the target organ of toxicity is the bone marrow.
Further information can be found in the current version of the olaparib IB.

1.2.1. Clinical experience

Clinical experience with olaparib is fully described in the current version of the olaparib IB.
A full description of the emerging safety profile for olaparib, with guidance for investigators, is provided in the IB.

1.3. STUDY RATIONALE

Multiple preclinical data demonstrate that PARP inhibition increases cytotoxicity and tumor growth delay in combination with ionizing radiation. The mechanisms of these radiosensitiving effects are well understood in vitro but are less clear in vivo.
The cytotoxic effects of radiotherapy are mediated by DNA damages: SSBs, DSBs at a ratio of 25:1. SSBs are not directly cytotoxic but during DNA replication may generate potentially lethal DSBs by collapse of stalled replication forks. Radiation-induced SSBs are primarily repaired by base excision repair of which PARP-1 is a key component. Inhibition of PARP increases also sensitivity to ionizing radiation in cells.

Preclinical in vitro studies
The study of PARP-1 as a potential molecular target in cancer therapy began in the 1980s. Early studies revealed that inhibition of PARP led to radiosensitization of mammalian cells [4]. Subsequently, cells with genetic delation of PARP-1 were shown to be more sensitive to ionizing radiation than cells with functionnal PARP-1 [5]. Additional studies have demonstrated radiosensitization by a variety of PARP inhibitors in multiple cell line models with dose-enhancement ratios of 1.3-1.7 [6–10]. In some studies, PARP inhibitors selectively radiosensitize actively replicating S-phase cells [11] and it is proposed that

the mechanism by which PARP inhibition increases ionizing radiation sensitivity is by inhibiting the repair of SSBs that convert to DSBs upon collision with replication forks in S-phase [12]. Such lesions can be visualized by persistence of ionizing radiation-induced γH2AX foci following PARP inhibitor treatment [8, 9]. These data were supported by the observation that PARP inhibition increased the γH2AX foci and RAD51 foci [13]. However, PARP has also been implicated in DSBs repair through interaction with non-homologous end joining (NHEJ) and has been shown to exist in a complex with DNA-PKcs and Ku70/80, that are important components of the NHEJ pathway [14, 15].

Preclinical in vivo studies
Some studies have demonstrated better in vivo radiosensitization by PARP inhibitors than expected by in vitro studies. In mice bearing SCC7, RIF-1 , KHT sarcomas and Ewing ,sarcomas , PARP inhibitor caused an up to 3 fold enhancement of the therapeutic effect of X-rays [16,29]. In combination with fractionated X-rays PARP inhibitor doubled the tumor growth delay in mice bearing LoVo xenografts [17] and orally administered PARP inhibitor prior to irradiation significantly enhanced the irradiation-induced growth inhibition in HNSCC xenografts [18]. Many preclinical studies have been shown significant increase of the anti-tumor activity of ionizing radiation xenograft models of human colon, lung, prostate, breast cancers and gliomas [9, 19–23]. Olaparib in combination with radiotherapy caused significant tumor regression of Calu-6 NSCL carcinoma xenografts when compared to radiotherapy alone [24].
One explanation to these good in vivo results could be the enhancement of tumor vascularization and oxygenation by PARP inhibitors by vasoactive properties of these molecules. Indeed, oxygene is a key component of the radiation-induced DNA damages with hypoxia inducing radioresistance. Studies revealed that PARP inhibitor also increased the transient perfusion of the tumors [17]. Further investigations revealed that PARP inhibitors cause vasodilatation of pre-constricted rat arteries ex vivo and improved vascular perfusion of tumors in vivo [25, 26]. Olaparib was also demonstrated to have vasoactive effects ex vivo and in vivo and enhanced the antitumor activity against human NSCLC xenografts [24].

Clinical studies
As a consequence of these collective preclinical data, ongoing phase 1 clinical trials assess the combination of PARP-1 inhibitors with radiotherapy. However, no trial focus on radiotherapy of STS.

1.4. BENEFIT/RISK AND ETHICAL ASSESSMENT

Some clinical trials (phase 1 trials essentially) are ongoing to explore the role of PARP inhibitors in combination with radiotherapy but no final results are available. Only, an interim report of a phase I trial testing a PARP inhibitor in combination with whole brain radiotherapy showed a good tolerance of the combination and further dose escalation is planned [27]. Elsewhere, a recent study shows that the radiosensitizing effects can be observed at much lower Olaparib doses than the single agent effects [28]. Previous clinical studies showed that as single agent Olaparib was well tolerated with maximal tolerated dose for monotherapy at bi-daily 400mg capsules. Also it can be expected that lower Olaparib doses delivered in combination with radiotherapy were safe and sufficient to increase radiosensitivity and efficacy of radiotherapy.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

2.1.1. Dose escalation
To establish the recommended phase II dose (RP2D), the maximum tolerated dose (MTD), the safety profile and the dose limiting toxicities (DLT) of Olaparib given with concomitant radiotherapy in patients with locally advanced/unresectable soft-tissue sarcoma.

2.1.2. Expansion cohort
To determine preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in patients with locally advanced/unresectable soft-tissue sarcoma in terms of 6-month non-progression (complete response, partial response, stable disease as per RECIST v1.1) after centralized radiological review.

2.2. SECONDARY OBJECTIVES

2.2.1. Dose escalation

- Preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in terms of 6-month non-progression, 6-month objective response, objective response under treatment, best response under treatment, 1-year progression-free survival (PFS) and 1-year overall survival (OS). Subgroup analyses will be conducted for metastatic and non-metastatic patients.
- Functional assessment before and after treatment using the Muskuloskeletal Tumor Society functional form (MSTS ; Enneking et al. Clin Orthop 1993).
- Pharmacokinetics (PK) of Olaparib.

2.2.2. Expansion cohort

- Preliminary signs of anti-tumor activity of Olaparib given with concomitant radiotherapy in terms of 6-month objective response, objective response under treatment, best response under treatment, 1-year progression-free survival (PFS) and 1-year overall survival (OS). Subgroup analyses will be conducted for metastatic and non-metastatic patients.
- Toxicity profile of Olaparib given with concomitant radiotherapy.
- Pharmacokinetics (PK) of Olaparib.
- Functional assessment before and after treatment using the Muskuloskeletal Tumor Society functional form (MSTS; Enneking et al. Clin Orthop 1993).
- Pharmacodynamics (translational research): Prognostic markers of anti-tumor activity of Olaparib given with concomitant radiotherapy will be investigated.

3. STUDY DESIGN

3.1. OVERALL STUDY DESIGN

This is a multicenter, prospective phase Ib trial based on a dose escalation study design assessing four dose levels of Olaparib given with concomitant radiotherapy, followed by an expansion cohort once the recommended phase II dose (RP2D) has been established.

3.2. RATIONALE FOR STUDY DESIGN AND DOSES

Few clinical data about combination of Olaparib and radiotherapy are available and more or less about Olaparib and STS radiotherapy. Therefore, a phase 1 dose escalation trial has been designed in order to determine the MTD and the safety of the combination. An expansion cohort should allow to appreciate anti-tumor activity of the combination.
Study population was defined as patients with locally advanced/unresectable STS (with or without metastases) because their outcome with radiotherapy alone is very poor.
The choice of olaparib doses was based on preclinical data showing that low doses are sufficient with radiotherapy.

3.3. DEFINITIONS

Dose-limiting toxicity (DLT)

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

- Occurs during the period of observation of DLTs defined as the period between the first day of treatment administration and up to 6 weeks after the end of radiotherapy.
- Is considered to be at least possibly related to the treatment strategy (radiotherapy or Olaparib).
- Is unrelated to disease, disease progression, inter-current illness, or concomitant medications.
- Meets one of the criteria below, graded as outlined or according to NCI CTCAEv4.0:
    - Any grade ≥ 3 musculoskeletal or cutaneous toxicity within the field of radiation:
        - Occurring at a radiotherapy dose < 30Gy
        - Occuring at a radiotherapy dose ≥ 30Gy and without regress to a grade ≤ 2 in a time limit of 4 weeks
    - Any non-hematological toxicity ≥ grade 3 (except for nausea, vomiting, fatigue, alopecia and fever)
    - Laboratory abnormality ≥ grade 3 lasting > 5 days (except for lymphopenia, hyperglycaemia and changes in serum electrolytes/enzymes without clinical impact)

- Febrile neutropenia (absolute neutrophil count [ANC] < 1.0 x109/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0 x 109/L
- Grade 4 neutropenia (absolute neutrophil count < 500) lasting ≥ 7 days
- Grade 4 thrombocytopenia or bleeding requiring a platelet transfusion
- Any other toxicity grade ≥ 4
- Any other study drug related toxicity considered significant enough to be qualified as DLT in the opinion of the investigators after discussion with the sponsor.

In addition, the following events, in case they are related to the toxicity of the treatments, will also be considered as DLT:

- Interruption of radiotherapy for seven consecutive days or longer,
- Interruption of Olaparib for 14 days or longer, whether this interruption happens on consecutive days or not.

A **DLT validation committee** will be consulted before the first escalation to a new dose level (see section 12.1.2).

Maximum tolerated dose (MTD)

The MTD for Olaparib is defined as the dose at which an unacceptable frequency of DLT is observed (33%). Conclusions of the steering committee for the definition of the MTD will be submitted to an independent committee (IDMC) before opening the expansion cohort.

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 Olaparib will be identified by the steering committee based on the MTD for Olaparib as defined following the dose escalation trial, as well as additional safety data, including acute and late toxicities, PK and PD data. Data from all patients (dose escalation trial and expansion cohort) will be used to define the RP2D.

3.4. DOSE ESCALATION PART

3.4.1. Treatment scheme and DLT observation period

- Olaparib will be given orally, continuously, twice a day, as appropriate for assigned dose level, from D1 to the end of radiotherapy. Olaparib will be started one week before the start of radiotherapy and will be continued until the last day of radiotherapy. Beyond this period, Olaparib could be continued until progression, at the investigator's discretion and sponsor approval.
- Radiotherapy consists of fractionated focal irradiation at a dose of 1.8 Grays (Gy) per fraction given once daily five days per week (Monday through Friday), for a total dose of 59.4 Gy (i.e 33 fractions). Radiotherapy starts at D8.
- The DLT observation period is defined as the first day of Olaparib intake and up to 6 weeks after the end of radiotherapy (13.5 weeks).

3.4.2. Dose levels

- Dose escalation study assessing 4 dose levels of Olaparib in association with concomitant radiotherapy.

