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

Protocol RADIOSARP

STATISTICAL ANALYSIS PLAN (SAP)

VERSION N°2.0 March 29, 2021

EudraCT n° 2015-003722-13

This trial is supported by 'Institut National du Cancer'

Document sources : Protocol Radiosarp v11.0 10/09/2020
Annoted CRF v5.2 18/03/2021

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SPONSOR **INSTITUT BERGONIE**

1 STUDY PROTOCOL (SUMMARY)

1.1 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	6 centres: - Institut Bergonié, Bordeaux - Centre Léon Bérard, Lyon - IUCT Oncopôle, Toulouse - Institut Gustave Roussy, Villejuif - Institut du Cancer, Montpellier - Centre Oscar Lambret, Lille
Number of patients	41 patients
Duration of the study	Planned enrollment period: 24 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: at least 1 year Study period: 3 years
Medical conditions	**Adult patients with locally advanced/unresectable soft-tissue sarcoma**
Objectives	**<u>Primary objective</u>** **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. **<u>Secondary objectives</u>**

	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). - 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). - 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 (3+3 traditional 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 hyperglycaemia and changes in serum electrolytes/enzymes without clinical impact) ▪ Febrile neutropenia (absolute neutrophil count [ANC] < 1.0 $x10^9$/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0 x 10^9/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 at each DLT notification for validation of the DLT status (see section 12.1.2).

Maximum tolerated dose (MTD)
The MTD for Olaparib is defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced a DLT during the period of observation of DLTs. 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.
- Patients will be allocated to 4 doses levels following a 3 + 3 design.
- A minimum of 3 patients and a maximum of 6 patients will be entered on each dose level.
- All 3 patients within a dose level will be observed during after the period of observation of DLTs before accrual to the next higher dose level may begin.
- For the dose escalation part, a DLT validation committee will be consulted at each DLT notification for validation of the DLT status (see section 12.1.2).
- Dose escalation will proceed according to the following scheme:

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

- As described above, the maximum administered dose (MAD) for Olaparib is the dose in which $\geq$2/3 or $\geq$2/6 patients experience DLT.
- If the MAD for Olaparib is seen at the starting dose level, then dose level "-1" will be the recommended dose.
- The MTD for Olaparib is defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced a DLT during the period of observation of DLTs (i.e. MTD corresponds to 25% DLT). A DLT validation committee will be consulted at each DLT notification for validation of the DLT status (see section 12.1.2).

	• The steering committee will meet before proceeding to each dose escalation. • 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
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 inoperable tumor, outside any previously irradiated field (inoperable status must be assessed by staff including a surgeon specialized in sarcoma), 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, 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 10. 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 French social security in compliance with the Law relating to biomedical research (Article L.1121-11 of French Public Health Code).
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

<table>
<tr><td></td><td>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. No prior or concurrent malignant disease diagnosed or treated in the last 2 years, except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
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 CYP3A4 inhibitors such as ketokonazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir,
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 and patients must have recovered from any effects of any major surgery,
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.</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 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></td></tr>
</table>

<table>
<tr><td></td><td>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.</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</td></tr>
</table>

	action/pharmacodynamic activity on fresh biopsy (pre-treatment and week 4 of treatment). **EXPANSION COHORT** *Primary Endpoint* • 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. *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 3 patients and a maximum of 6 patients per dose level • 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). • 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.

2 DEFINITION OF THE STUDY POPULATIONS

2.1 DÉFINITIONS

2.1.1 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.

Criteria	eFORM variable	Control

DLT-assessable	**EXA_RAD**
	DLT_RA
	EXA_ONC
	DLT_ON
	TRT_OLA
	TH_2O,…,**TH_5O** (4 variables therapy change)
	CH_2O,…,**CH_5O** (4 variables reason of change)
	
	TRT_RAD
	TH_2R,…,TH_10R (9 variables therapy change)
	CH_2R,…,CH_10R (9 variables reason of change)
		ELI_DLT=0
		If (DLT_RA =1 or DLT_ON=1) then ELI_DLT=1
		
		Check if treatment stopped
		If ((TH_20 and … andTH_50) in (0 -7) and (TH_2R and … and TH_10R in (0 -7)) then ELI_DLT=1
		
		if treatment stopped check the reason (toxicity) and 7 consecutive days
		If ((TH_20 or … or TH_50) in (2 3 4 5) or (TH_2R or … orTH_10R in (2 3 4 5)) then {if (respectively)
		((CH_20 or … or CH_50) in (1 2 3) or (CH_2R or … or CH_10R in (1 2 3)) and (check start and end dates for seven consecutive days of olaparib and radiotherapy)
		then ELI_DLT=1 }

