Ensemble, prenons le cancer de vitesse.

EUDRACT Number : 2016-001837-28

IC 2016-01

RadioPARP

A Phase I of Olaparib With Radiation Therapy in Patients With Inflammatory, Loco-regionally Advanced, or Metastatic TNBC (triple negative breast cancer) or Patient with Operated TNBC with Residual Disease.

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APPROVAL AND RESPONSABILITIES

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SYNOPSIS – PROTOCOL N° IC 2016-01

RadioPARP

A) CLINICAL TRIAL IDENTIFICATION	
Protocol number: IC 2016-01 **Version and date:** Version 4.0 du 31.07.2019	
Title of the trial: A Phase I of Olaparib with Radiation Therapy in Patients With Inflammatory, Loco-regionally Advanced or Metastatic TNBC (triple negative breast cancer) or Patient With Operated TNBC with Residual Disease.	
Running title: RadioPARP	
Coordinator: Dr. Youlia KIROVA	
Estimated number of centers: 1	**Number of patients:** 24

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C) GENERAL TRIAL INFORMATION
Indication: Triple negative inflammatory, loco-regional advanced or metastatic breast cancer either inoperable after neoadjuvant chemotherapy or operated patient with residual disease (after neoadjuvant chemotherapy).
Methodology: Open label phase I, dose escalation trial
Primary objective of the study: To determine the Maximal Tolerated Dose of Olaparib administered with concurrent loco regional radiotherapy in patients who have triple negative inflammatory, loco-regional advanced or metastatic breast cancer either inoperable after neoadjuvant chemotherapy or operated patient with residual disease (after neoadjuvant chemotherapy).

Secondary objectives:

- To assess the safety profile of Olaparib administered with concurrent radiotherapy.

- To evaluate Olaparib administered with concurrent loco regional radiotherapy efficacy profile
  - To evaluate the Objective Response Rate (ORR) and the complete Response Rate
  - To evaluate Pathological Response Rate (pRR) after salvage surgery
  - To evaluate the loco-regional Progression Free Survival (l-PFS)

- To evaluate patient outcome :
  - To evaluate the Progression Free Survival (PFS) or Disease Free Survival (DFS) according to stage of disease
  - To evaluate distant relapse rate
  - To evaluate Overall Survival (OS).
  - To evaluate disease specific survival rate.

- To explore biomarkers of Olaparib activity in combination with concurrent radiotherapy.

Inclusion criteria:

1. **Woman aged >18 years.**

2. **Histologically confirmed triple negative breast cancer with loco-regional radiotherapy indication :**

   a) **Non-operated with either:**

   1) Inflammatory breast cancer in progression during neoadjuvant chemotherapy or inoperable after neoadjuvant chemotherapy.

   2) Loco-regional advanced breast cancer in progression during neoadjuvant chemotherapy or inoperable after neoadjuvant chemotherapy (T ≥ 3 and/or N ≥ 1; with evaluable disease according to RECIST 1.1 criteria).

   3) Non operable metastatic breast cancer (all T, all N, M1; with evaluable disease according to RECIST 1.1 criteria) needing local and regional treatment in case of good metastatic control after chemotherapy.

   b) **Or patient operated after neoadjuvant treatment and surgery with residual disease (non-pCR and/or pN+ disease).**

3. **Neoadjuvant chemotherapy** (containing anthracyclines or taxanes or the combination of both or containing platinum-based chemotherapy) **willingness to discontinue any cytotoxic chemotherapeutic agents, immunotherapy, and targeted therapies at least two weeks prior to start of Olaparib.**

4. **ECOG performance status < 2** (cf. Appendix 2)**.**

5. **Life expectancy greater than 6 months.**

6. **Adequate hematologic, renal and hepatic function** (assessed within the two weeks prior to inclusion and within the month prior to the commencement of protocol treatment). **For patients who have stopped chemotherapy two weeks prior to protocol treatment, hematologic function re-assessment in the 1 or 2 days before the first Olaparib intake.**

   a) Haemoglobin ≥ 10.0 g/dL.

   b) Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L.

   c) White Blood Cells (WBC) > 3 x 10^9/L.

   d) Platelet count ≥ 100 x 10^9/L.

   e) Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (except in case of Gilbert syndrome).

   f) AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5 x ULN.

   g) Patients must have Creatinine Clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min:

   $$\text{Estimated Creatinine Clearance} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times (F)^a}{\text{serum creatinine (mg/dL)} \times 72}$$

   [a] : where F=0.85 for females and F=1 for males.

7. **Urine or serum negative pregnancy test** within two weeks prior to inclusion. Negative pregnancy test confirmed within 1 or 2 days prior to first Olaparib intake.

8. For woman with child-bearing potential, **an efficacious contraception** following sponsor recommendations used during the whole treatment period and up to three months after the last Olaparib administration (cf. Appendix 4).

9. **Ability to swallow and retain oral medications without gastrointestinal disorders likely to interfere with absorption of the study medication.**

10. **Affiliation to the French Social Security System.**

11. **Ability to understand and the willingness to sign a written informed consent document.**

Exclusion criteria:

1. **Radiation therapy:** prior history of radiation therapy to the ipsilateral breast and/or regional nodes (except prior radiation therapy to other sites).

2. **Patient with unresolved or unstable, NCI-CTCAE v4.03 Grade 3 or greater toxicity**

from prior administration of prior anti-cancer treatment (cf. Appendix 3).

3. Patient with clinically and uncontrolled **significant comorbidity**: major cardiac, respiratory, renal, hepatic, gastrointestinal, hematologic or neurological/psychiatric disease or disorder, including but not limited to: active uncontrolled infection; symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia; any other illness condition(s) that could exacerbate potential toxicities, require excluded therapy for management, or limit compliance with study requirements.

4. Patient with second primary cancer, except : adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for ≥ 5 years.

5. Concomitant anti-neoplasic treatment during protocol treatment and not completed at least 2 weeks prior to Olaparib initiation, except bisphosphonates and RANK inhibitors without restriction even during protocol treatment as long as these where started at least 4 weeks prior to study treatment initiation.

6. Any previous treatment with a PARP inhibitor, including Olaparib.

7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Olaparib.

8. Patient being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itroconazole, Voriconazole, Ritinavir, Telithromycin) **within the last 7 days before first Olaparib intake.**

9. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome (cf. Appendix 5).

10. Blood transfusions within 14 days prior to treatment start.

11. Patient with myelodysplastic syndrome / acute myeloid leukaemia.

12. Pregnant or breastfeeding woman.

13. Patient already included in another clinical trial with an investigational drug.

14. Patient individually deprived of liberty or placed under the authority of a tutor.

15. Patient with any **psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol** and follow-up schedule.

Primary endpoint of the study:

To determine the incidence of early DLTs (early adverse effects related to Olaparib administered with concurrent radiotherapy) and to determine the Maximal Tolerated Dose (MTD) of Olaparib administered with concurrent loco regional radiotherapy.

Secondary endpoints of the study:

- Safety profile will be assessed using :
  - Incidence of SAEs
  - Incidence and severity of AEs, graded according to NCI-CTCAE version 4.03 criteria
  - Incidence and severity of laboratory abnormalities, graded according to NCI-CTCAE version 4.03 criteria
  - Incidence of acute toxicity (e.g.; radio dermatitis, pain, dyspnea, dysphagia, pericarditis) 2 weeks and 6 weeks after the end of radiotherapy
  - Incidence of late toxicity (e.g.; fibrosis, necrosis, pain, telangiectasia, arm lymphedema, paresis, cardiovascular events, dyspnea, dysphagia) at 1 year and at 2 years as of initiation of radiation therapy
  - Incidence of treatment discontinuations and treatment modifications due to AEs
- Efficacy profile will be assessed using :
  - Objective Response Rate (ORR) and Complete Response (CR) by imaging according to RECIST 1.1 criteria and Tumor Volume estimation (Lenght×Width×Depth) (WHO criteria).
  - Pathological Response Rate (pRR) after salvage surgery according to Symmans *et al* to determine the Residual Cancer Burden (JCO, 2007).
  - Loco-regional Progression Free Survival (lPFS) at one year, defined as the time between any loco-regional recurrence (either at the site of the primary tumor and/or lymph nodes) and patient inclusion date.
- Patient outcome will be assessed using :
  - Progression free survival (PFS) or Disease Free Survival (DFS) (according to disease staging) rate at one year, defined as the time from patient inclusion to the first radiologic confirmation of disease progression or death from any cause, whichever comes first.
  - Distant relapse rate at one year.
  - Overall Survival (OS) defined as the time from patient inclusion to death from any cause.
  - Disease specific survival rate one year and two years defined as the time from patient inclusion to death from her breast cancer.
- Exploration of biomarkers of Olaparib associated with radiotherapy on biopsies (angiogenesis assay, PARP-1 expression, Large-scale State Transitions score, immune cells biomarkers such as CD8, FOXP3, CD68, PD1-PDL1, and other markers of macrophages). The somatic and germline status of BRCA1 and BRCA2 will be also determined.