Level	***-1***	**1**	**2**	**3**	**4**
Olaparib	*25 mg (daily)*	25 mg (b.i.d)	50 mg (b.i.d)	100 mg (b.i.d)	150 mg (b.i.d)

- The starting dose of Olaparib is 25 mg b.i.d.
- The maximum dose of Olaparib administered (150 mg x 2) will not be exceeded.
- No skipping of the dose will be allowed.
- For a given patient, dose will never be escalated.

- **As long as no DLT is observed,** patients will be allocated to 4 dose levels following a 3+3 design with the following characteristics:
    - Inclusions of cohorts of 3 patients,
    - At dose levels 1 and 2, before accrual to next higher dose level, at least 2 patients with 6-week follow-up will be required,
    - At dose level 3, before accrual to dose level 4, at least 2 patients with 8-week follow-up will be required

- **As soon as the first DLT is observed**, patients will be allocated following a TITE-CRM design [Normolle et al. Statistics in Medicine 2003]. When a patient is eligible for enrollment, the probability of DLT is estimated for each dose level, based on the trial experience up to that time and the prior expectations for toxicity.
    - Each new patient is assigned to the currently estimated target dose, defined as the dose having an estimated probability of toxicity closest to but not greater than the target rate (33%), subject to the following restrictions :
        - A minimum of 2 patients will be entered on each dose level,
        - At dose levels 1 and 2, before accrual to next higher dose level, at least 2 patients with 6-week follow-up will be required,
        - At dose level 3, before accrual to next higher dose level, at least 2 patients with 8-week follow-up will be required,
        - In case of important accrual rate, to maintain operating characteristics of TITE-CRM design and patient safety, the Sponsors might decide to suspend the inclusions.
    - The prior distribution of the dose-toxicity model will be chosen to control the expected number of toxicities in the trial under a variety of scenarios about the true relationship between dose and toxicity.
    - In the TITE-CRM paradigm, patients who have been enrolled in the trial but have not experienced DLT are included in the probability calculation with a weight equal to the proportion of the 13.5-week DLT observation period they have completed; patients who experience toxicity or completed the observation period without toxicity are assigned full weight.
    - Stopping rule: inclusions will stop in the dose escalation trial after 24 eligible and assessable patients enrolled.

- For the dose escalation part, a DLT validation committee will be consulted before the first escalation to a new dose level (see section 12.1.2).
- Conclusions of the steering committee for the MTD definition will be submitted to an independent committee (IDMC) before opening the expansion cohort.

3.5. EXPANSION COHORT

- Once the MTD and the RP2D have been defined based on the dose escalation study, the expansion cohort will be opened. All patients will be treated at the RP2D of Olaparib (as defined in the escalation trial) given in association with concomitant radiotherapy at a dose that depends on tumor status:
    - Resectable tumor or potentially resectable tumor after study treatment: up to 50 Gy
    - Unresectable tumor: up to 59.4 Gy.

- Following the expansion cohort, the **RP2D for Olaparib** may be refined by the steering committee based on the MTD and RP2D (as defined at the end of the dose escalation trial), as well as additional safety data including safety data from the expansion cohort, PK and PD data. Data from all patients (escalation + expansion) will be used to refine the RP2D.

3.6. PATIENT'S REPLACEMENT

See section 10.2

4. SELECTION OF PATIENTS

4.1. INCLUSION CRITERIA

1. Histology: patients with soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Upper/Lower limb or trunk wall soft-tissue sarcoma,
3. Age ≥ 18 years,
4. Locally advanced or locally recurrent primitive tumor, outside any previously irradiated field Patients presenting operable locally advanced or locally recurrent tumor can be included. Patients with metastases can be included in the protocol,
5. Eastern Cooperative Oncology Group (ECOG), performance status ≤ 2,
6. Life expectancy ≥ 6 months,
7. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements,
8. Adequate hematological, renal, metabolic and hepatic function:
   - Haemoglobin ≥ 9 g/dL and no blood transfusions in the 14 days prior to study entry
   - Absolute neutrophil count (ANc) ≥ 1.5 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x upper limit of normality (ULN),
   - Alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) ≤ 2.5 x ULN,
   - Serum creatinine ≤ 150 µmol/L or creatinine clearance ≥ 50 mL/min (according to local institution) in case of serum creatinine > 150 µmol/L,
   - TP, INR ≤ 1.5 x ULN
9. Women of childbearing potential must have a negative serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1. Female patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug. Males patients, who are sexually active, and their partners of child bearing potential must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 3 month after last dose of study drug. Acceptable birth control methods are described in appendix 6. Subjects of non-childbearing potential are those who have:
   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,
   - LH and FSH levels in the post menopausal range for women under 50,
   - radiation-induced oophorectomy with last menses >1 year ago,
   - chemotherapy-induced menopause with >1 year interval since last menses,
   - or surgical sterilisation (bilateral oophorectomy or hysterectomy).
10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up,
11. Voluntary signed and dated written informed consent prior to any specific procedure,
12. Patients with a social security in compliance with the law.

4.2. NON-INCLUSION CRITERIA

1. Any previous treatment with a PARP inhibitor, including Olaparib,
2. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication,
3. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy,
4. Patients with known active hepatic disease (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids,
5. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), superior vena cava syndrome, extensive bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent,
6. Patients with uncontrolled seizures,
7. Men or women of childbearing potential who are not using an effective method of contraception as previously describes; women who are pregnant or breast feeding,

8. Prior or concurrent malignant disease diagnosed or treated in the last 2 years, except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
9. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used),
10. Concomitant use of known strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, boosted protease inhibitors, indinavir, saquinavir, telithromycin, clarithromycin, nelfinavir, boceprevir and telaprevir), moderate CYP3A4 inhibitors (such as ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil), strong CYP3A4 inducers (such as phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) and moderate CYP3A4 inducers (such as bosentan, efavirenz, modafinil),
11. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome,
12. Blood transfusions within 14 days prior to study start,
13. Patients with myelodysplastic syndrome/acute myeloid leukaemia,
14. Major surgery within 14 days of starting study treatment
15. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
16. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
17. Previous enrolment in the present study,
18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product,
19. Patients who not have recovered from any effects of any major surgery,
20. Individuals deprived of liberty or placed under legal guardianship.
21. Patients who have tumor in contact with, invading or encasing for more than 50% any major blood vessels and/or patients requiring vascular reconstruction.

5. STUDY PLAN

5.1. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 68 months, including about 56 months of active enrollment.
Planned start date (first patient on study): October 2016.
Within each cohort (dose escalation and expansion cohort), the planned cohort termination (clinical cutoff) corresponds to the date when each patient has been followed-up for 12 months or is deceased.

- End of study occurs when all of the following criteria have been satisfied:
  - The trial is closed to recruitment
    AND
  - All participants have disease progression or are no longer on study medication
    AND
  - The last included participant has been followed for 12 months, or if deceased each participant has been followed up for 12 months or is deceased

5.2. DEFINITIONS OF DURATION OF STUDY AND TREATMENT (PER PATIENT)

Patients will receive study treatment until the end of the radiotherapy and as long as it is considered to be in their best interest. After the end of radiotherapy, Olaparib could be continued until progression (locoregional and/or metastatic progression) at the investigator's discretion and sponsor should be informed. 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 defined as :
  - 30 days after the last dose of treatment of Olaparib and/or
  - 6 weeks after the last dose of radiotherapy.

Note: if surgery performed, patient will be followed up at D30, D60 and D90 post surgery. Then the patient will be followed up according to FUP below.

- **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.

After documented progression (locoregional and/or metastatic progression) or start of a new antitumor therapy, patients will be **followed every 3 months until**:

1. Death, or
2. The end of the follow-up period, 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 after the last dose of Olaparib and/or 6 weeks after the last dose of radiotherapy, except if the patient starts a new antitumor therapy before this period.

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 last dose of Olaparib and/or 6 weeks after the last dose of radiotherapy, 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 treatment should be 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:

- Disease progression (locoregional and/or metastatic progression),
- Unacceptable toxicity,
- Intercurrent illness of sufficient magnitude to preclude safety 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 rate after the end of the radiotherapy will then be able to continue Olaparib at the discretion of the investigator and after sponsor approval.
Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.8). 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.

5.3. 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 (plitidepsin) 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, etc.

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.

5.4. 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 in Table below.

Table. 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 (+1 week tolerance)
	◆ Vital signs: heart rate, blood pressure, body temperature, weight and height	Within 7 days prior to Day 1 (+1 day tolerance)
	◆ 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 (+2 weeks tolerance)
2. Pathology	◆ Central review to confirm soft-tissue sarcoma diagnosis, except in case of diagnosis confirmed by RRePS Network	Material sent within 7 days next to signed informed consent
3. Laboratory tests	◆ **Hematology**: differential WBC, ANC, haemoglobin, platelets, RBC, MCV, MCHC, MCH **Biochemistry**: Serum electrolytes (Na^+, K^+, $Mg^{++}$and Ca^{++}), liver function tests (AST, ALT, total bilirubin, GGT and AP), LDH, creatinine, fasting glucose, total proteins, urea, albumin ◆ **Coagulation**: TP, INR, aPTT ◆ **Urinary**: dipstick	Within 7 days prior to Day 1 (+3 days tolerance). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the treatment Within 7 days prior to Day 1 (+3 days tolerance)
4. Creatinine clearance	◆ Calculated according local institution (see Appendix 2)	Within 7 days prior to Day 1 (+3 days tolerance)
5. Pregnancy test, if applicable	**Measurement** of serum human chorionic gonadotropin (HCG)	Within 28 days prior to Day 1 (+1 day tolerance).
6. ECG	◆ QTc measurement: twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. ECGs will be recorded at 25 mm/sec.	Within 7 days prior to Day 1 (+3 days tolerance) and repeated within 24 hours if > 470msec
7. Tumor assessment	◆ MRI for upper/lower limb or trunk wall sarcoma of all measurable sites, as per RECIST (Appendix 3) ◆ CT Scan only for patients with metastatic disease	Within four weeks prior to Day 1 (+1 week tolerance)
8. Other tests	◆ Intercurrent events, concomitant diseases and treatments.	Within two weeks prior to Day 1.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; INR, International Normalized Ratio; LDH, lactate dehydrogenase; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume; MRI, magnetic resonance imaging; RBC, red blood cell; RECIST v1.1, Response Evaluation Criteria In Solid Tumors; TP, prothrombin Rate; WBC,

	ASSESSMENT	TIME

white blood cells.