Safety Population	**TRT_RAD** **CD_1R (cumulative dose d1)** **TRT_OLA** **DS_1O (total daily dose)**	ELI_SAF=0 If (CD_1R > 0 or DS_10 >0) then ELI_SAF=1

CREATION OF A NEW INDICATOR VARIABLE
Patients who completed the DLT assessment period and received concomitantly at least seven consecutive days of Olaparib and radiotherapy treatment or who developed DLT are included in the analysis (ELI_DLT = 1)
Label: "DLT- assessable"
ELI_DLT=1 if the patient is assessable for DLT
ELI_DLT=0 otherwise

CREATION OF A NEW INDICATOR VARIABLE
Patients who received radiotherapy or olaparib, at least once, irrespective of the dose. (ELI_SAF = 1)
Label: "Safety Population"
ELI_SAF=1 if the patient is assessable for safety
ELI_SAF=0 otherwise

2.1.2 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.

2.2 ELIGIBILITY STATUS

2.2.1 INCLUSION CRITERIA

Criteria	eFORM variable	Control
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,	**ELIGFORM** **C1I** **PRE2TRT** **HIS_REV**	C1I=1 HIS_REV=1
2. Upper/Lower limb or trunk wall soft-tissue sarcoma,	**ELIGFORM** **C2I** **PRE2TRT** **HIS_DIA**	C2I=1 HIS_DIA in (1 2 3)
3. Age ≥ 18 years,	**ELIGFORM** **C3I** **INCFORM** **DT_CONS** **DT_BIRTH**	C3I=1 (DT_CONS-DT_BIRTH) GE 18
4. Locally advanced or locally recurrent inoperable tumor, outside any previously irradiated field (inoperable status must be assessed by staff including a surgeon specialized in sarcoma),	**ELIGFORM** **C4I** **PRE2TRT** **LOC_ADV** **LOC_INO**	C4I=1 (LOC_ADV =1 or LOC_INO=1)
5. Eastern Cooperative Oncology Group (ECOG), performance status ≤ 2,	**ELIGFORM** **C5I** **PRE1TRT** **ECOG_PTR**	C5I=1 ECOG_PTR in (0 1 2)
6. Life expectancy ≥ 6 months,	**ELIGFORM** **C6I**	C6I=1 Investigator decision
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,	**ELIGFORM** **C7I** **TUM_ASS** **NUM_LM** **MEA1L,...,MEA5L** (5 variables)	C7I=1 NUM_LM > = 1 and Depending on NUM_LM value (MEA1L and … and MEA5L) >= 10 + Investigator decision regarding irradiation and suitability for repeated measurements
8. Adequate hematological, renal, metabolic and hepatic	**ELIGFORM** **C8I** **PRE3TRT**	C8I=1 HEMO >= 9 NEUT >= 1.5 x 10^9

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	**HEMO** **NEUT** **PLAT** **BIL_TOT** **ALT** **AST** **CREA** **CCLE** **TP** **INR**	PLAT >= 100 x 10^9 CREA <= 150 or CCLE >=50
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, 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 10. Subjects of non-childbearing	**ELIGFORM** **C9I** **INCFORM** **FEM_STA** **DT_PREG** **RES_PREG** **FEM_REA** (non childbearing potential) **REA_OTH** **TRT_OLA** **DT_S1O** (D1 olaparib) **PRE3TRT** **CONT_PTR** (contraception) **SPE_CONT**	C9I=1 (FEM_STA =1 and RES_PREG=0 and (DT_S10-DT_PREG <= 28)) (CONT_PTR =1 and check SPE_CONT) If (FEM_STA =0) then Check FEM_REA and REA_OTH

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,	**ELIGFORM** **C10I**	C10I=1 Investigator decision
11. Voluntary signed and dated written informed consent prior to any specific procedure,	**ELIGFORM** **C1I** **INCFORM** **DT_CONS**	C11I=1 DT_CONS filled in
12. Patients with a French social security in compliance with the Law relating to biomedical research (Article L.1121-11 of French Public Health Code).	**ELIGFORM** **C12I**	C12I=1 Investigator decision