- Evaluation and banking of the Residual Cancer Burden.

D) DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

Drug:

Drug Name (IDN)	Commercial Name	Pharmaceutical Form	Administration Route	Posology (mg BID)
Olaparib	Lynparza®	Tablets	P.O.	Dose escalation : 25, **50***, 100, 150, 200 bid.

Associated treament: 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT)

Therapeutic scheme:

Olaparib (oral administration) will be administered at a **starting dose of 50 mg bid**. The other dose levels will be: 100 mg bid, 150 mg bid, 200 mg bid. The 25 mg bid dose will be included in the model to deal with unexpected high toxicity of the starting dose.

Seven days prior to their first fraction of radiation therapy, patients will begin taking Olaparib at the assigned dose twice daily each day. All patients will receive radiotherapy on day 8 after the start of Olaparib as following:

In case of mastectomy or preoperative irradiation :

- 50 Gy to the whole breast in 25 daily fractions and 5 weeks.
- 50 Gy to the supra/infra-clavicular areas in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the internal mammary chain in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the axillary areas in 25 daily fractions and 5 weeks according to the center guidelines.

In case of breast conserving surgery:

- 50.4 Gy to the whole breast in 28 daily fractions and 5.6 weeks.
- 63 Gy to the tumor bed boost area in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the supra/infra-clavicular areas in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the internal mammary chain in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the axillary areas in 28 daily fractions and 5.6 weeks according to the center guidelines.

Treatment duration:

Olaparib will be administered one week before and during breast radiation (5 to 6 weeks).
Total treatment duration will be: 6 to 7 weeks.

Definition of Dose Limiting Toxicities (DLTs): Dose limiting toxicity definition includes any Grade ≥ 3 adverse event (AE) scored by the NCI-CTCAE v.4.03, which is related to Olaparib and/or radiation therapy.

- **DLT definition**

- Grade 3 dermatitis at irradiation dose < 40Gy
- Grade 4 dermatitis at irradiation dose < 50Gy
- Grade 3 or 4 dermatitis present 6 weeks or more after the end of treatment
- Grade 3 pain due to dermatitis present 6 weeks or more after the end of treatment
- Grade 3 breast edema in presence of maximal support/treatment.
- Grade 3 or 4 esophagitis.
- Soft tissue necrosis.
- Febrile neutropenia (grade 3/4 neutropenia associated with >38.3 fever).
- Grade 4 neutropenia lasting more than 7 days.
- Grade 4 thrombocytopenia or grade 3 with bleeding.
- Grade 3 or 4 anaemia in presence of maximal support/treatment.
- Grade 3 or 4 nausea in presence of maximal support/treatment.
- Grade 3 or 4 vomiting in presence of maximal support/treatment.
- Grade 3 or 4 diarrhea in presence of maximal support/treatment.
- Any other grade 3/4 non hematological adverse events except non-clinically significant lab abnormalities (i.e. GGT increase)
- Inability to receive more than 4 weeks of Olaparib.
- Radiotherapy discontinuation, for toxicity reasons, longer than 7 successive radiotherapy fractions.

However, dysphagia and skin disorders grade 2 or 3 are part of the well-known safety profile observed in relationship to locoregional radiotherapy. Therefore, only unusual severity and precocity may be considered as early DLT.

Local adverse events of unusual duration whatever the severity may be also considered as dose limiting toxicity after evaluation of its clinical course and unusual outcome.

Any other toxicity that the investigator or the sponsor medical expert deems to be dose-limiting, regardless of the grade, may be considered as a DLT.

Early DLT assessment period will end, for every patient, 6 weeks after the last radiation fraction.

Study treatment must be withheld for any patient who experiences an early DLT.
Study treatment may be resumed at fewer radiation fractions after the toxicity has resolved to acceptable grade or baseline level, following discussion between the investigator and the sponsor.
Radiotherapy fraction treatment may be delayed to permit resolution of any product/radiation-related toxicity.

E) STATISTICAL ANALYSIS
Phase I dose-finding based on toxicity will be conducted in a sequential and adaptive Bayesian scheme, using the method of Time-to-event Continual Reassessment Method **[15-16]** to determine the Maximum Tolerated Dose (MTD) of Olaparib associated with radiotherapy. The primary endpoint is Dose-Limiting Toxicity (DLT) occurring during the treatment and until 6 weeks after the end of the radiotherapy. Dose allocation will be centrally defined, based on DLT observed in all patients previously evaluated, by modeling the probability of DLT. An empiric model will be used for the dose-toxicity relationship. No intra-patient dose-escalation is permitted. No dose skipping in escalation is permitted. The MTD is defined as the dose associated with a probability of DLT the closest, but inferior or equal, to 25%. As the expected number of patients to be enrolled per month is equal to 2, this method allows the inclusion of patients continuously without stopping inclusions. It allows taking into account the full information available regarding patients included without waiting 6 weeks after the end of the radiotherapy. This method will shorten the duration of the trial **[15-16]**. A safety period of three weeks is requested between two consecutive patients of the first cohort (i.e. the first three patients) at each new explored dose level. Four dose levels are considered (50mg bid, 100mg bid, 150mg bid and 200mg bid daily). For a safety reason, a dose level of 25mg bid (dose level -1) is included in case that the first dose level at 50mg bid is found to be toxic. Cohort of size 3 is used with the TITE-CRM design. So, three patients will be included at the first dose level (50mg bid daily). At least three patients fully observed are required at a given dose level before dose escalation following the TITE-CRM method. Every new patient will be treated at the best current recommended dose proceed (50mg bid, 100mg bid, 150mg bid and 200mg bid daily), i.e. the dose associated with an estimated level of toxicity that is judged acceptable (the highest dose with a DLT probability ≤25% DLT). Given the number of pre-specified dose levels in the study, it is planned to include a maximum of 30 patients if no stopping rule is reached earlier. A stopping rule will advise the dose escalation termination in case of a high probability (>90%) for the next 6 patients to be assigned to the same dose level, *O'Quigley and Reiner (1998).* The sample size in TITE-CRM Phase I studies is fixed in advance. There are no explicit rules built into the approach. TITE-CRM trials generally recruit between 24 and 36 participants (*Daniel Normolle JCO 2006*). Simulation studies demonstrated that 30 patients lead to good operating characteristics of the method in terms of correct selection of the MTD.