5.5. EVALUATIONS DURING TREATMENT

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

Table. 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	Repeat up to 48 hours before Day 1 Repeat on Day 1 of each subsequent week during radiotherapy: on Day 8, 15, 22, 29, 36, 43 and 50. Repeat on week 10 , 12, 14 and 24 thereafter in case of Olaparib discontinuation after the end of radiotherapy Repeat on Day 1 of each subsequent month in case of Olaparib continuation after the end of radiotherapy.
	◆ Assessment of baseline signs and symptoms	Throughout the treatment period
	◆ Concomitant diseases and treatments	Throughout the treatment period
	◆ Functional assessment MSTS	Completed by the radiotherapist at baseline and at the end of radiotherapy treatment
2. Laboratory tests*	◆ **Hematology**: differential WBC, ANC, haemoglobin, platelets, RBC, MCV, MCHC, MCH ◆ **Biochemistry**: Serum electrolytes (Na^+, K^+, $Mg^{++}$and Ca^{++}), liver function tests (AST, ALT, total bilirubin, GGT and AP), LDH, creatinine, fasting glucose, total proteins, urea, albumin ◆ **Coagulation**: TP, INR, aPTT, if clinically indicated ◆ **Urinary**: dipstick if clinically indicated	Repeat up to 48 hours before Day 1 Repeat every two weeks, on Days 15, 29 and 43 Repeat on week 10, 12, 14 and 24 thereafter in case of Olaparib discontinuation after the end of radiotherapy Repeat on Day 1 of each subsequent month in case of Olaparib continuation after the end of radiotherapy. ◆ If clinically indicated
3. Creatinine clearance	◆ Calculated according local institution (see Appendix 2)	Repeat up to 48 hours before Day 1 Repeat every two weeks, on Days 15, 29 and 43 Repeat on week 10, 12, 14 and 24 thereafter in case of Olaparib discontinuation after the end of radiotherapy Repeat on Day 1 of each subsequent month in case of Olaparib continuation after the end of radiotherapy.
4. Pregnancy test, if applicable	◆ **Measurement** of serum human chorionic gonadotropin (HCG)	On day 1 prior to the start of study treatment. In the event of a suspected pregnancy during the study, the test should be repeated.
5. ECG	◆ QTc measurement: twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. ECGs will be recorded at 25 mm/sec.	At week 10 ◆ If clinically indicated
6. Tumor assessment	◆ MRI of all measurable sites, as per RECIST (see Appendix 3) ◆ CT Scan only for patients with metastatic disease	Tumor assessment must be repeated – MRI: every twelve weeks (±7 days) and at least four weeks after first documentation of objective response even if there are treatment delays: on weeks 12 and 24. – CT Scan: every 8 weeks.
7. PK study	◆ Blood samples	See section 17.1.1
8. Optional biopsy	◆ Predictive markers of treatment outcome from tumor samples	See section 17.2.1
9. AEs	As per NCI-CTCAE, version 4.	Throughout the treatment period

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

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time;

	ASSESSMENT	TIME

AST, aspartate aminotransferase; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; INR, International Normalized Ratio; LDH, lactate dehydrogenase; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume; MRI, magnetic resonance imaging; RBC, red blood cell; RECIST v1.1, Response Evaluation Criteria In Solid Tumors; TP, prothrombin Rate; WBC, white blood cells.

5.6. EVALUATION AT END OF TREATMENT

The end-of-treatment visit will be scheduled:

- 30 days (4 weeks) after the last Olaparib administration (a window of ±1 week is allowed) and/or
- 6 weeks after the last dose of radiotherapy.

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, and temperature].
- Hematology.
- Biochemistry.
- Calculated CrCl.
- Electrocardiogram (QTc measurement: twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. ECGs will be recorded at 25 mm/sec.)
- Clinical and radiological tumor assessment (MRI and CT Scan if metastatic disease at inclusion) (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 dose of Olaparib and/or 6 weeks after the last dose of radiotherapy administration or until the start of a new antitumor therapy, whichever occurs first. All SAEs occurring within 30 days after the last dose of Olaparib and/or 6 weeks after the last dose of radiotherapy 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 (Olaparib/radiotherapy) or research-related (diagnostic procedures, examinations carried out during the research…) will be reported (see Section 11).
In case of surgery, post surgery complications must be reported during 12 months after the surgery unless start of a new anti-tumor therapy.

5.7. FOLLOW-UP AFTER END-OF-TREATMENT VISIT

- Each patient will be followed-up for 12 months after inclusion.
- 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 every 3 months until death or until the end of the follow-up period, whichever occurs first.
- Patients who withdraw consent will not be followed with any study procedures.

All AEs (including SAEs) suspected to be treatment-related (Olaparib and/or radiotherapy) 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.

6. REGISTRATION PROCEDURES

6.1. SCREENING

Upon signature of consent, screened patient will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator as described in a specific Standar Operating Procedure (SOP) provided by the Sponsor.

The screening form should be faxed as soon as possible to the Bergonie Institute Data Center.

If applicable, the site will send to Bergonie Institute within 7 days after the signature of informed consent:

- Pathology request form completed
- 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.

To complete the registration process, the Coordinator will assign a patient screening number.

Upon results of pathological review will be available, the CRA at Institut Bergonie should inform site by e-mail and return results by fax.

6.2. INCLUSION

Upon signature of consent, eligible patient will be entered in the study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator as described in a specific SOP provided by the Sponsor. The registration form should be faxed as soon as possible to the Bergonie Institute Data Center.

This must be done **before the start of the protocol treatment which should begin within one week (7 days) following registration**.
To complete the registration process, the Coordinator will:

- Assign a patient study number
- Assign a patient dose level for patients included in the dose escalation part
- Register the patient on the study
- Fax or e-mail the patient study number

The patient study number attributed at the end of the registration procedure identifies the patient and must be reported on all case report forms.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive the protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

7. STUDY TREATMENTS

7.1. OLAPARIB

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply Olaparib to the investigators as round or oval green-film-coated tablet.
Olaparib will be provided with identifying labels that will include all the information required by local regulations.
Olaparib have to be requested following pharmacy manual provided as a separate document and using appropriate forms provided by the Sponsor.
The study sites will have to ensure drug traceability at all times.

7.1.1. Description of treatment

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the IMP Investigator's Brochure, provided as separate documents.

7.1.2. Pharmaceutical Informations

Investigational product	Dosage form and strength
Olaparib	100 mg tablet
Olaparib	150 mg tablet
Olaparib	25 mg tablet

Descriptive information for olaparib can be found in the Investigator's Brochure

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

7.1.3. Administration of treatment

Treatment will be administered on an outpatient basis.
For all centres, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.
Olaparib will be dispensed to patients on Day 1 and every month thereafter until the patient completes the study, withdraws from the study or closure of the study.
The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.
If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.
Patients will continue with olaparib until the end of radiotherapy or until objective disease progression (determined by RECIST) as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

Agent	Dose	Route	Schedule
Olaparib	Dose as appropriate assigned dose level	Oral	Twice a day Continuously In the morning and evening (approximately 12 hours apart)
Radiotherapy	59.4 Gy	NA	1.8 Gy per fraction given once daily five days per week (Monday to Friday) over a period of 6.5 weeks.

Reported adverse events and potential risks are described in Section 11.

7.1.4. Restrictions during the study

7.1.4.1. CONTRACEPTION

Females of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 1 months after last dose of study drug(s).
Males patients, who are sexually active, and their partners of child bearing potential must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 3 month after last dose of study drug. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.
Acceptable birth control methods are described in appendix 6.

7.1.4.2. FOOD INTAKES RESTRICTION

Olaparib tablets can be taken with or without food. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.
It is not recommended to consume grapefruit juice while on olaparib therapy.

7.1.4.3. OTHER CONCOMITANT TREATMENT

- No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the course of the study for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above).
- Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 days follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days

after the last dose of study medication. In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.

7.1.5. General Concomitant Medication

7.1.5.1. EFFECT OF OTHER DRUGS ON OLAPARIB

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the eCRF.
In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.
While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- Strong CYP3A4 inhibitors: ketoconazole, itraconazole, boosted protease inhibitors, indinavir, saquinavir, telithromycin, clarithromycin, nelfinavir, boceprevir and telaprevir.
- Moderate CYP3A4 inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil.
- Moderate and strong CYP3A4 inhibitors should not be taken with olaparib.

For patients taking any of the above, the required wash-out period prior to starting olaparib is 2 weeks.

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided:

- Strong inducers : Phenobarbital, Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, , nevirapine, enzalutamide and St John's Wort (Hypericum perforatum)
- Moderate CYP3A4 inducers : bosentan, efavirenz, modafinil

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbital and enzalutamide 5 weeks, and for any of the others, 3 weeks.

After inclusion if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the Sponsor. A decision to allow the patient to continue in the study will be made on a case-by-case basis.
It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

7.1.5.2. EFFECT OF OLAPARIB ON OTHER DRUGS

Olaparib is an investigational drug for which no data on in vivo interactions are currently available.
Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract.

Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine).

Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Examples of substrates include:

- CYP1A2: duloxetine, melatonin
- CYP2B6: bupropion, efavirenz
- OATP1B1: (organic anion transport protein 1B1) bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT (organic cation transporter) 1, MATE (multi-drug and toxin extrusion protein) 1, MATE2K (multi-drug and toxin extrusion protein 2K): metformin
- OAT (organic anion transport protein) 3: furosemide, methotrexate

7.1.5.3. OTHER CONCOMITANT MEDICATION

Any medications, with the exceptions noted in Section 7.1.5.1 above, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be

given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.
In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.
The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.
All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

7.1.5.4. ADMINISTRATION OF OTHERS ANTI-CANCER AGENTS

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF.

7.1.5.5. MEDICATIONS THAT MAY NOT BE ADMINISTERED

No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

7.1.6. Dosing delays/dose modifications and adverse event management

7.1.6.1. DOSE ESCALATION PHASE

Level	**-1**	**1**	**2**	**3**	**4**
Olaparib	25 mg (daily)	25 mg (b.i.d)	50 mg (b.i.d)	100 mg (b.i.d)	150 mg (b.i.d)

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

7.1.6.2. EXPANSION PHASE

Any toxicity observed during the course of the study could be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Dose adjustments are to be made according to the greatest degree of toxicity, and in accordance with validated RP2D and table below:

Level	**-2**	**-1**	**RP2D**
Olaparib	25 mg (b.i.d)	50 mg (b.i.d)	100 mg (b.i.d)

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE).
Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the Sponsor must be informed. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (version 4) grade 1 or less.
Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment with olaparib.
Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

7.1.6.3. MANAGEMENT OF ANAEMIA

Adverse events of anaemia CTCAE grade 1 or 2 (Haemoglobin (Hb) > 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to > 10 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or

coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions in accordance with table above
If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be permanently discontinued.