2.2.2 NON-INCLUSION CRITERIA

Criteria	eFORM variable	Control
1. Any previous treatment with a PARP inhibitor, including Olaparib,	**ELIGFORM** **C1NI** **PRE2TRT** **NAM_TRT** (chemo treatment)	C1NI=0 Check NAM_TRT Investigator decision
2. Patients unable to swallow orally administered medication and patients with	**ELIGFORM** **C2NI** **PRE1TRT**	C2NI=0 Check if (PAT1_PTR and … and PAT10PTR NE 3)

gastrointestinal disorders likely to interfere with absorption of the study medication,	**PAT1_PTR,...,PAT10PTR** (10 variables)	Investigator decision
3. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy,	**ELIGFORM** **C3NI** **PRE3TRT** **HIV**	C3NI=0 HIV=0 Investigator decision
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,	**ELIGFORM** **C4NI** **PRE3TRT** **HEP_B** **HEP_C**	C4NI=0 HEP_B=0 HEP_C=0
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,	**ELIGFORM** **C5NI** **PRE1TRT** **PAT1_PTR,...,PAT10PTR** (10 variables) Pathology codes : 1=Cardiovascular 9= psychiatric 15= Other	C5NI=0 Check if (PAT1_PTR and … and PAT10PTR not in (1 9 15)) + Investigator decision
6. Patients with uncontrolled seizures,	**ELIGFORM** **C6NI** **PRE1TRT** **PAT1_PTR,...,PAT10PTR** (10 variables) Pathology codes : 8=Neurological	C6NI=0 Check if (PAT1_PTR and … and PAT10PTR not in (8))
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,	**ELIGFORM** **C7NI** **INCFORM** **FEM_STA** **DT_PREG** **RES_PREG**	C7NI=0 (CONT_PTR =1 and check SPE_CONT) (FEM_STA =1 and RES_PREG=0)

	FEM_REA (non-childbearing potential) **REA_OTH** **TRT_OLA** **DT_S1O** (D1 Olaparib) **PRE3TRT** **CONT_PTR** (contraception) **SPE_CONT**	
8. No prior or concurrent malignant disease diagnosed or treated in the last 2 years, except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,	**ELIGFORM** **C8NI**	C8NI=0 Investigator decision
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),	**ELIGFORM** **C9NI** **PRE2TRT** **DT_LSEQ** **DT_ECHE** **TRT_OLA** **DT_S1O** (D1 Olaparib)	C9NI=0 (DT_S10-DT_LSEQ >2) and (DT_S10-DT_ECHE >2) + Investigator decision
10. Concomitant use of known CYP3A4 inhibitors such as ketokonazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir,	**ELIGFORM** **C10NI**	C10NI=0 Investigator decision
11. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome,	**ELIGFORM** **C11NI** **PRE1TRT** **ECG_PTR** **QT_PTR**	C11NI=0 (ECG_PTR=1 and QT_PTR < 470)
12. Blood transfusions within 14 days prior to study start,	**ELIGFORM** **C12NI**	C12NI=0 Investigator decision
13. Patients with myelodysplastic syndrome/acute myeloid leukaemia,	**ELIGFORM** **C13NI** **PRE1TRT** **PAT1_PTR,…,PAT10PTR** (10 variables) Pathology codes : 7 = Hemato-immunological	C13NI=0 Check if (PAT1_PTR and … and PAT10PTR not in (7))
14. Major surgery within 14 days of starting study treatment and patients must	**ELIGFORM** **C14NI** **PRE2TRT**	C14NI=0 (DT_S10-DT_SURG >14) and (DT_S10-DT_SURM >14)

have recovered from any effects of any major surgery,	**DT_SURG** **DT_SURM**	+ Investigator decision
15. Participation to a study involving a medical or therapeutic intervention in the last 30 days,	**ELIGFORM** **C15NI**	C15NI=0 Investigator decision
16. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,	**ELIGFORM** **C16NI**	C16NI=0 Investigator decision
17. Previous enrolment in the present study,	**ELIGFORM** **C17NI**	C17NI=0 Investigator decision
18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.	**ELIGFORM** **C18NI**	C18NI=0 Investigator decision

Criteria	eFORM variable	Control
Eligible Population	**ELIGIBILTY FORM** **C1I C2I C3I C4I C5I C6I C7I C8I C9I C10I C11I C12I** **C1NI C2NI C3NI C4NI C5NI C6NI C7NI C8NI C9NI C10NI C11NI C12NI C13NI C14NI C15NI C16NI C17NI C18NI**	**ELI=1** **If (C1I=0 OR C2I=0 OR C3I=0 OR C4I=0 OR C5I=0 OR C6I=0 OR C7I=0 OR C8I=0 OR C9I=0 OR C10I=0 OR C11I=0 OR C12I=0 OR C1NI=1 OR C2NI=1 OR C3NI=1 OR C4NI=1 OR C5NI=1 OR C6NI=1 OR C7NI=1 OR C8NI=1 OR C9NI=1 OR C10NI=1 OR C11NI=1 OR C12NI=1 OR C13NI=1 OR C14NI=1 OR C15NI OR C16NI=1 OR C17NI=1 OR C18NI=1) then ELI=0**