F) TRIAL DURATION
Inclusion period: 36 months
Treatment and follow-up period: 3 months
Estimated Total trial duration: 39 months

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Glossary of Abbreviations

AE	Adverse Events
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic-Pyruvic Transaminase)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ANI	Poly(ADP-ribose) polymerase (PARP) inhibitor 4-amino-1,8-naphthalimide
ANSM	Agence Nationale du Médicament (French competent authority for clinical trials)
APTT	Activated Partial Thromboplastin Time
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BID	Bis in die (*latin*) (twice daily each day)
CPP	Committee for the Protection of Persons (French Ethic Commitee)
CR	Complete Response
CRA	Clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450, Family 3, Subfamily A, member 4
DFS	Disease Free Survival
dfcrm	Dose-finding by the continual reassessment method
DLT	Dose Limiting Toxicity
DNA	Deoxiribonucleic Acid
DSB	Double Stand Break (DNA)
EC	Ethic Committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EE	Elston and Ellis
EMA	European Medicines Agency
ER	Estrogen Receptor
E-SAE	Expected Serious Adverse Event
FCPRCC	Federation of the Patient Committees for Clinical Research in Cancerology
FISH	Fluorescence in situ hybridisation
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
G-CSF	Granulocyte colony-stimulating factor
Hb	Hemoglobin
Hct	Haematocrit
HDPE	High-density polyethylene
HR	Homologous recombination
HRD	Homologous recombination deficiencies
IB	Investigator's Brochure

IDN	International Drug Name
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiotherapy
INR	International Normalized Ratio
l-PFS	Loco-regional Progression Free Survival
LH	Luteinizing hormone
LMWH	Low Molecular Weight Heparin
LNCC	National League for Treating Cancer
LST	Large-scale State Transition
MDS	Myelodysplastic syndrome
MTD	Maximal Tolerated Dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PARP	The poly(adenosine diphosphate [ADP]–ribose) polymerase
PFS	Progression Free Survival
PgR	Progesterone Receptor
pRR	Pathological Response Rate
PCS	Probability of Correction Selection
pCR	Pathological Complete Response
pCR	PostChemoRadiotherapy
RECIST	Response Evaluation Criteria in Solid Tumors
RI	Reticulocyte Index
RT	Radiotherapy
SAE	Serious Adverse Event
SIB	Simultaneous Integrated Boost
SSB	Double Stand Break (DNA)
SUSAR	Unexpected Serious Adverse Events
TITE-CRM	Time-to-event Continual Reassessment Method
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Triple negative breast cancer and its treatment

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women. In Europe, the estimated age adjusted annual incidence in 2008 was 88.4/ 100 000 and the mortality 24.3/100 000 **[1]**. TNBC is a particular subset of breast cancer defined by lack or low immunohistochemical expression of ER (Estrogen Receptor) and PgR (Progesterone Receptor) and HER2 negative status (IHC 0, 1+ or 2+ /FISH non-amplified) and represents approximately 12-17% of breast cancer overall **[2]**. Although it is a heterogeneous group, patients with TNBC have generally poor prognosis. The fundamental clinical characteristic of TNBC is early recurrence with likely early visceral metastases, as well as shorter period from time to recurrence to death as compared with other breast cancer types **[3]**. In addition to surgery and radiotherapy, chemotherapy remains the ultimate treatment option for those patients with varied impact on long-term prognosis. No targeted treatment has been developed for TNBC, in contrast to endocrine treatment and anti-HER2 treatments, which have significantly improved the clinical outcomes in ER/PgR positive and HER2 positive breast cancer patients, respectively. Patient with no response to neoadjuvant chemotherapy have very poor outcome **[22]**. In a curative strategy, after failure of neoadjuvant chemotherapy for patients with locally advanced breast cancer or inflammatory breast cancer, currently for all non-operable patients with metastatic locally advanced or inflammatory breast cancer, the treatment option is association of radiotherapy with or without chemotherapy, this therapeutic option is used also in case of patients with poor response (residual disease in the breast and the lymph nodes) **[23]**.

A new strategy with preoperative radiotherapy in combination with new drugs could increase breast conservation approach and could improve locoregional outcome. For patients with triple negative metastatic breast cancer in progression after initial treatment, radiotherapy in combination with new drugs could also increase breast conservation approach and could improve locoregional outcome.

Targeted therapy with Olaparib for *BRCA* mutation positive breast cancer

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. 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). Tumours with HR deficiencies (HRD), such as serous ovarian cancers and breast cancer, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, Olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. 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 anticancer agents.

Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to Olaparib treatment.

Cellular DNA is continually subject to damage, which coordinated pathways act to repair, thereby maintaining genomic integrity and cell survival **[1-3]**. The poly(adenosine diphosphate [ADP]–ribose) polymerases (PARPs) are a large family of multifunctional enzymes, the most abundant of which is PARP1. It plays a key role in the repair of DNA single-strand breaks through the repair of base excisions **[4-5]**. The inhibition of PARPs leads to the accumulation of DNA single-strand breaks, which can lead to DNA double-strand breaks at replication forks. Normally, these breaks are repaired by means of the error-free homologous-recombination double-stranded DNA repair pathway, key components of which are the tumor-suppressor proteins BRCA1 and BRCA2. PARP inhibitors such as Olaparib show promising results in clinical trials, especially in triple negative breast (or ovarian cancer) with BRCA mutations **[4]**.

PARP inhibitors activity in triple negative breast cancer (TNBC) without *BRCA* mutation

The challenges of TNBC are in fact more fundamental than insensitivity to current available therapeutics. TNBC shares clinical and pathological features with hereditary BRCA1-related breast cancers, and in sporadic TNBC; dysregulation of BRCA1 has been frequently observed together with other defects in homologous recombination pathways **[5]**. Preclinical studies have shown that breast cancer cell lines with a triple-negative phenotype are more sensitive to PARP1 inhibitors compared with non-TNBC cells, and that PARP inhibition synergizes with gemcitabine and cisplatin in triple-negative cells but not in luminal cancers **[6]**. All these lines of evidence provide a strong rationale for developing a new therapeutic approach to TNBC based on targeting the DNA-repair defects via PARP inhibition in these cancers that the most aggressive are the inflammatory, loco-regional advanced and metastatic breast cancer.

1.2 Research hypothesis

For patients with inoperable triple negative inflammatory, locally advanced breast cancer or metastatic breast cancer, there is a lack of systemic therapy to combine with radiotherapy in order to control the loco-regional disease. A new strategy with preoperative radiotherapy in combination with new drugs could increase breast conservation approach and could improve loco regional outcome.

For patients with triple negative inflammatory, loco-regional advanced or metastatic breast cancer operated with residual disease (after neoadjuvant chemotherapy), a new strategy with postoperative radiotherapy in combination with new drugs could improve loco regional outcome.

1.3 Rational for the study

One of the unique aspects of this research is the radiosensitization by Olaparib in triple negative breast cancer.

The aim of the proposed phase I study is to determine the Maximal Tolerated Dose of Olaparib monotherapy administered with concurrent locoregional radiotherapy in patients who have triple negative inflammatory, loco-regional advanced or metastatic breast cancer, inoperable after neoadjuvant chemotherapy or with residual disease after surgery and neoadjuvant chemotherapy.

Mechanisms of radiosensitization by Olaparib

- Molecular mechanism: increase of double strand breaks :

  DNA is the principal target for the biologic effects of radiation. For radiotherapy, this comprises single strand breaks (SSB) and double-strand breaks (DSB). SSB are not directly cytotoxic but during DNA replication may generate potentially lethal DSB by collapse of stalled replication forks **[7]**. Radiation-induced SSB are primarily repaired by base excision repair, of which poly (ADP-ribose) polymerase-1 (PARP-1) is a key component. PARP-1 binds to SSB, activating poly ADP-ribosylation of itself and other proteins, triggering recruitment of repair factors and release of PARP-1 from the damaged site. PARP inhibitors inhibit SSB repair and the unrepaired SSB generate collapsed replication forks which give rise to potentially lethal DSB, leading to radio sensitization **[8]**.

- Cellular mechanism: radiosensitization during the S phase :

  Experiments using synchronized HeLa cells showed that radiosensitization induced by PARP inhibition is specific of the S phase of the cell cycle and involves stalled replication forks **[9]**. Under these conditions, prolonged contact with ANI ended in the formation of de novo DNA double-strand breaks hours after irradiation, evoking collision with uncontrolled replication forks of DNA lesions whose repair was impaired by inhibition of the PARP catalytic activity. The data suggest that increased response to radiotherapy by PARP inhibitors may be achieved only in rapidly growing tumors with a high S-phase content.