7.1.6.4. MANAGEMENT OF NEUTROPENIA AND LEUKOPENIA

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.
Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTC AE grade >1 (ANC > 1.5 x 10^9/L). Growth factor support should be stopped at least 24 hours before restarting study drug (7 days for pegylated G-CSF).
Any subsequent interruptions will require study treatment dose reductionsin accordance with table above.

7.1.6.5. MANAGEMENT OF THROMBOCYTOPENIA

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

7.1.6.6. MANAGEMENT OF PROLONGED HAEMATOLOGICAL TOXICITIES WHILE ON STUDY TREATMENT

If a patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) (1,2) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.
Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to the Sponsor. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

The dose of olaparib must not be adjusted under any other circumstances unless the Sponsor gives prior agreement.

7.1.6.7. MANAGEMENT OF NEW OR WORSENING PULMONARY SYMPTOMS

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Sponsor.
All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.
Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

7.1.6.8. MANAGEMENT OF NAUSEA AND VOMITING

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity,

intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.
No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines

7.1.6.9. RENAL/HEPATIC IMPAIRMENT

If a patient develops moderate or severe renal/hepatic impairment whilst on treatment, it should be referred to the principal investigator in order to decide management in the best interest of the patient.

7.1.6.10. MYELODYSPLASTIC SYNDROME/ACUTE MYELOID LEUKAEMIA

Olaparib treatment should be discontinued if patient's diagnosis of myelodysplastic syndrome and/or acute myeloid leukaemia is confirmed and the patient should be treated appropriately. Development of a confirmed myelodysplastic syndrome and/or acute myeloid leukaemia whilst on treatment with olaparib or following treatment discontinuation should be reported to Sponsor as an SAE/ECI (see section 11.5).

7.1.6.11. PNEUMONITIS

If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs in the absence of a clear diagnosis, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately. It should be reported to Sponsor as an SAE/ECI (see section 11.5)

7.1.7. Packaging and Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.
Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include the dosing instructions and a space for the enrolment code (site number-patient number) to be completed at the time of dispensing.
The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrolment code (patient number)
- date of dispensing
- Name of the Sponsor
- Study number
- Quantity or contents of container.
- Batch number/packaging number
- Expiration date and storage conditions
- Local legal information, as appropriate.

7.1.8. Supplies and Drug Accountability

Olaparib is an investigational agent supplied under a collaborative agreement with the agent manufacturer, AstraZeneca.
Confer process of this study and pharmaceutical procedure for request.
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. Documentation of this procedure must be provided to the clinical trial monitor.

7.1.9. Treatment Compliance

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

7.2. RADIOTHERAPY

7.2.1. Radiotherapy with quality control

An investigator's meeting will be organized at the beginning of the present study in order to harmonize management (contouring, margin, irradiated volume).

7.2.2. RT planning

A three-dimensional conformal RT (3D-CRT) with photons ≥ 6MV will be realized based on the acquisition of a CT-scan performed in treatment position. Intensity modulated RT (IMRT), volumetric modulated arctherapy (VMAT) and tomotherapy are authorized.
Treatment position will be defined according to the location of the tumor and personalized contention could be used. Surgical scar, drain orifices or biopsy path could be spotting with radio opaque markers.

7.2.3. Volume definition

The definition of volumes will be in accordance with ICRU (International Commision of radiotherapy Unit) reports #50, #62 and #83.

Targets volume need to be define as report in Haas et al. report (International Journal of Radiation Oncology, Biology and Physics 2012)

- The GTV (Gross Tumor Volume) will be defined on CT, ideally after fusion with MRI (axial T1 contrast-enhanced sequence).
- The CTV (Clinical Tumor Volume) will be defined by adjunction of a 4 cm margin around the GTV, in the longitudinal directions and 1.5 cm in others directions. This margin could be shortened according to anatomical barriers as bone, interosseous membranes or fascial planes. Margin could be extended too in order to include an entire anatomical compartment or identified peri-tumoral oedema. The CTV will have to include surgical scar or biopsy paths.
- The PTV (Planning Target Volume) will be defined by adjunction of a set-up margin around the CTV to take into account patient set-up uncertainties. This margin will have to be selected by each participating center depending on their equipment, irradiation techniques and experiences.
- The OAR (Organs At Risk) as bone, neurovascular axis, muscular compartments, spinal cord, brachial plexus will be defined according to the location of the tumor (Cancer Radiotherapy, vol 14, 2010, special issue).

7.2.4. Dose prescription, specification and reporting in the PTV

Dose prescription, specification and reporting will be done according to ICRU report 83 recommandations.

During DOSE ESCALATION PHASE:
The prescribed dose at the median of the PTV (for IMRT treatments) or at the ICRU point (for non-IMRT treatments) will be 59.4Gy in 33 fractions of 1.8Gy, with 5 fractions per week.

During EXPANSION PHASE: Total radiotherapy dose will be adapted with patient condition (operable patient/inoperable patient):

- Up to 50 Gy for resectable disease or potentially resectable disease after study treatment (in 25 fractions of 2 Gy, with 5 fractions per week)
- Up to 59.4 Gy for unresectable disease (in 33 fractions of 1.8Gy, with 5 fractions per week).

95% of the PTV will have to receive at least 95% of the prescriped dose. Dose homogeneity inside the PTV will have to be comprised between 95% and 107% of the prescribed dose. The maximal dose should not exceed 107% of the prescribed dose.

7.2.5. Adverse effects management

Acute toxicities of radiotherapy of STS are essentially musculoskeletal or cutaneous toxicities. They will be evaluated through a clinical examination performed each week during radiotherapy and one month after the end of radiotherapy (D8, D15, D22, D29, D36, D43, D50, D64, D78, D92) or until regression of a grade 3. Grading of adverse events will be done according to the CTCAE v.4.

- If a grade ≥ 3 musculoskeletal or cutaneous toxicity is observed before a radiotherapy dose of 30Gy, Olaparib and radiotherapy were stopped (DLT) but radiotherapy could be continued when regression to a grade ≤ 2 will be achieved.
- If a grade ≥ 3 musculoskeletal or cutaneous toxicity is observed after a radiotherapy dose of 30Gy, radiotherapy will be stopped until regression to a grade ≤ 2 and then will be continued. Olaparib will be continued during radiotherapy interruption. If grade ≥ 3 persits more than 4 weeks, Olaparib will be stopped (DLT).

The irradiated skin area that will be included in the operative volume must be identified during contouring and protected during planification (ALARA) in order to limit the occurrence of post-operative acute cutaneous and mucous complications [30 - 31].

7.3. ASSOCIATED TREATMENT: SURGERY FOR RESECTABLE DISEASE

Surgery will be performed by expert surgeon within 12 weeks of radiotherapy completion in reference centers labelled by the French NCI and NETSARC network.

Post-operative complications will be recorded up to 12 months after surgical complication.
Surgical sample will be analyzed to determine histological response and data will be collected in case report form.
The decision of surgery has to be taken by the investigational site during Multidisciplinary Tumor Board (RCP),
The decision of surgery has to be notified to the sponsor as soon as possible (i.e. before surgery).
Post-surgery clinical exam: addition of 3 visits after surgery (D30, D60 and D90). The next visits remain unchanged (follow-up every 3 months).
Post-surgery complications grade 3 should be reported immediately as serious adverse event to the Vigilance Unit of the Sponsor.

8. STUDY EVALUATIONS

Study evaluations aim to assess:

- Diagnosis
- Efficacy
- Safety

8.1. CENTRAL REVIEW FOR DIAGNOSIS OF SARCOMA

8.1.1. Diagnosis of sarcoma

If diagnosis of sarcoma was not confirmed by the RRePS Network, pathological central review will be performed to confirm histological diagnosis of sarcoma by Pr. Coindre and collaborators, Department of Pathology, Institut Bergonié, Bordeaux, France. The reviewer will assess 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 sarcoma will be considered ineligible and will not be included in the study.

8.1.2. 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.

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

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

- Pathology request form completed
- 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 as described in a specific SOP provided by the Sponsor.

8.2. EFFICACY ONLY FOR EXPANSION COHORT

The antitumor activity of Olaparib given in association with radiotherapy will be evaluated in terms of Objective response under treatment, 6-months Objective response rate (ORR), 6-months Non-progression rate (NPR), 1-year Progression-free survival (PFS), 1-year Overall survival (OS). Non-progression rate and best objective response are defined as per the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

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

- A comprehensive workup will be performed at baseline, and every 12 weeks.
- Whenever 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).

8.2.2. Centralized Radiological Review (Institut Bergonié)

8.2.2.1. GENERAL PROCEDURE

Centralized radiological review will be performed to confirm disease status at 6 months in comparison with baseline, Week#12 and Week#24 and every 8 weeks for patients with metastatic disease at inclusion. For patients included in the reference center, MRI and CT scan (for patients with metastatic disease) 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.
In case of discordance between the local radiologist and the expert reviewer, the judgment provided by the expert reviewer will be retained and used in statistical analyses.

8.2.2.2. REVIEW PROCESS SCHEDULE

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

8.2.2.3. PRACTICAL IMPLEMENTATION

For each shipment, each media should be accompanied by the Radiological Forms provided by the sponsor.
All CDs must be sent as described in a specific SOP provided by the Sponsor.

8.3. 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, and/or 6 weeks after the last dose of radiotherapy. All AEs will be classified according to the NCI-CTCAE, version 4.0.
Note: if surgery performed, patient will be followed up at D30, D60 and D90 post surgery.

9. STUDY ENDPOINTS

9.1. DOSE ESCALATION

Primary endpoint

- Toxicity graded using the common toxicity criteria from the NCI v4.03.
- Incidence rate of DLT at each dose level during treatment period up to six weeks after end of radiotherapy.

Secondary endpoints

Antitumor activity observed with Olaparib given in association with radiotherapy in terms of

- 6-month non progression, defined as complete (CR) or partial response (PR) at 6 months confirmed ≥ 4 weeks after initial documentation, or stable disease more than 24 weeks (RECIST v1.1, as determined by investigator review of tumor assessments)
- 6-month objective response, defined as CR or PR at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1
- Best objective response under treatment is defined as complete (CR) and partial response (PR) recorded from the start of study treatment until the treatment with confirmation ≥ 4 weeks after initial documentation, as per RECIST 1.1. Objective response under treatment is determined once all the data for the patient is known.
- Best response under treatment is defined as the best response (CR, PR, SD) as per RECIST 1.1 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. It is determined once all the data for the patient is known.
- 1-year Progression-free survival (PFS): 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 Overall Survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
- Functional assessment
    - Graded using the Muskuloskeletal Tumour Society Rating Scale (Enneking, Modification of the system for functional evaluation in the surgical management of musculoskeletal

turnours. In: Enneking WF, ed. Limb Salvage in Musculoskeletal Oncology. New York, NY: Churchill Livingston, 1987:626A39.