CREATION OF A NEW INDICATOR VARIABLE

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

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

3 STATISTICAL METHODS

3.1 STATISTICAL ANALYSIS

3.1.1 DOSE ESCALATION AND EXPANSION COHORT PART

- 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 endpints will be reported in terms of counts and proportions for each dose levels.
- 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.

3.1.2 PHARMOCOKINETICS AND PHARMACODYNAMICS

- 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.

3.2 ENDPOINT ANALYSIS

3.2.1 PRIMARY ENDPOINT

3.2.1.1 DOSE ESCALATION PART

- 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.

Criteria	eFORM variable	Control
Toxicity	EXA_RAD **TOXI_RA** EXA_ON **TOXI_ON** AEV4 **AEVENT,** **AEECI** (clinically interesting), **DT_EIC, SOC, AESAE** **DT_SAE , DT_AE,** **DTENDAE** (date of the end or death), **INIT_INT, MAX_INT**	Check if the following variables are completed : TOXI_RA TOXI_ON AEVENT AEECI DT_EIC SOC AESAE DT_SAE , DT_AE DTENDAE INIT_INT, MAX_INT Data will be gathered in tables summarizing toxicities and side effects for each dose level and cycle.
Incidence rate of DLT	EXA_RAD **DLT_RA** EXA_ON **DLT_ON** DS_TOX **DS_C1OL** (dose Olaparib) **DT_TOX** (Date tox)	Check if the following variables are completed : DLT_RA DLT_ON DS_C1OL DT_TOX

3.2.1.2 EXPANSION COHORT

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).

For the expansion cohort, radiological data will be centrally reviewed. The primary analysis will be based on reviewed data.

Criteria	eFORM variable	Control
6-month non progression	**TUM_CYC (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2, SD=3 **TRT_OLA** **DT_S1O** (D1 Olaparib)	**DT_S10** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) and check **recist1.1 criteria** check for each patient ((**DT_MEAC-DT_SI10≥6**) and **OV_RESP**=(1 or 2 or 3)) Count number of non-progression case

3.2.2 SECONDARY ENDPOINT

3.2.2.1 DOSE ESCALATION PART

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.

Criteria	eFORM variable	Control
6-month non progression	**TUM_CYC (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2, SD=3 **TRT_OLA** **DT_S1O** (D1 Olaparib)	**DT_S10** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) and check **recist1.1 criteria** check for each patient ((**DT_MEAC-DT_SI10≥6**) and **OV_RESP**=(1 or 2 or 3)) Check confirmation ≥ 4 weeks Count number of non-progression case

6-month objective response	**TUM_CYC (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2 **TRT_OLA** **DT_S1O** (D1 Olaparib)	**DT_S10** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) and check **recist1.1 criteria** check for each patient ((**DT_MEAC-DT_SI10≥6**) and **OV_RESP**=(1 or 2)) Check confirmation ≥ 4 weeks Count number of objective case
Best objective response	**TUM_CYC (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2 **TRT_OLA** **DT_S1O** (D1 Olaparib)	**DT_S10** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) and check **recist1.1 criteria** check the response for each patient across all time points **OV_RESP**=(1 or 2) Check confirmation ≥ 4 weeks
Best response	**TUM_CYC (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) **TRT_OLA** **DT_S1O** (D1 Olaparib)	**DT_S10** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) and check **recist1.1 criteria** check the response for each patient across all time points **OV_RESP**=(1 or 2 or 3) Check confirmation ≥ 4 weeks Data will be gathered in tables summarizing number of CR, PR, SD, PD

Progression-free survival (PFS)	**END OF TREATMENT FORM**
	DT_STA (Date of start of Olaparib)
	EOT_STA (Status)
	EOT_REA (Reason end)
	DT_PROG (Date of progression)
	END OF STUDY (END_STU)
		Check if everything is filled in and
		If (DT_PROG is NA) then
		{
		If (PRO_LAS=0) then {
		PFS= DT_EOS-DT_STA ;
		If (EOS_REA ='death') then
		IND_PFS=1