- Tissular mechanism: vasoactive effects contributing to tumor reoxygenation :

  Recently, at least 2 new generation PARP inhibitors (AG014699 and AG14361) have been reported to have vasoactive properties, and AG14361 has been shown to enhance the response to radiation **[10-11]**. The new generation PARP inhibitors, including Olaparib, are all structurally related to nicotinamide which can prevent intermittent vascular shutdown in

tumors. Senra *et al.* showed in preclinical studies that Olaparib is a more potent vasorelaxant than nicotinamide, and its effects are maintained during treatment with drug alone and when drug and radiation are combined in a fractionated treatment schedule **[12]**.

Results of in vivo studies of Olaparib with concurrent radiotherapy in triple negative breast cancer xenografts

Results from Inserm U612 have shown that Olaparib radiosensitizes TNBC models **[13]**. The BRCA2-/- HBCx-17 and the wild-type HBCx-12A xenografts were subcutaneously transplanted into the flanks of nude mice. In both TNBC models, individual group comparisons showed that treatment with 4-[(3-[(4-cyclopropylcarbonyl)piperazin-4-yl]carbonyl)-4-fluorophenyl]methyl(2H)phthalazin-1 alone for 4 weeks markedly inhibited tumor growth compared with the untreated controls. Treatment with radiotherapy alone also resulted in significant growth inhibition whereas combination of 4-[(3-[(4-cyclopropylcarbonyl)piperazin-4-yl]carbonyl)-4-fluorophenyl]methyl(2H)phthalazin-1and radiotherapy showed the best treatment response.

Today, no targeted therapy in combination with breast radiotherapy has shown an improvement of loco-regional control and there is no data about the benefit/risk of Olaparib in combination with breast radiotherapy [14].

Based on the above mentioned rationale, the goal of this study is to evaluate the impact of the PARP inhibitor Olaparib concurrently with radiotherapy in toxicities in patients who have triple negative inflammatory, loco-regional advanced or metastatic breast cancer inoperable after neoadjuvant chemotherapy or operated with residual disease after surgery and neoadjuvant chemotherapy.

1.4 Rational for ancillary studies

1.4.1 BRCAness:

This phase I clinical trial is testing the safety and efficacy of combining Olaparib and radiotherapy in loco-regional advanced, inflammatory, or metastatic TNBC. Efficacy of Olaparib has been associated with the alteration of the main and most faithful pathway to repair DNA double strand breaks: the homologous recombination (HR) pathway. The most frequent genetic alteration leading to HR deficiency (HRD) is the inactivation of BRCA1 by germinal or somatic mutations (~14% of TNBC) or methylation of the promoter (~11% of TNBC) **[17]**, and more rarely by BRCA2 inactivation, RAD51C methylation or others. It should be noticed that while HRD is frequent but far from constant in TNBC (~50% of cases). This may explain some negative results in unselected TNBC for PARPi sensitivity. However, our results as well as others indicate that responses of therapies targeting HRD (platinum) may vary according to the causes of HRD: putatively better responses for cases with genetic alterations than with epigenetic inactivation **[17]**.

Considering the importance and difficulties for a robust genetic detection of HRD in tumors, surrogate markers are searched, such as genomic instability measured from tumor genomic profiling. Several teams including ours have demonstrated that TNBCs and serous ovarian carcinomas with BRCA1/2 or RAD51C inactivation exhibit an increased number of large-scale structural chromosomal alterations. To detect tumors with HRD we have suggested the number of LSTs (Large-scale State Transitions), which referred to the number of large-scale chromosomal breaks in tumor genomic profile, evaluated after smoothing and filtering small-scale alterations **[18]**. LST score displayed excellent performance on TNBC cohort reaching almost 100% in sensitivity and specificity. We propose to define the HR status for at maximum the 30 tumors included in this trial by the LST genomic signature.

1.4.2 Other analyses on biopsies and mastectomy samples

Other explorations of biomarkers of Olaparib associated with radiotherapy on biopsies (angiogenesis assay, immune cells biomarkers such as CD8, FOXP3, CD68, PD1-PDL1, and other markers of macrophages) will be investigated.
Tissue samples will be fixed in 10% formalin and routinely processed for paraffin embedding. Histologic sections cut with 4-µm thickness will be stained with hematoxylin, eosin, and safran.
Tumors will be classified according to the method of the World Health Organization (WHO) for carcinomas of the breast, and tumor grading will be done in accordance with Elston and Ellis (EE) grading system.
Immunohistochemistry will be performed on 4-µm paraffin-embedded sections with an indirect immunoperoxidase method, using antibodies directed against CD31 protein, and CD105 protein.
The number of vessels staining positively for CD31 or CD105 will be counted on 10 consecutive fields at ×400 magnification in the area with carcinoma invasion. Vessels with a clearly defined lumen or well-defined linear vessel shape, but not single endothelial cells, will be considered for microvessel assessment.

These analyses are related to the every patient's situation (neo adjuvant or adjuvant setting).

2. OBJECTIVES

2.1 Primary objective

To determine the Maximal Tolerated Dose of Olaparib administered with concurrent loco regional radiotherapy in patients who have triple negative inflammatory, loco-regional advanced or metastatic breast cancer either inoperable after neoadjuvant chemotherapy or operated patient with residual disease (after neoadjuvant chemotherapy).

2.2 Secondary objectives

- To assess the safety profile of Olaparib administered with concurrent radiotherapy.

- To evaluate Olaparib administered with concurrent loco regional radiotherapy efficacy profile
    - To evaluate the Objective Response Rate (ORR) and the complete Response Rate
    - To evaluate Pathological Response Rate (pRR) after salvage surgery
    - To evaluate the loco-regional Progression Free Survival (l-PFS).

- To evaluate patient outcome :
    - To evaluate the Progression Free Survival (PFS) or Disease Free survival (DFS) according to stage of disease
    - To evaluate distant relapse rate
    - To evaluate Overall Survival (OS)
    - To evaluate disease specific survival rate.

- To explore biomarkers of Olaparib activity in combination with concurrent radiotherapy.

3. STUDY DESIGN

This phase I trial is an open-label non-randomized, dose-escalation study of safety and tolerability evaluation of Olaparib administered with concurrent loco regional radiotherapy in triple negative inflammatory, loco regional advanced and metastatic inoperable breast cancer as well as the breast cancer patients operated with residual disease after neo-adjuvant treatment.

Prior to radiotherapy, neoadjuvant chemotherapy is allowed and may contained anthracyclines or taxanes or the combination of both or may contained platinum-based chemotherapy.

Pre-treatment evaluation will be done within 4 weeks before the beginning of the treatment.

After inclusion, seven days prior to their first fraction of radiation therapy, patients will begin taking Olaparib at the assigned dose twice daily each day. All patients will receive radiotherapy on day 8 after the start of Olaparib as following:

In case of mastectomy or preoperative irradiation:

- 50 Gy to the whole breast in 25 daily fractions and 5 weeks.
- 50 Gy to the supra/infra-clavicular areas in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the internal mammary chain in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the axillary areas in 25 daily fractions and 5 weeks according to the center guidelines.

In case of breast conserving surgery:

- 50.4 Gy to the whole breast in 28 daily fractions and 5.6 weeks.
- 63 Gy to the tumor bed boost area in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the supra/infra-clavicular areas in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the internal mammary chain in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the axillary areas in 28 daily fractions and 5.6 weeks according to the center guidelines.

Patients will be assigned to receive Olaparib at the assigned dose twice daily each day in combination with radiotherapy until the end of radiotherapy. The starting dose will be 50 mg BID (a total daily dose of 100 mg). Other dose levels are 100, 150 and 200 mg BID (respectively 200, 300 and 400 mg daily). If starting dose is found to be toxic, a 25mg bid dose will be allocated (a total daily dose of 50 mg).

Dose escalation guidelines are detailed in section 6.3.

Patients will be followed for global clinical parameters and safety assessment. Patients will be evaluated for global clinical parameters once a week during radiotherapy and then 2 weeks and 6 weeks after the end of radiotherapy

According to Time-to-event Continual Reassessment Method (TITE-CRM), a further dose level may be considered if the assigned dose is well tolerated in this radiation therapy combination schedule.