- MSTS will be completed by the radiotherapist at baseline and at the end of radiotherapy treatment.
- The MSTS score is calculated from 6 functional criteria.
  - Three subjective criteria are common to the upper and lower limbs: pain, function, emotional acceptance of the surgical procedure (psychological acceptance).
  - The other three are objective criteria:
    - For the lower limb: support, walking and gait.
    - For the upper limb: the position relative to shoulder, dexterity, muscle strength
  - Each criterion is evaluated with a question (eg, pain is assessed by the consumption of analgesic drugs). The evaluation of each test contains six levels of achievement or scores, four defined scores (0, 1, 3, 5) and two intermediate (2, 4). The four scores are defined the score 5: absence of impact; the score 3: minor impact; the score 1: major repercussions; the score 0: disability.
- Concerning the analysis of MSTS,
  - The total score will be described at each measurement time
  - A difference of 10 points or more will be used to define a clinically significant difference. There is particular focus on the difference between the observed scores before surgery and 1 year post surgery.

- PK measurements expressed as AUC, half-life and concentration peak for Olaparib.

9.2. EXPANSION COHORT

Primary endpoint

6-month non progression as defined for the dose escalation part. For the expansion cohort, radiological data will be centrally reviewed. The primary analysis will be based on reviewed data.

Secondary endpoints

- Antitumor activity observed with Olaparib given in association with radiotherapy in terms of 6-month objective response, best response under treatment, best objective response under treatment, 1-year PFS and 1-year OS, as defined for the dose escalation part.
- Toxicity graded using the common toxicity criteria from the NCI v4.03.
- PK measurements expressed as AUC, half-life and concentration peak for Olaparib.
- Pharmacodynamics (translational research): Prognostic markers of anti-tumor activity of Olaparib given with concomitant radiotherapy will be investigated.

10. STATISTICAL CONSIDERATIONS

10.1. HYPOTHESES AND NUMBER OF SUBJECTS NEEDED

Dose escalation part

- 4 dose levels
- A minimum of 2 patients per dose level
- Rule of thumb is to set the sample size to be six times the number of dose levels. Therefore, the maximum number of patients is estimated to be 24 eligible and assessable patients. To account for patients not eligible/assessable, we anticipate accruing a maximum of **26 patients for the dose escalation part.**

Expansion 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 non-progression (CR, PR or SD) 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.**

10.2. DEFINITION OF STUDY POPULATIONS

Dose escalation part

- Population assessable for DLT assessment :
    - Patients assessable for the DLT assessment must fulfill all the following criteria:
        - Completed the DLT assessment period
        - Received concomitantly at least seven consecutive days of Olaparib and radiotherapy treatment (any dose) at least once.
    - Unless they develop a DLT, the following patients will not be included in the population assessable for DLT :
        - Patients who did not receive radiotherapy
        - Patients who did not receive nor Olaparib;
        - Patients who did not complete the full DLT evaluation period and goes off-treatment for reasons other than toxicity;

These patients will be replaced to reach the sample size requirement for dose escalation study.

- Safety population: patients who received radiotherapy or olaparib, at least once, irrespective of the dose. .

Expansion cohort

- Eligible population: All patients included without major violation of eligibility criteria.
- Population eligible and assessable for the primary endpoint : patients who fulfill all criteria below:
    - Eligible patients
    - Received concomitantly at least seven consecutive days of Olaparib and radiotherapy treatment (any dose) at least once.
    - at least one disease measurement recorded not less than eight weeks after treatment onset.

  The following patients will also be included in the population evaluable for efficacy; they will be considered as failures for the primary endpoint (i.e. progressive disease at 6 months) and not be replaced in the efficacy analysis:
    - Eligible patients withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment.
    - Eligible patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, or unrelated AEs without any tumor assessments after the start of study treatment.
- ***Replacement of patients: patients who do not comply with the definition of the population "eligible and assessable for the primary endpoint" will be replaced to reach the sample size requirement for expansion cohort.***
- Safety population: patients who receive at least one administration of Olaparib, or radiotherapy treatment at least once.

10.3. STATISTICAL ANALYSIS

A statistical Analysis Plan (SAP) will be produced by the statistician of the study and validated by the steering committee. A preliminary version will be produced prior to the first inclusion. The SAP will be updated when necessary (Substantial modification of the protocol, IDMC recommandations, etc) and systematically validated by the steering committee.

Dose escalation part

- Dose-toxicity modeling
    - At the end of the trial, the posterior distribution of the dose-toxicity parameter α and DLT at each dose, will be estimated using the power dose-toxicity model and normal prior distribution on α used to conduct the trial.
    - 95% posterior intervals for the toxicity probabilities will be reported.
- Patient characteristics at baseline will be provided
    - Compliance with eligibility criteria,
    - Epidemiological characteristics,
    - Clinical and laboratory characteristics,
    - Treatment characteristics.
- Toxicities observed at each dose level 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.
- Efficacy analysis: efficacy endpoints will be reported in terms of counts and proportions for each dose levels. Subgroup analyses will be conducted for metastatic and non-metastatic patients.
- All analyses will be descriptive; no p-values will be calculated.
- Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate.
- For continuous variables, summary statistics will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
- Categorical endpoints will be summarized using number of patients, frequency, percentages.
- For survival endpoints, median survival time will be reported.
- Missing data will not be imputed.

Expansion cohort

- Patient characteristics at baseline will be provided
    - Compliance with eligibility criteria,
    - Epidemiological characteristics,
    - Clinical and laboratory characteristics,
    - Treatment characteristics.
- Toxicities 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.
- Efficacy analysis: efficacy endpoints will be reported in terms of counts and proportions. Subgroup analyses will be conducted for metastatic and non-metastatic patients.
- All analyses will be descriptive; no p-values will be calculated.
- For continuous variables, summary statistics will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
- Categorical endpoints will be summarized using number of patients, frequency, percentages.
- For survival endpoints, median survival time will be reported.
- Missing data will not be imputed.
- Pharmacokinetics
    - PK analyses will be based on all subjects who receive at least one dose of Olaparib, if appropriate. Deviations from this will be documented.
    - PK parameters (AUC, Cmax, t.,) of Olaparib will be calculated using noncompartmental methods, and the systemic clearance (CL) will be derived from the plasma concentrations via standard methods.
    - All pharmacokinetic parameters will be presented descriptively including arithmetic means, standard deviations, geometric means, and coefficients of variation, medians and ranges.

- Pharmacodynamics (translational research). Given the small number of subjects, analyses will be descriptive. The distribution of the biomarkers will be reported for subgroups of patients defined by their response to treatment.

11. ADVERSE EVENTS

11.1. DESCRIPTION OF SAFETY EVALUATION CRITERIA

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG Appendix 1), a physical exam, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the NCI-CTCAE scale, version 4 available on website: http://ctep.info.nih.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

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.

11.2. DEFINITION

11.2.1. Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

11.2.2. Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Sponsor.

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.

Any abnormal laboratory's result resulting as a grade 4 in the CTCAE version 4 will be considered as 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 as serious by any IMP, any healthcare professional or any investigator should be handled as a serious adverse event.

NB. Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs.

11.2.2.1. 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.

11.2.2.2. 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.

11.2.2.3. 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.

11.2.3. 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.

11.2.4. Adverse effect

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

11.2.5. Expected/Unexpected character

An unexpected adverse event is an event whose nature, severity/intensity 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) of Olaparib and protocol for radiotherapy (section 11.8).
In practice, the term "new effect" is sometimes used as a synonymous of "unexpected adverse effect".

11.2.6. Intensity criterion

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.2.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.
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).

11.2.7. New event

Any new data that may lead to a re-assessment of the benefit/risk ratio of the clinical trial or the investigational medicinal product (IMP), to modifications of the use of the IMP or the conduct of the trial or modifications of documents regarding the trial or to the suspension or termination of the clinical trial or to modify the protocol of the trial concerned or other similar trials.
For a first in man study conducted in healthy volunteers: any serious adverse reaction (SAR) of the IMP is considered to be a new event.

11.2.8. 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,
- occupational exposure.

Some of these special circumstances are considered in more details below.

Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

If an overdose drug occurs in the course of the study, the sponsor inform appropriate AstraZeneca representatives within one day, i.e., immediately but no later than the end of the next business day of when he or she becomes aware of it.

The sponsor works with the investigator to ensure that all relevant information is provided.

For overdoses associated with SAE, standard reporting timelines apply, see Section 11.3. For other overdoses, reporting should be done within 30 days.

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.

11.3. SERIOUS ADVERSE EVENT AND NEW INFORMATION NOTIFICATION (RESPONSIBILITY OF THE INVESTIGATOR)

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

The investigator will notify 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 30 days after the last dose of Olaparib and/or 6 weeks after the last dose of radiotherapy,
- Beyond this period of time, only those SAEs suspected to be related to the study treatment or the research (diagnostic procedures, examinations carried out during the research, surgery …) 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.

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 4) 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) – Institut Bergonié
Fax: +33 5 56 33 04 85
Contact : Promotion Tél : 05.47.30.61.83 –
Mail : promotion-essaisprecoces@bordeaux.unicancer.fr
Ludivine Poignie (pharmacien) Tél : 05 56 33 33 94 –
Mail : Vigilance-promotion-essaiscliniques@bordeaux.unicancer.fr

For each event, the investigator will record:

- A description of the event that is as clearly as possible, using medical terminology,
- The date AE met criteria for serious AE,
- The seriousness criteria,
- The date of hospitalization and the date of discharge,
- The probable cause of death and the date of death if appropriate,
- The date the event started and ended,
- The patient's relevant medical history,
- The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Concomitant medications / therapies
- The causal link between this event and the study treatment (Olaparib and/or radiotherapy), disease treated or an intercurrent disease or treatment, surgery or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.),
- 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.

11.4. REPORTING PREGNANCY CASES OCCURRED WITHIN THE CLINICAL TRIAL

If a patient becomes pregnant during the course of the study, olaparib should be discontinued immediately.
The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.
Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.
If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform Sponsor within one day i.e., immediately but no later than the end of the next business day of when he or she becomes aware of it. Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Vigilance Unit immediately by facsimile using the Pregnancy Report form (appendix 5).

Paternal exposure: Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.
Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.
The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.
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 30 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.
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.

11.5. REPORTING POST-SURGERY COMPLICATIONS

In case of surgery, post-surgery complications grade ≥ 3 should be reported immediately as serious event to the Vigilance Unit of the Sponsor, during 12 months after surgery unless start of a new anti-tumor therapy (reporting procedures on section 11.3).