	DT_EOS (date of end of study) **FOLLOW UP FORM** **DT_FUP** (date of visit) **STA_FUP** (Vital status) **PRO_LAS, DT_FPRO** (date of progression) **DT_LNEW** **DT_DEAT** **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **EOS_REA** (reason)	**Else IND_PFS=0** **}** **Else {** **PFS=DT_FPRO – DT_STA;** **IND_PFS=1}** **}** **Else {** **PFS= DT_PROG – DT_STA;** **IND_PFS=1}**
Overall Survival (OS)	**END OF TREATMENT** **DT_STA** (Date of start of Olaparib) **EOT_STA** (Status) **EOT_REA** (Reason end) **FOLLOW UP FORM** **DT_LNEW** / **DT_DEAT** **STA_FUP** (Vital status) **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **EOS_REA** (reason) **DT_DEATH** (date of death)	**If (STA_FUP NE 'dead') then do;** **if (EOS_REA='death') then {** **OS= DT_DEATH-DT_STA;** **IND_OS=1;** **}** **Else {OS= DT_EOS-DT_STA;** **IND_OS=0;** **}** **end;** **Else { OS= DT_DEAT-DT_STA;** **IND_OS=1; }**
Functional assessment	**EXA_RAD** **MSTS_RA** (msts score)	Check if MSTS_RA is completed by the radiotherapist at baseline and at the end of radiotherapy treatment.

3.2.2.2 EXPANSION COHORT

- 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.

The previous criteria will be analyzed in the same way as for the dose escalation part (see section 3.2.2.1).

3.3 ADDITIONAL ANALYSIS

In addition to the above endpoints, further analyses will be conducted to assess the potential impact of COVID-19 on patient care.

Criteria	eFORM variable	Control
Covid-19 infection	**COV_INF INF_COV**	**INF_COV EQ 1**

The number of patients infected with covid-19 will be reported. In case of high numbers, the previous endpoints could be evaluated among the population of infected patients for comparison (no formal test).

4 APPENDICES

4.1 LIST OF DATALISTING

4.1.1 INCLUSION FORM

Datalisting 1.1. Demographic characteristics: patient's number, patient's code, investigator center, date of birth, date of inclusion, sex, signed and dated written informed consent, dose level

Datalisting 1.2. Major and minor protocol deviations by patient

4.1.2 DRUG DELIVERY

Datalisting 2.1. Treatment up-to-date: treatment continuation, dose modification.

Datalisting 2.2. Olaparib: start date 1, stop date 1, start date 2, stop date 2, therapy change 2 , reason for change 2, start date 3, stop date 3, therapy change 3 , reason for change 3, start date 4, stop date 4, therapy change 4 , reason for change 4, start date 5, stop date 5, therapy change 5 , reason for change 5

Datalisting 2.3. Radiotherapy : start and end dates, cumulative dose, number of fractions, therapy change

4.1.3 DOSE-LIMITING TOXICITY

Datalisting 3.1. Date of Cycle 1 Day 1, Dose of Olaparib, Date of last intake, Date of the event, imputability, grade, another DLT

4.1.4 END OF TREATMENT

Datalisting 4.1. End of treatment: start and end dates of treatment, status, reason for the end of the treatment, date of progression, type of progression

4.1.5 ADVERSE EVENT (if required)

Datalisting 5.1. Adverse event, date of event, SOC, initial intensity, maximum intensity, treatment modification, imputability, date of the end or death, treatment introduced, concomitant treatment

4.1.6 SERIOUS ADVERSE EVENT

Datalisting 6.1. Serious adverse event, date of event, SAE start date, SOC, initial intensity, maximum intensity, treatment modification, imputability, date of the end or death, treatment introduced, concomitant treatment

4.1.7 END OF STUDY

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- Table 9.6. Grade 4 neutropenia (absolute neutrophil count < 500) lasting ≥ 7 days by dose level
- Table 9.7. Grade 4 thrombocytopenia or bleeding requiring a platelet transfusion by dose level
- Table 9.8. Any other grade ≥ 4 by dose level
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4.2.10 SAFETY: ADVERSE EVENTS

- Table 10.1 Adverse events by patient
    - Table 10.1.1 : Number of patient with at least one AE
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- Table 10.2 Adverse events by term
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4.2.11 EFFICACY: Response, Progression and Survival

- Table 14.1. Frequency distribution of objective response on population evaluable for efficacy
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4.3 LIST OF FIGURES