At completion of radiotherapy and Olaparib, after the healing of the epidermitis, i.e. a minimal interval of 6 weeks after radiotherapy, surgery may be performed (axillary lymph node dissection of the first two levels and, depending on the relative volumes of the residual tumor and of the breast as assessed both clinically and by the same breast imaging modalities as at inclusion, of either a tumorectomy or a modified radical mastectomy).

The pathological response rate will be assessed after surgery. If there is no complete response after radiotherapy and Olaparib, angiogenesis assay and PARP-1 expression will be performed on mastectomy pieces.

3.1 Primary endpoint

To determine the incidence of early DLTs (early adverse effects related to Olaparib administered with concurrent radiotherapy) and to determine the Maximal Tolerated Dose (MTD) of Olaparib administered with concurrent loco regional radiotherapy.

3.2 Secondary endpoints

- Safety profile will be assessed using :
  - Incidence of SAEs
  - Incidence and severity of AEs, graded according to NCI-CTCAE version 4.03 criteria (cf. Appendix 3)
  - Incidence and severity of laboratory abnormalities, graded according to NCI-CTCAE version 4.03 criteria
  - Incidence of acute toxicity (e.g.; radio dermatitis, pain, dyspnea, dysphagia, pericarditis) 2 weeks and 6 weeks after the end of radiotherapy
  - Incidence of late toxicity (e.g.; fibrosis, necrosis, pain, telangiectasia, arm lymphedema, paresis, cardiovascular events, dyspnea, dysphagia) 1 year and at 2 years as of initiation of radiation therapy
  - Incidence of treatment discontinuations and treatment modifications due to AEs
- Efficacy profile will be assessed using :
  - Objective Response Rate (ORR) and Complete Response (CR) by imaging according to RECIST 1.1 criteria and Tumor Volume estimation (Lenght×Width×Depth) (WHO criteria).
  - Pathological Response Rate (pRR) after salvage surgery according to *Symmans et al* to determine the Residual Cancer Burden *(JCO, 2007).*
  - Loco-regional Progression Free Survival (lPFS) at one year, defined as the time between any loco-regional recurrence (either at the site of the primary tumor and/or lymph nodes) and patient inclusion date.
- Patient outcome will be assessed using :
  - Progression free survival (PFS) or Disease Free Survival (DFS) (according to disease staging) rate at one year, defined as the time from patient inclusion to the first radiologic confirmation of disease progression or death from any cause, whichever comes first.

- Distant relapse rate at one year.
- Overall Survival (OS) defined as the time from patient inclusion to death from any cause.
- Disease specific survival rate at one year and two years defined as the time from patient inclusion to death from her breast cancer.

♦ Exploration of biomarkers of Olaparib associated with radiotherapy on biopsies (angiogenesis assay, PARP-1 expression, Large-scale State Transitions score, immune cells biomarkers such as CD8, FOXP3, CD68, PD1-PDL1, and other markers of macrophages). The somatic and germline status of BRCA1 and BRCA2 will be determined.

♦ Evaluation and banking of the Residual Cancer Burden *(JCO, 2007).*

4. PATIENT SELECTION AND INCLUSION

4.1 Patient's selection

Patients must fulfill following all inclusion and exclusion criteria.

4.1.1 Inclusion criteria

1. **Woman aged >18 years.**

2. **Histologically confirmed triple negative breast cancer with loco-regional radiotherapy indication :**

   a) **Non-operated with either:**
      1) Inflammatory breast cancer in progression during neoadjuvant chemotherapy or inoperable after neoadjuvant chemotherapy.
      2) Loco-regional advanced breast cancer in progression during neoadjuvant chemotherapy or inoperable after neoadjuvant chemotherapy (T ≥ 3 and/or N ≥ 1; with evaluable disease according to RECIST 1.1 criteria).
      3) Non operable metastatic breast cancer (all T, all N, M1; with evaluable disease according to RECIST 1.1 criteria) needing local and regional treatment in case of good metastatic control after chemotherapy.

   b) **Or patient operated after neoadjuvant treatment and surgery with residual disease (non-pCR and/or pN+ disease).**

3. **Neoadjuvant chemotherapy** (containing anthracyclines or taxanes or the combination of both or containing platinum-based chemotherapy) **willingness to discontinue any cytotoxic chemotherapeutic agents, immunotherapy, and targeted therapies at least two weeks prior to start of Olaparib.**

4. **ECOG performance status < 2** (cf. Appendix 2).

5. **Life expectancy greater than 6 months.**

6. **Adequate hematologic, renal and hepatic function** (assessed within the two weeks prior to inclusion and within the month prior to the commencement of protocol treatment). **For patient who stop chemotherapy in the two weeks prior to protocol treatment, hematologic function re-assessment in the 1 or 2 days before the study treatment period (Olaparib intake):**
   - **a.** Haemoglobin ≥ 10.0 g/dL.
   - **b.** Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L.
   - **c.** White Blood Cells (WBC) > 3 x 10^9/L.
   - **d.** Platelet count ≥ 100 x 10^9/L.
   - **e.** Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (except in case of Gilbert syndrome).
   - **f.** AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5 x ULN.
   - **g.** Patients must have Creatinine Clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min:

     $$\text{Estimated Creatinine Clearance} = \frac{(140-\text{age [years]}) \times \text{weight (kg)} \quad (\times F)^a}{\text{serum creatinine (mg/dL)} \times 72}$$

     [a] : where F=0.85 for females and F=1 for males.

7. **Urine or serum negative pregnancy test** within two weeks prior to inclusion. Negative pregnancy test confirmed within 1 or 2 days prior to first Olaparib intake.

8. For woman with child-bearing potential, an **efficacious contraception** used during the whole treatment period and up to three months after the last Olaparib administration (cf. Appendix 4).

9. **Ability to swallow and retain oral medications without gastrointestinal disorders likely to interfere with absorption of the study medication.**

10. **Affiliation to the French Social Security System.**

11. **Ability to understand and the willingness to sign a written informed consent document.**

4.1.2 Exclusion criteria

1. **Radiation therapy:** prior history of radiation therapy to the ipsilateral breast and/or regional nodes (except prior radiation therapy to other sites).

2. **Patient with unresolved or unstable, CTCAE v4.03 Grade 3 or greater toxicity** from prior administration of prior anti-cancer treatment (cf. Appendix 3).

3. Patient with clinically and uncontrolled **significant comorbidity**: major cardiac, respiratory, renal, hepatic, gastrointestinal, hematologic or neurological/psychiatric disease or disorder, including but not limited to: active uncontrolled infection; symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia; any other illness condition(s) that could exacerbate potential toxicities, require excluded therapy for management, or limit compliance with study requirements.

4. **Patient with second primary cancer, except**: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for ≥ 5 years.

5. **Concomitant anti-neoplasic treatment during protocol treatment and not completed at least 2 weeks prior to Olaparib initiation,** except bisphosphonates and RANK inhibitors without restriction even during protocol treatment as long as these where started at least 4 weeks prior to study treatment initiation.

6. **Any previous treatment with a PARP inhibitor, including Olaparib.**

7. **History of allergic reactions** attributed to compounds of similar chemical or biologic composition to Olaparib.

8. **Patient being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A** (Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itroconazole, Voriconazole, Ritinavir, Telithromycin) **within the last 7 days before first Olaparib intake.**

9. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome (cf. Appendix 5).

10. Blood transfusions within 14 days prior to treatment start.

11. Patient with myelodysplastic syndrome / acute myeloid leukaemia.

12. **Pregnant or breastfeeding woman.**

13. **Patient already included in another clinical trial with an investigational drug.**

14. **Patient individually deprived of liberty** or placed under the authority of a tutor.

15. Patient with any **psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol** and follow-up schedule.

4.2 Patient's registration and inclusion

Following adequate informed consent form signature and validation of the selection criteria, eligible patients will be registered by completing the patient's screening form of the eCRF *(please refer to Study Procedures Manual).* After validation of the inclusion and exclusion criteria and the inclusion assessment, the patient will be included into the study.