11.6. REPORTING ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS (MyeloDysplastic Syndrome)/AML (Acute Myeloid Leukemia), new primary malignancy (other than MDS/AML) and pneumonitis.

Any event of MDS/AML, new primary malignancy, or pneumonitis should be collected in the patient's CRF whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality.
Adverse events that are both an SAE and an AESI should be reported as an SAE following 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).
If necessary, a questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event.

11.7. 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.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Minimum and maximum intensity
- Whether the AE is serious or not
- Outcome
- Investigator causality rating against the Investigational Product (yes or no) radiotherapy (yes/no)
- Action taken with regard to investigational product/comparator/combination agent
- Treatments given to treat AE

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

If the investigator would like to decrease trial treatment dose or temporarily stop study management without respecting protocol procedures, he/she should have previously discussed 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.

11.8. HOW TO RECORD ADVERSE EVENT

11.8.1. Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

11.8.2. Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated (laboratory values, vital signs, etc…) should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.
If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).
Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.
NB. Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs.

11.8.3. New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 11.2.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer.

11.9. EXPECTED ADVERSE EFFECTS OF RADIOTHERAPY

The adverse effects of radiotherapy depend on the localization of the sarcoma and the irradiated area.

The expected acute adverse effects of radiotherapy are the following:

- Fatigue;
- Subcutaneous, musculosqueletal and skin toxicities including dermatitis, enanthema, redness, ulceration, bleedings, desquamation, necrosis, osteonecrosis, myositis, pain and infection ;
- Edema.

According to the irradiated area, blood toxicity (such as decrease in red blood cells, anemia, decrease in platelets and white blood cells) and digestive toxicity (such as enteritis, diarrhea, nausea, vomitis and stenosis) may occur.

The adverse effects may occur several months after the end of treatment, including:

- Loss of skin suppleness, skin atrophy;
- Pain or modification of sensibility;
- Fibrosis;
- Necrosis;
- Induration of tissue;
- Wound complication after a surgery
- Joint stiffness
- Secondary cancer.

11.10. 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 treatment Investigator's Brochure (IB) for Olaparib, protocol for radiotherapy (see section 11.8).

11.11. 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.

12. QUALITY ASSURANCE AND TRIAL MONITORING

12.1. MONITORING OF THE TRIAL

12.1.1. Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Dr P. Sargos, Co-ordinating Investigator and Chairman of the Commitee,
- Pr A. Italiano, Investigator and medical oncologist, (or a substitute)
- A representative of the sponsor (Pr S. Mathoulin-Pélissier or a substitute).
- The biostatistician of the trial (Ms. C.Bellera, or a substitute).
- The pharmacist of the trial (EL.Poignie, or a substitute).
- Co-ordinating Clinical research assistant (S. Sellan-Albert 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.

It 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.

12.1.2. DLT validation committee

For the dose escalation part, the DLT validation committee will be consulted before the first escalation to a new dose level.

Members for the DLT validation committee are the following (all at Institut Bergonié):

- An investigator ,
- A statistician,
- A pharmacist.

12.1.3. 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 and RP2D definitions based on the dose escalation trial will be submitted to the IDMC before opening the expansion cohort. If necessary, a second IDMC may be set up at the end of the expansion cohort.
- 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 radiotherapist, one pharmacologist and one statistican:
    - Qualified oncologist (Dr Esma Saada)
    - Radiotherapist (Dr Rick Haas)
    - Pharmacologist (Dr Francesco SALVO)
    - Statistician (E. Chamorey)

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.

Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data, specifically the statistical report presenting results for the dose escalation part will be presented to the IDMC experts;
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) 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)].

12.2. QUALITY ASSURANCE

12.2.1. 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.

12.2.2. 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.

- The possible audit 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.

12.2.3. 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.

12.2.4. Audits

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.

12.2.5. 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.

13. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

Clinical Research Management Unit – Institut Bergonié
Contacts: Lucie Bard – Tel.: +33 5 56 33 32 70 –
or Marie-Laure Marty – Tel.: +33 5 47 30 60 79 – e-mail: drci@bordeaux.unicancer.fr

The study will be carried out in accordance with:

- Law no. 2012-300 dated 5 March 2012 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).
- 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, text 64).
- 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 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.

13.1. CLINICAL TRIAL AUTHORIZATION

This trial is registered under Eudract N° 2015-003722-13.

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on 25/11/2015.

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 07/01/2016.

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.

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.

13.2. INSURANCE POLICY

The Institut Bergonié has taken out an insurance policy (policy No 0100871914011 – 150006 – 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.

13.3. 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.

13.4. 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.

13.5. 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.

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.

13.6. 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.

13.7. 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.

13.8. FEDERATION DES COMITES DE PATIENTS POUR LA RECHERCHE CLINIQUE EN CANCEROLOGIE (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.

13.9. 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.

14. 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 ponsor's consent.

15. PUBLICATION AND VALORISATION

15.1. 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 according to degree of involvement in the preparation of publications)

15.2. 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.

16. REFERENCES

1. Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere A-V, Péoc'h M, Istier L, Chalabreysse P, Muller C, Alberti L, Bringuier P-P, Scoazec J-Y, Schott A-M, Bergeron C, Cellier D, Blay J-Y, Ray-Coquard I: **Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing**. *PloS One* 2011, **6**:e20294.

2. Slater JD, McNeese MD, Peters LJ: **Radiation therapy for unresectable soft tissue sarcomas**. *Int J Radiat Oncol Biol Phys* 1986, **12**:1729–1734.

3. Kepka L, DeLaney TF, Suit HD, Goldberg SI: **Results of radiation therapy for unresected soft-tissue sarcomas**. *Int J Radiat Oncol Biol Phys* 2005, **63**:852–859.

4. Ben-Hur E, Lindquist K, Elkind MM: **Poly(ADP-ribose) and the recovery from damage in Chinese hamster cells due to 5-bromodeoxyuridine photolysis**. *Int J Radiat Biol Relat Stud Phys Chem Med* 1985, **48**:33–43.

5. Masutani M, Nozaki T, Nakamoto K, Nakagama H, Suzuki H, Kusuoka O, Tsutsumi M, Sugimura T: **The response of Parp knockout mice against DNA damaging agents**. *Mutat Res* 2000, **462**:159–166.

6. Bowman KJ, Newell DR, Calvert AH, Curtin NJ: **Differential effects of the poly (ADP-ribose) polymerase (PARP) inhibitor NU1025 on topoisomerase I and II inhibitor cytotoxicity in L1210 cells in vitro**. *Br J Cancer* 2001, **84**:106–112.

7. Brock WA, Milas L, Bergh S, Lo R, Szabó C, Mason KA: **Radiosensitization of human and rodent cell lines by INO-1001, a novel inhibitor of poly(ADP-ribose) polymerase**. *Cancer Lett* 2004, **205**:155–160.

8. Dungey FA, Löser DA, Chalmers AJ: **Replication-dependent radiosensitization of human glioma cells by inhibition of poly(ADP-Ribose) polymerase: mechanisms and therapeutic potential**. *Int J Radiat Oncol Biol Phys* 2008, **72**:1188–1197.

9. Russo AL, Kwon H-C, Burgan WE, Carter D, Beam K, Weizheng X, Zhang J, Slusher BS, Chakravarti A, Tofilon PJ, Camphausen K: **In vitro and in vivo radiosensitization of glioblastoma cells by the poly (ADP-ribose) polymerase inhibitor E7016**. *Clin Cancer Res Off J Am Assoc Cancer Res* 2009, **15**:607–612.

10. Schlicker A, Peschke P, Bürkle A, Hahn EW, Kim JH: **4-Amino-1,8-naphthalimide: a novel inhibitor of poly(ADP-ribose) polymerase and radiation sensitizer**. *Int J Radiat Biol* 1999, **75**:91–100.

11. Banasik M, Komura H, Shimoyama M, Ueda K: **Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase**. *J Biol Chem* 1992, **267**:1569–1575.

12. Saleh-Gohari N, Bryant HE, Schultz N, Parker KM, Cassel TN, Helleday T: **Spontaneous homologous recombination is induced by collapsed replication forks that are caused by endogenous DNA single-strand breaks**. *Mol Cell Biol* 2005, **25**:7158–7169.

13. Harper JV, Anderson JA, O'Neill P: **Radiation induced DNA DSBs: Contribution from stalled replication forks?**. *DNA Repair* 2010, **9**:907–913.

14. Mitchell J, Smith GCM, Curtin NJ: **Poly(ADP-Ribose) polymerase-1 and DNA-dependent protein kinase have equivalent roles in double strand break repair following ionizing radiation**. *Int J Radiat Oncol Biol Phys* 2009, **75**:1520–1527.

15. Spagnolo L, Barbeau J, Curtin NJ, Morris EP, Pearl LH: **Visualization of a DNA-PK/PARP1 complex**. *Nucleic Acids Res* 2012, **40**:4168–4177.

16. Leopold W.R, Sebolt-Leopold J.S: **Chemical approaches to improved radiotherapy.** In *Cytotoxic Anticancer Drugs:Models and Concepts for Drug Discovery and Development*. Valeriote F.A, Corbett T.H, Baker L.H. Kluwer, Boston; :179–196.

17. Calabrese CR, Almassy R, Barton S, Batey MA, Calvert AH, Canan-Koch S, Durkacz BW, Hostomsky Z, Kumpf RA, Kyle S, Li J, Maegley K, Newell DR, Notarianni E, Stratford IJ, Skalitzky D, Thomas HD, Wang L-Z, Webber SE, Williams KJ, Curtin NJ: **Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361**. *J Natl Cancer Inst* 2004, **96**:56–67.

18. Khan K, Araki K, Wang D, Li G, Li X, Zhang J, Xu W, Hoover RK, Lauter S, O'Malley B, Lapidus RG, Li D: **Head and neck cancer radiosensitization by the novel poly(ADP-ribose) polymerase inhibitor GPI-15427**. *Head Neck* 2010, **32**:381–391.

19. Albert JM, Cao C, Kim KW, Willey CD, Geng L, Xiao D, Wang H, Sandler A, Johnson DH, Colevas AD, Low J, Rothenberg ML, Lu B: **Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models**. *Clin Cancer Res Off J Am Assoc Cancer Res* 2007, **13**:3033–3042.

20. Barreto-Andrade JC, Efimova EV, Mauceri HJ, Beckett MA, Sutton HG, Darga TE, Vokes EE, Posner MC, Kron SJ, Weichselbaum RR: **Response of human prostate cancer cells and tumors to combining PARP inhibition with ionizing radiation**. *Mol Cancer Ther* 2011, **10**:1185–1193.