4.3 Patient's withdrawal and trial termination

Patient will be followed according to the study protocol up to 6 weeks after end of treatment.

Patient who discontinues Olaparib, radiotherapy, or both, will be followed up to 6 weeks after end of treatment.

Then, only information's will be collected without any study specific procedure regarding relapse, DFS, PFS, OS, and late toxicities.

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be prematurely withdrawn from the study if any of the following occur:

- AEs
- Subject withdrew consent
- Lost to follow-up
- Death
- Pregnancy during Olaparib administration
- Disease progression during DLT window
- It is no longer considered to be in the patient's best interest.

If the patient is withdrawn from the study, the patient will be considered to have completed treatment and the reason for discontinuation will be recorded.

Patients who are prematurely withdrawn from the study are not eligible to re-enter study at a later date.

Patients will not be replaced on study. However, if a patient is considered to be non-evaluable for DLT evaluation of the dose level, enrollment of a new patient will be considered using the same rules as a new patient (cf. section 6.3.3).

Sponsor reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons. Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (e.g., EC, regulatory authorities, etc.).

5. VISITS AND ASSEMENTS SCHEDULE

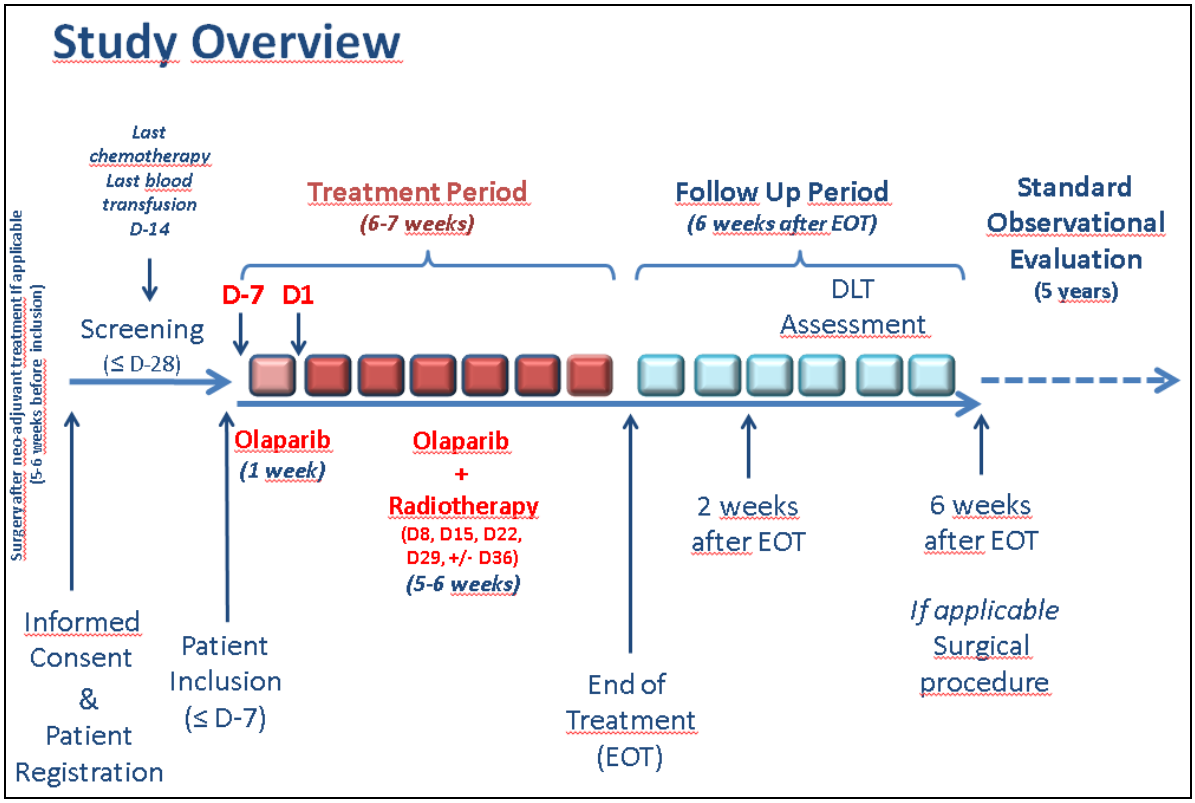
Screening assessments and all on study scheduled visits and assessments are outlined in appendix 1: Flow-Chart.

The study will consist of 3 periods:

- A 28 days screening period.
- A treatment period: 1 week of Olaparib administration followed by 5 to 6 weeks of Olaparib administration and concomitant radiotherapy.
- A follow-up period: 2 and 6 weeks after end of treatment.

All assessment described below can be added with any other exam or assessment medically needed at investigator's discretion.

All data should be collected in the Study eCRF (please refer to *Study Procedures Manual).*



5.1 Screening period

Screening assessments should be performed within 28 days before patient inclusion. This period includes inclusion and exclusion criteria assessment.
For operated patients, wounds from surgery after neoadjuvant treatment will need to be clean and healed before inclusion. Accordingly, for those patients, inclusion is allowed 5 to 6 weeks after surgery.

The following procedures should be performed:

- Adequate subject Information and Consent Form signature (to be chosen between *IC 2016-01 RadioPARP_NI-CE_TNBC and IC 2016-01 RadioPARP_NI-CE_TNBC after surgery*).
- Assess inclusion/exclusion criteria.
- Medical history recording.
- Physical examination (Height, weight, ECOG Performance status).
- Twelve-leads ECG (twice within 24h, with at least 5 minutes in between) *within 7 days before patient inclusion)*.
- Pathological assessment on diagnosis samples (ER, PgR, Her2, Ki 67 Mitotic Index, EE Grade).
- Laboratory exams *(within 14 days before patient inclusion)* :
    - Hematology: white blood count, hemoglobin, platelet count, absolute neutrophil count and absolute lymphocyte count.
    - Blood Chemistry: total protein, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, GGT, sodium, potassium, chloride, creatinine and lactate dehydrogenase.
- Pregnancy test for non-postmenopausal* females *(within 14 days before patient inclusion **and** within one or two days before first study drug intake)*.
- Breast imaging exams (except in case of previous mastectomy): breast mammogram and/or ultrasound and/or breast MRI.
- Optionnal (according to disease status): CT-scan and/or [^{18}F]-FDG PET-scan.
  CT-scan is mandatory for metastatic patients.
- Prior treatments / procedures & prior anti-cancer therapies recording.
- Concomitant treatments and existing signs recording.

Ancillary studies biological samples should be collected:

- Blood sampling for ancillary studies: 2 x 6 ml of peripheral blood must be sampled on EDTA tubes, simultaneously together, with biological analyses.

- Tumor sampling for ancillary studies, including genomic HRD determination should be recovered from mastectomy piece or from diagnostic biopsies:
    - In adjuvant patients (after surgery) :

- 1 Frozen and 1 formalin fixed material (tumor + normal breast parenchyma)

- In Neoadjuvant advanced and metastatic diseases :
  - 2 frozen and 2 formalin fixed samples of the tumor before any treatment (tumor + normal breast parenchyma)

Sample recovery or handling and conservation procedure are described in the *Study Procedures Manual*.

*Postmenopausal status is defined as:

- 12 months of amenorrhea with an appropriate clinical profile (e.g. age appropriate, cessation of exogenous hormonal treatment, history of vasomotor symptoms, LH and FSH levels in the post-menopausal range for women under 50).
- Have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5.2 Treatment period

Patient visits are performed weekly (+/-2 days) during treatment period: At days D-7, **D1***, D8, D15, D22, D29, (+/- D36 according to radiotherapy duration).
If radiation treatment is delayed for any reason, protocol's visits should be delayed accordingly to the standard practices.

**Day 1 is the first day of breast radiation treatment.*

The following procedures should be performed:

- Perform physical examination (weight, ECOG Performance status), skin status.
- Perform laboratory exams :
  - Hematology: white blood count, hemoglobin, platelet count, absolute neutrophil count and absolute lymphocyte count.
  - Blood Chemistry: total protein, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, GGT, sodium, potassium, chloride, creatinine and lactate dehydrogenase.
- Record concomitant treatments and adverse events.
- Olaparib and patient diary (cf. section 6.1.4) dispensation at designated dose level.
- Study drug accountability with the help of fulfilled patient diary.

NB : Handling instructions for Olaparib are described in section 6.2.1.

Ancillary studies biological samples should be collected:

- Blood sampling for ancillary studies: Each week, 2 x 6 ml of peripheral blood must be sampled on EDTA tubes, simultaneously together, at same time with biological analysis. Sample handling and conservation procedure is described in the *Study Procedures Manual*.

5.3 Follow-up period

Follow-up assessments should be performed up to 6 weeks after end of radiotherapy. If possible, in case of premature patient withdrawal, follow-up assessments described below should be done.

5.3.1 Two weeks after end of radiotherapy (+/- 2 days)

The following procedures should be performed:

- Physical examination (weight, ECOG Performance status), skin status.

- Laboratory exams :
  - Hematology: white blood count, hemoglobin, platelet count, absolute neutrophil count and absolute lymphocyte count.
  - Blood Chemistry: total protein, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, GGT, sodium, potassium, chloride, creatinine and lactate dehydrogenase.
- Blood sampling for ancillary study: 2 x 6 ml of peripheral blood.
- Concomitant treatments and adverse events recording.
- Study drug accountability with the help of fulfilled patient diary.

5.3.2 Six weeks after end of radiotherapy (DTL period) (+/- 2 days)

For patients with planned surgery, some of the assessments below can be done at the same time as the pre-surgical visit.

<u>The following procedures should be performed</u>:

- Physical examination (weight, ECOG Performance status), skin status.
- Laboratory exams :
  - Hematology: white blood count, hemoglobin, platelet count, absolute neutrophil count and absolute lymphocyte count.
  - Blood Chemistry: total protein, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, GGT, sodium, potassium, chloride, creatinine and lactate dehydrogenase.
- Blood sampling for ancillary study: 2 x 6 ml of peripheral blood.
- Tumor sampling from surgery piece (2 Frozen and 2 formalin fixed material (tumor + normal breast parenchyma)
- Concomitant treatments and adverse events recording.

Treatment evaluation should also be done either:

- On radiological exams for response evaluation: Breast mammogram +/- ultrasound +/- MRI according to disease status (except in case of previous mastectomy). A CT-scan must be done in case of metastatic disease.
- Or pathological evaluation to be done after salvage surgery according to Symmans *et al* to determine the Residual Cancer Burden (JCO, 2007).

In case of previous mastectomy and no metastatic disease, no imaging exam is mandatory.

5.3.3 Disease/Progression free and overall survival Evaluation, late toxicity events recording.

After the “6 weeks” follow-up visit (end of the DLT window), disease evaluation for secondary endpoints assessments will be performed according to local standard evaluation procedure:

- Local and/or metastatic relapse's information.
- Late toxicities of Olaparib concurrent with radiation therapy using NCI-CTCAE v4.03 evaluation scale assessed at 1 and 2 years.
- Patient last follow-up date (or date of patient death).

Data will be recorded in study eCRF for each patient during **two years** for late toxicities and between **five and eight years** for survival (PFS, OS, DFS) or until death.

6. TREATMENTS

Olaparib administration will start seven days prior to the first fraction and until the end of the last fraction of radiation.
All patients will receive normofractionated radiotherapy as described below:

In case of mastectomy or preoperative irradiation:

- 50 Gy to the whole breast in 25 daily fractions and 5 weeks.
- 50 Gy to the supra/infra-clavicular areas in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the internal mammary chain in 25 daily fractions and 5 weeks according to the center guidelines.
- 50 Gy to the axillary areas in 25 daily fractions and 5 weeks according to the center guidelines.

In case of breast conserving surgery:

- 50.4 Gy to the whole breast in 28 daily fractions and 5.6 weeks.
- 63 Gy to the tumor bed boost area in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the supra/infra-clavicular areas in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the internal mammary chain in 28 daily fractions and 5.6 weeks according to the center guidelines.
- 50.4 Gy to the axillary areas in 28 daily fractions and 5.6 weeks according to the center guidelines.

Radiotherapy is conducted according to local standard guidelines.
For radiation-toxicity management please refer to section 6.1.2 and 6.1.3.

In case of surgical procedure, it must be realized 6 weeks after the end of the radiotherapy.

6.1 Study Treatment Administration / Concomitant treatments

6.1.1 Olaparib dosing regimen

Olaparib will be given to patients on Day “D-7” until the end of the 5 or 6 weeks radiotherapy (for a total duration of 6 to 7 weeks), premature withdrawal from the study or end of the study.
Each week, the investigator informs the patient if the treatment is continued at same dose or adaptated in case of toxicity.

In this study, dose levels are:

Dose Level	Investigational product	Dosage BID	Total daily dose
-1	Olaparib	25 mg	*50 mg*
1 (starting dose level)	**Olaparib**	**50 mg**	**100 mg**
2	Olaparib	*100 mg*	*200 mg*
3	Olaparib	*150 mg*	*300 mg*
4	Olaparib	*200 mg*	*400 mg*

Dose levels for Olaparib

Study dose level escalation modalities are detailed in section 6.3.

Toxicity and treatment discontinuation management are described in sections 6.1.2 and 6.1.3.

6.1.2 Toxicity management : dose continuation/reduction/interruption

Any toxicity observed during the course of the study may be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 28 days on each occasion (except for anemia and thrombocytopenia). If the interruption is any longer than this the Sponsor study team 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 v 4.03 grade 1 or less.

When toxicity reoccurs following re-challenge with Olaparib at same dose, or when further dose interruption is 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.

6.1.2.1. Haematological toxicities management

All kind of cytopenia can occur during Olaparib treatment. Detailed haematological toxicity management for each type is described in the section below and in the corresponding table.

In case **of prolonged haematological toxicities while on study treatment 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) 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 study pharmacovigilance.

Study treatment should be discontinued if diagnosis of myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) is confirmed.

The dose of Olaparib **must not** be adjusted under any other circumstances unless the AstraZeneca Study Physician gives prior agreement.

6.1.2..1.1 Management of anaemia

Adverse events of anaemia CTCAE grade 1 or 2 (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 investigated and appropriately managed. 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 2 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 ≥ 9 g/dl. Any subsequently required anaemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions.
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, Olaparib should be permanently discontinued.

Management of anaemia is summarized in the table below.

Anaemia	**Action Olaparib**
CTCAE grade 2 (Hemoglobin (Hb) ≥ 8 g/dL and < 10g/dL)	First occurrence: • Give appropriate supportive treatment and investigate causality. • Investigator judgment to continue Olaparib or interrupt dose for a maximum of 2 weeks. Second (or more) occurrence : • Interrupt Olaparib up to maximum of 2 weeks to allow for bone marrow recovery and patient should be managed appropriately. If resolution needs more than 2 weeks, the patient must be referred to hematologist for further investigations and the investigator will have to contact the sponsor to discuss options. • When Hb ≥ 9 g/dL, administrate Olaparib at the reduced dose level (n-1) (two dose reduction maximum = dose level n-2).

Anaemia	Action Olaparib
CTCAE grade 3 (Hb < 8g/dL) or worse	• Interrupt study treatment Olaparib for up to maximum of 4 weeks to allow for bone marrow recovery and patient should be managed appropriately. If resolution needs more than 4 weeks, the patient must be referred to hematologist for further investigations and the investigator will have to contact the sponsor to discuss options. • When Hb ≥ 9 g/dL, skip the first reduced dose level and restart Olaparib directly at the second reduced dose level (n-2) if possible.
CTCAE grade 3 (Hb < 8g/dL) or worse despite repeated blood transfusions	Olaparib should be permanently discontinued.