21. Donawho CK, Luo Y, Luo Y, Penning TD, Bauch JL, Bouska JJ, Bontcheva-Diaz VD, Cox BF, DeWeese TL, Dillehay LE, Ferguson DC, Ghoreishi-Haack NS, Grimm DR, Guan R, Han EK, Holley-Shanks RR, Hristov B, Idler KB, Jarvis K, Johnson EF, Kleinberg LR, Klinghofer V, Lasko LM, Liu X, Marsh KC, McGonigal TP, Meulbroek JA, Olson AM, Palma JP, Rodriguez LE, et al.: **ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models**. *Clin Cancer Res Off J Am Assoc Cancer Res* 2007, **13**:2728–2737.

22. Wang L, Mason KA, Ang KK, Buchholz T, Valdecanas D, Mathur A, Buser-Doepner C, Toniatti C, Milas L: **MK-4827, a PARP-1/-2 inhibitor, strongly enhances response of human lung and breast cancer xenografts to radiation**. *Invest New Drugs* 2012, **30**:2113–2120.

23. Clarke MJ, Mulligan EA, Grogan PT, Mladek AC, Carlson BL, Schroeder MA, Curtin NJ, Lou Z, Decker PA, Wu W, Plummer ER, Sarkaria JN: **Effective sensitization of temozolomide by ABT-888 is lost with development of temozolomide resistance in glioblastoma xenograft lines**. *Mol Cancer Ther* 2009, **8**:407–414.

24. Senra JM, Telfer BA, Cherry KE, McCrudden CM, Hirst DG, O'Connor MJ, Wedge SR, Stratford IJ: **Inhibition of PARP-1 by olaparib (AZD2281) increases the radiosensitivity of a lung tumor xenograft**. *Mol Cancer Ther* 2011, **10**:1949–1958.

25. Ali M, Kamjoo M, Thomas HD, Kyle S, Pavlovska I, Babur M, Telfer BA, Curtin NJ, Williams KJ: **The clinically active PARP inhibitor AG014699 ameliorates cardiotoxicity but does not enhance the efficacy of doxorubicin, despite improving tumor perfusion and radiation response in mice**. *Mol Cancer Ther* 2011, **10**:2320–2329.

26. Ali M, Telfer BA, McCrudden C, O'Rourke M, Thomas HD, Kamjoo M, Kyle S, Robson T, Shaw C, Hirst DG, Curtin NJ, Williams KJ: **Vasoactivity of AG014699, a clinically active small molecule inhibitor of poly(ADP-ribose) polymerase: a contributory factor to chemopotentiation in vivo?**. *Clin Cancer Res Off J Am Assoc Cancer Res* 2009, **15**:6106–6112.

27. Mehta MP, Wang D, Wang F, Kleinberg L, Brade A, Robins HI, Turaka A, Leahy T, Medina D, Xiong H, Mostafa NM, Dunbar M, Zhu M, Qian J, Holen K, Giranda V, Curran WJ: **Veliparib in combination with whole brain radiation therapy in patients with brain metastases: results of a phase 1 study**. *J Neurooncol* 2015, **122**:409–417.

28. Verhagen CVM, de Haan R, Hageman F, Oostendorp TPD, Carli ALE, O'Connor MJ, Jonkers J, Verheij M, van den Brekel MW, Vens C: **Extent of radiosensitization by the PARP inhibitor olaparib depends on its dose, the radiation dose and the integrity of the homologous recombination pathway of tumor cells**. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2015.

29. Lee HJ1, Yoon C, Schmidt B, Park do J, Zhang AY, Erkizan HV, Toretsky JA, Kirsch DG, Yoon SS. **Combining PARP-1 inhibition and radiation in Ewing sarcoma results in lethal DNA damage**.

Mol Cancer Ther. 2013 Nov;12(11):2591-600. doi: 10.1158/1535-7163.MCT-13-0338. Epub 2013 Aug 21.

30. Sargos P. et al, "**Pre-and postoperative radiotherapy for extremity soft tissue sarcoma. Evaluation of inter-observer target volume contouring variability among French sarcoma group radiation oncologists"**, Cancer Radiother. 2018 Apr;22(2):131-139.

31.O'Sullivan B et al, **"Phase 2 study of preoperative image-guided intensity modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma"**, Cancer. 2013 May 15;119(10):1878-84.

17. PHARMACOKINETIC, AND ANCILLARY STUDIES

17.1. PHARMACOKINETIC STUDY

17.1.1. Collection of available specimens

Pharmacokinetics of Olaparib in blood will be assessed on C1D1, C1D8 and C1D28. The main objectives of the pharmacokinetic study are to assess interactions between Olaparib and radiotherapy, at initial administration (D1) and after repeated dosing, at the higher theoretical point (D28).
For each patient, blood samples, will be collected at predefined time points.

Pharmacokinetics schedules *of Olaparib*

	H0	H1	H2	H3	H4	H6	H12*
C1D1	X	X	X	X	X	X	X
C1D8	X	X	X	X	X	X	X
C1D28	X	X	X	X	X	X	X

*before next dose

Pharmacokinetics method guidelines will be provided by the sponsor as a separate document.

17.1.2. PK analysis

Area under the curve (AUC), maximum and minimum trough concentration (C_{max} and C_{min}) and half-life ($t_{1/2}$) will be calculated.

17.1.3. Site performing PK study

This study will be performed as notified to Competant Authorities.

17.1.4. Shipping of specimens

The container containing the samples will be labelled with coded numbers to ensure full compliance with privacy policy. Samples will be grouped in each institution and sent frozen for centralized processing as described in a specific SOP provided by the Sponsor.
Shipping will only be performed by a promoter authorized transporter with respect to good practice.

17.2. ANCILLARY STUDY

17.2.1. Collection of Specimen(s)

Tumor biopsies will be performed on consented adult patients at Day 1 of cycle 1 predose, on day 8 before the start of radiotherapy and at week 12.
Moreover, for all patients who have undergone surgery after initial treatment, surgical sample will be collected.

17.2.2. Handling and shipping of Specimen(s)

Biopsy:
One half of the specimen will be formalin fixed and paraffin embedded [FFPE (Formalin-Fixed Paraffin-Embedded)] and the second half will be fresh frozen at -80°C.
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).
Surgery:
Formalin fixed and paraffin embedded [FFPE] will be collected.
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.

17.2.2.1. ALL SAMPLES WILL BE STORED BEFORE THEY ARE ANALYZED.SITE(S) PERFORMING CORRELATIVE STUDY

All pathological specimens sampling with documents must be sent as described in a specific SOP provided by the Sponsor.

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.

APPENDIX 2: MDRD 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].*

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.

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).

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.

APPENDIX 4: SERIOUS ADVERSE EVENT NOTIFICATION FORM

Bergonié UNICANCER NOUVELLE-AQUITAINE

SERIOUS ADVERSE EVENT NOTIFICATION FORM

TO BE FAXED TO THE VIGILANCE UNIT–N° + 33 (0)5.56.33.04.85

PROTOCOL : **RADIOSARP**	EUDRACT/ ID-RCB N°:**2015-003722-13**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |___|___|___|___|___|___|	INITIAL REPORT ☐ FOLLOW-UP REPORT N°|___|	FINAL REPORT ☐

1. PARTICIPANT IDENTIFICATION

IDENTIFICATION N°: |_____| DATE OF INCLUSION: |___\|___\|___\|___\|___\| TREATMENT ARM: |___| DOSE LEVEL (PHASE I STUDY): |__|

SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER):|__| AGE AT THE TIME OF THE EVENT (YEARS OLD): |___|

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

DISEASE UNDER STUDY (*diagnosis, localization and metastases site if applicable*): .....

2. INFORMATION ON EVENT

DATE OF INVESTIGATOR AWARENESS OF SAE: |___\|___\|___\|___\|___\| DATE OF EVENT ONSET: |___\|___\|___\|___\|___\|

DATE OF SERIOUSNESS 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 or ☐ PROLONGING HOSPITALIZATION:

DATE OF ADMISSION:|___\|___\|___\|___\|___\|

☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY

☐ CONGENITAL ANOMALY/BIRTH DEFECT

☐ MEDICALLY RELEVANT

ADVERSE EVENT OF SPECIAL INTEREST (AESI) (SEE PROTOCOL) YES ☐ NO ☐

SPECIAL CONSIDERATIONS (SEE PROTOCOL) YES ☐ NO ☐

☐ SERIOUS (COMPLETE SECTION 3) OR ☐ NOT SERIOUS

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 ☐

PLEASE, SPECIFY ABOVE THE OUTCOME OF THE EVENT AT THE TIME OF UNRELATED DEATH

☐ AUTOPSY: YES ☐ NO ☐ UNKNOWN ☐

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

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S)) ..... TICK IF NA ☐

INVESTIGATIONAL PROCEDURE(S) Indicate the International Common Denomination of the IMP & other combined	ROUTE	SAE CYCLE NUMBER	DATES		DOSE & UNITS			
			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	
1.			|___|___|___|___|___|	|___|___|___|___|___|				
2.			|___|___|___|___|___|	|___|___|___|___|___|				
3.			|___|___|___|___|___|	|___|___|___|___|___|				
4.			|___|___|___|___|___|	|___|___|___|___|___|				
5.			|___|___|___|___|___|	|___|___|___|___|___|				

UNBLINDING : YES ☐ NO ☐ NA ☐

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

☐ YES N°|_| N°|_| N°|_| N°|_| Date: |___\|___\|___\|___\|___\| ☐ NO ☐ NA

IF YES, SPECIFY: ☐ TEMPORALLY ☐ DEFINITIVELY

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°|_| ☐ NO ☐ NA

IF YES, SPECIFY: Date: |___\|___\|___\|___\|___\| Dose: .....

DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCTION?

☐ YES ☐ NO ☐ NA

PROTOCOL :**RADIOSARP**	EUDRACT/ ID-RCB N°: **2015-003722-13**	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): |__| AGE (YEARS OLD) : |__|_____|		

6. RADIOTHERAPY ..... TICK IF NA ☐

		DATES		DOSE (GY)	
TECHNIQUE	FIELD(S)	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 Date: |__|__|_____| ☐NO ☐NA	☐YES Date: |__|__|_____| ☐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. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USED TO TREAT REACTION)

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

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

MEDICAL HISTORY	START DATE	STOP DATE	ONGOING
1.	FROM |__|__|___|	TO |__|__|___|	☐
2.	FROM |__|__|___|	TO |__|__|___|	☐
3.	FROM |__|__|___|	TO |__|__|___|	☐
4.	FROM |__|__|___|	TO |__|__|___|	☐
5.	FROM |__|__|___|	TO |__|__|___|	☐

PROTOCOL : **RADIOSARP**	EUDRACT/ ID-RCB N°: **2015-003722-13**	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): |__| Age (YEARS OLD): |__|		

9. ASSESSMENT: IN YOUR OPINION **(INVESTIGATOR)**, THIS EVENT IS RELATED TO:

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S))

☐ INVESTIGATIONAL RADIOTHERAPY

IF NOT RELATED TO INVESTIGATIONAL MP / RADIOTHERAPY, **PLEASE SPECIFY**:

☐ PROTOCOL/STUDY PROCEDURE, SPECIFY: .....

☐ DISEASE UNDER STUDY, SPECIFY: .....

☐ CONCOMITANT TREATMENT(S), SPECIFY: .....

☐ CONCOMITANT DISEASE(S), SPECIFY: .....

☐ OTHER, SPECIFY: .....

10. SAE NOTIFICATED BY:

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

SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

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

SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

TYPE OF REPORT: ☐ SAE ☐ ADVERSE EVENT OF SPECIAL INTEREST ☐ SPECIAL CONSIDERATIONS

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

ASSESSMENT:

1 ☐ INVESTIGATIONAL **MP**
2 ☐ INVESTIGATIONAL **RADIOTHERAPY**

UNEXPECTED: YES ☐ NO ☐

REFERENCE SAFETY INFORMATION (TYPE, VERSION): .....

IF NOT RELATED TO EITHER 1 OR 2, PLEASE SPECIFY

3 ☐ PROTOCOL /STUDY PROCEDURE, SPECIFY: .....
4 ☐ DISEASE UNDER STUDY
5 ☐ CONCOMITANT TREATMENT(S) SPECIFY: .....
6 ☐ CONCOMITANT DISEASE(S), SPECIFY .....
7 ☐ OTHER, SPECIFY .....

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

APPENDIX 5: PREGNANCY NOTIFICATION FORM

Bergonié
UNICANCER
NOUVELLE-AQUITAINE

Pregnancy Notification Form

TO BE FAXED TO VIGILANCE UNIT–N° + 33 (0)5.56.33.04.85

PROTOCOL : **RADIOSARP**	EUDRACT/ ID-RCB N°:**2015-003722-13**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |___|__|___|__|___|___|___|___|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|___| / FINAL REPORT ☐	

THIS NOTIFICATION CONCERNS: ☐ PREGNANCY ☐FEEDING

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| AGE (AT TIME OF DISCOVERY): |____| YEARS GENDER: FEMALE ☐ MALE ☐

TREATMENT ARM |_____| DOSE LEVEL (ONLY FOR PHASE I STUDIES) |_____| WEIGHT (Kg): |_____| HEIGHT (CM): |_____| BODY SURFACE AREA (M²): |_____|

2. INFORMATION ON PREGNANT

THE PREGNANT IS: THE PATIENT ☐

A PATIENT PARTNER ☐ ☞ SPECIFY AGE (AT TIME OF DISCOVERY): |____| WEIGHT (Kg): |_____| HEIGHT (CM): |_____| BODY SURFACE |_____|

DATE OF LAST MENSTRUAL PERIOD (DD/MM/YYYY): |____/____/_____| ESTIMATED DATE OF DELIVERY (DD/MM/YYYY): |____/____/_____|

WAS THE PATIENT USING CONTRACEPTION? YES ☐ SPECIFY..... NO ☐ UNCERTAIN ☐

DO YOU THINK THERE WAS A FAILURE IN CONTRACEPTION? YES ☐ NO ☐ UNKNOWN ☐

CAUSE/REASON FOR FAILURE (NON-COMPLIANCE, MECHANICAL, DRUG INTERACTION...) .....

MATERNAL PREGNANCY ASSOCIATED EVENTS (if yes, specify): .....

IF THE MOTHER EXPERIENCED A SERIOUS ADVERSE EVENT DURING PREGNANCY, PLEASE COMPLETE A SAE FORM.

3. DRUGS INFORMATION

DESCRIBE ALL RELEVANT TREATMENTS ADMINISTERED TO THE PREGNANT AND HER PARTNER IF APPLICABLE (Date and dose of investigational drugs and concomitant treatments):

CONCERNING PATIENT INCLUDED IN THE STUDY:

INVESTIGATIONAL PROCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP* & OTHER COMBINED AND/OR RADIOTHERAPY AND/OR DEVICE AND/OR METHOD OR ACTION	ROUTE	EVENT CYCLE NUMBER	DATES		DOSES AND UNIT			
			DATE OF FIRST ADMINISTRATION/USE (1st DAY OF 1st CYCLE)	DATE OF LAST ADMINISTRATION/USE (1st DAY OF 1st CYCLE)	LAST DAILY DOSE ADMINISTRATED BEFORE PREGNANCY DISCOVERY		CUMULATIVE DOSE SINCE THE 1st ADMINISTRATION IF APPLICABLE	
					DOSE	UNIT	DOSE	UNIT
1.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|				
2.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|				
3.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|				
4.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|				
5.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|				

*IMP: INVESTIGATIONAL MEDICAL PRODUCT

DOES TREATMENT(S) STOPPED WHEN PREGNANCY WAS DISCOVERED: YES ☐ NO ☐

IF NO EXPLAIN AND GIVE THE STOP DATE FOR EACH TREATMENT OR PROCEDURE: .....

CONCERNING THE PREGNANT:

CONCOMITANT DRUGS (INN)	ROUTE	DAILY DOSE	START DATE	STOP DATE	CHECK BOX IF ONGOING	INDICATION
1.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	
2.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	
3.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	
4.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	
5.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	
6.			|__|__|/|__|__|/|__|__|__|	|__|__|/|__|__|/|__|__|__|	☐	

4. PARENTS RELEVANT MEDICAL HISTORY:

MOTHER:

RISK FACTORS (TICK IF YES): ☐SMOKING ☐ALCOHOL ☐DRUG-ABUSE ☐INFECTION ☐MEDICATION ☐HYPERTENSION ☐ECLAMPSIA ☐ OTHERS, Specify: .....

RELEVANT MEDICAL HISTORY (Include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy):

.....

.....

Pregnancy Notification Form

TO BE FAXED TO VIGILANCE UNIT–N° + 33 (0)5.56.33.04.85

PROTOCOL :**RADIO SARP**	EUDRACT/ ID-RCB N°: **2015-003722-13**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__/__/____|	INITIAL REPORT ☐ FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐
INCLUSION N°: |_____| Age (YEARS OLD) : |___/____|		

MOTHER:

PREVIOUS OBSTETRIC HISTORY (PROVIDE ALL PREVIOUS PREGNANCIES INCLUDING ABORTION AND STILLBIRTH)

DATE	GESTATION WEEK	OUTCOME
__/__/____		
__/__/____		
__/__/____		
__/__/____		

FATHER:

RELEVANT MEDICAL HISTORY:

.....

.....

5. PREGNANCY OUTCOME

☐ NOT APPLICABLE AT THE TIME OF DECLARATION ☐ APPLICABLE (COMPLETE BELLOW)

☐ DELIVERY __/__/____ (DD/MM/YYYY)	☐ NORMAL ☐ FORCEPS/VENTOUSE ☐ CAESARIAN	MATERIAL COMPLICATIONS OR PROBLEMS RELATED TO BIRTH .....
☐ ABORTION __/__/____ (DD/MM/YYYY)	☐ PLANNED ☐ THERAPEUTIC ☐ SPONTANEOUS	SPECIFY REASONS .....

OTHER INFORMATIONS (for exemple in case of not yet delivery provide results of specific tests performed e.g. amniocentesis, ultrasound, maternal serum afp, serology tests etc) :

.....

ASSESSMENT OF CAUSALITY PLEASE INDICATE THE RELATIONSHIP BETWEEN THE PREGNANCY OUTCOME AND IMP

☐ Not Related ☐ Related, specify IMP.....

6. CHILD INFORMATION (if applicable)

NEONATE:

☐ NORMAL ☐ STILLBIRTH ☐ ABNORMAL, SPECIFY: .....

OTHERS INFORMATIONS:

SEX: ☐ MALE ☐ FEMALE HEIGHT.....CM WEIGHT.....Kg OTHER.....

7. INFORMATION ON FEEDING

☐ NOT APPLICABLE ☐ APPLICABLE (COMPLETE BELLOW)

DATE OF FIRST FEEDING (DD/MM/AAAA): __/__/____ DATE OF LAST FEEDING (DD/MM/AAAA): __/__/____

DESCRIBE ALL RELEVANT INFORMATION:.....

8. FOLLOW-UP INFORMATION

FOLLOW-UP INFORMATION CAN BE OBTAINED FROM:

DOCTOR: ..... INSTITUTION: ..... ADDRESS: .....

E-MAIL: ..... PHONE: ..... FAX: .....

9. INVESTIGATOR

NAME..... INSTITUTION:.....

E-MAIL: .....

PHONE: .....

FAX: .....

DATE (DD/MM/YYYY): __/__/____ SIGNATURE: .....

APPENDIX 6: ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).
<include if recruiting male patients> Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

Acceptable Non-hormonal birth control methods include:
• Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for at least 1 month (for female patients) or at least 3 months (for male patients) after the last dose of study treatment. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
• Vasectomised sexual partner PLUS male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
• Tubal occlusion PLUS male condom.
• Intrauterine device (provided coils are copper-banded) PLUS male condom

Acceptable hormonal methods:
• Mini pill PLUS male condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
• Combined pill PLUS male condom: Normal and low-dose combined oral pills.
• Injection PLUS male condom: Medroxyprogesterone injection (eg, Depo-Provera [Pfizer]).
• Implants PLUS male condom: Etonorgestrel-releasing implants (eg, Nexplanon [Merck Sharp & Dohme]).
• Patch PLUS male condom: Norelgestromin/ethinyl estradiol transdermal system (eg, Xulane).
• Intravaginal device (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing [Merck Sharp & Dohme]) PLUS male condom.
• Levonorgestrel-releasing intrauterine system (eg, Mirena [Bayer]) PLUS male condom.

APPENDIX 7: MUSKULOSKELETAL TUMOR SOCIETY FUNCTIONAL FORM

SCORE	PAIN	FUNCTION	EMOTIONAL	SUPPORTS	WALKING	GAIT	Final Patient Score of FUNCTIONAL EVALUATION
5	No pain	No restriction	Enthused	None	Unlimited	Normal	
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	
3	Modest/Non-disabling	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic	
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	
1	Moderate/Disabling	Partial restriction	Accepts	One cane or crutch	Inside only	Major cosmetic	
0	Severe disabling	Total restriction	Dislikes	Two canes or crutches	Not independent	Major handicap	
Patient score							