6.1.2..1.2 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 leukopenia have been recovered up to CTC AE grade 1 or below (ANC $\geq$ 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug.

Management of neutropenia and leukopenia is summarized in the table below.
Pegylated G-CSF is not allowed in this study.

Neutropenia/Leukopenia	Action Olaparib
Grade ≤2	Neutropenia and leukopenia should be managed as deemed appropriate by the investigator.

Neutropenia/Leukopenia	Action Olaparib
Grade ≥ 3	First occurrence : Olaparib should be interrupted for up to a maximum of 2 weeks. If resolution needs more than 2 weeks, the patient must be referred to hematologist for further investigations and the investigator will have to contact the sponsor to discuss options. Manage as deemed appropriate by the investigator with close follow up, including G-CSF according to local hospital guidelines.) G-CSF should not be used within at least 24 h of the last dose of study treatment. G-CSF should be stopped at least 24h before restarting study drug. (Pegylated G-CSF is not allowed in this study). When CTCAE grade ≤ 1, restart Olaparib at the same dose level. In case of repeated occurrence: Olaparib should be reduced at lower dose level (n-1) (two dose reduction maximum = dose level n-2).
CTCAE grade 3 or worse	• Interrupt study treatment Olaparib for up to maximum of 4 weeks to allow for bone marrow recovery and patient should be managed appropriately. If resolution needs more than 4 weeks, the patient must be referred to hematologist for further investigations and the investigator will have to contact the sponsor to discuss options. • When Hb > 10 g/dL, skip the first dose level and restart Olaparib directly at the second reduced dose level (n-2).
CTCAE grade 3 or worse despite repeated growth factor administration	Olaparib should be permanently discontinued.

6.1.2..1.3 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 2 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

6.1.2.2. Non haematological toxicities

6.1.2..2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) 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, this needs to be discussed with the AstraZeneca Study Physician, sponsor, and coordinating investigator to decide if Olaparib should be discontinued.
All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the patient diary and the eCRF.

6.1.2..2.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with Olaparib treatment. In *Ledermann et al* **[19-20]** studies, nausea was reported in 71% of the Olaparib treated patients and 36% in the treated 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.

Management of nausea and vomiting is summarized in the table below.

Nausea and Vomiting	Action Olaparib
Grade ≥ 1	Introduce antiemetics (ex. Metoclopramide 10 mg may be given half hour before Olaparib). If necessary, setrons may be used. First occurrence: When nausea have subsided, restart study treatment at the same dose. Second occurrence or more: When nausea have subsided, restart treatment at lower dose level (n-1) (two dose reduction maximum = dose level n-2). If antiemetics are not enough sufficient to control nausea, administrate Olaparib at the reduced dose level (n-1). If nausea still have not subsided, then administrate Olaparib at the reduced dose level (n-2). If those actions are not sufficient to control nausea, then interrupt temporarily Olaparib.

6.1.2..2.3 Management of epithelitis

In case of grade 2 toxicity related to the radiotherapy, local treatment and treatment split of 7-10 days (7 fractions maximum) can be accepted in the radiotherapy protocol without discontinuation of Olaparib during this period.
In case of grade 3 toxicity, the local treatment is indicated and the patient will prematurely discontinue radiation therapy.

6.1.3 Discontinuation of study treatment

If a patient becomes pregnant during the course of the study, Olaparib should be discontinued immediately.
Case must be reported to study pharmacovigilance according to section 8.

In case of metastatic progression during Olaparib and breast radiation treatment, both may be stopped. Assessment must be performed (even if these patients will not be considered as evaluable for DLT).

If a patient discontinues study treatment:

- In case of Olaparib discontinuation: radiotherapy must be performed as previously planned. Patient will undergo follow-up assessment as described in section 5.3 (if possible).

- In case of radiotherapy discontinuation: Olaparib must be stopped. Patient will undergo follow-up assessment as described in section 5.3.

- In case of both Olaparib and radiotherapy discontinuation: patient will undergo follow-up assessment as described in section 5.3.

Olaparib should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of Olaparib is required for any biopsy procedures.

Recommendation: In case of palliative radiation treatment for disease progression should be recommended during the study protocol, Olaparib should be discontinued for a minimum of 7 days before initiation of palliative radiation treatment.

6.1.4 Study drug compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Patients will be asked to return all their treatment (including empty bottles or any unused study drug) to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit. Bottle numbers must be recorded.
A “Patient diary” will be given at each Olaparib dispensation. It contains instructions for use and conservation. Patient will record drug intake and adverse event experienced.

6.1.5 Recommended concomitant therapy

6.1.5.1 Olaparib and CYP3A4

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 patient diary and the eCRF.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. 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. In vitro data have, however, also 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: ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin, nelfinavir, boceprevir and telaprevir.

NB : For patients taking any of the above, the required wash-out period prior to starting Olaparib is one week.

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: Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*).

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

- *For phenobarbitone, 5 weeks,*
- *For any of the others, 3 weeks.*

After patient registration, 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 CRA in charge of the study. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

6.1.5.2 Other Concomitant medications

Any medications, with the exceptions noted in sections 6.1.5.1 and 6.1.5.4, 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. Low Molecular Weight Heparin (LMWH) is permitted.

The reason(s) for the use, doses and dates of concomitant 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 8 weeks from the end of the last protocol treatment and different from the study medication must be documented.

6.1.5.3 Administration of other 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 and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF.

6.1.5.4 Prohibited concomitant therapy

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

6.2 Investigational products

6.2.1 Description and handling instruction

Sponsor will supply Olaparib to the investigator as round or oval *green film coated tablets.*
Multiple bottles of study treatment may be required for dispensing in order to make up the assigned dose.

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

NB : Descriptive information for Olaparib can be found in the Investigator's Brochure (IB)

The Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Patients should take Olaparib no sooner than 1 hour after food. They should then refrain from eating for a further 2 hours due to potential effect of food on absorption.

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.

If any case of schedule dose missing, schedule delay or vomiting occurs, the patient must notify the event in his patient diary.

6.2.2 Dosage form & packaging

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.

6.2.3 Labelling

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 of children. The label will include the dose and a space for the patient identification to be completed at the time of dispensing.

The label will include the following information:

- blank lines for
  - patient identification
  - expiratory date
  - investigator name
- Informations about batch numbers and instructions stating that the Olaparib tablets should be conserved at ambiant temperature.

6.2.4 Storage

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 (IB) specifies the appropriate storage.

6.2.5 Study drug accountability

Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the source documents and on patient's eCRF. Bottle numbers must be recorded when drug is dispensed.

The investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The investigator will verify the accuracy of the information on the form, sign and date it.

6.2.6 Study drug handling and disposal

The sponsor will instruct the investigator about the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the patient's and source documents.

6.3 Dose escalation guidelines

6.3.1 Dose levels

In this phase I study, dose levels are:

Dose Level	Investigational product	Dosage BID	Total daily dose
-1	Olaparib	25 mg	*50 mg*
1 **(starting dose level)**	**Olaparib**	**50 mg**	***100* mg**
2	Olaparib	*100 mg*	*200 mg*
3	Olaparib	*150 mg*	*300 mg*
4	Olaparib	*200 mg*	*400 mg*

Dose levels for Olaparib

As we have few preclinical data about the tolerance of concurrent RT and Olaparib and as we can obtain a radiosensitization with low dose of Olaparib, we decided to start with a less important dose of Olaparib than doses used in monotherapy or in combination with chemotherapy in clinical trials.

6.3.2 Definition of Dose Limiting Toxicities (DLTs)

From start of Olaparib to six weeks after the end of radiotherapy and Olaparib combination, patients will be evaluated for global clinical parameters (DLT window).

Dose limiting toxicity definition includes any Grade ≥ 3 adverse event (AE) scored by the NCI-CTCAE v. 4.03, which is related to Olaparib and/or radiation therapy.

These adverse events may represent disorders of the following categories and/or system organ class:

- Grade 3 dermatitis at irradiation dose < 40Gy.
- Grade 4 dermatitis at irradiation dose < 50Gy.
- Grade 3 or 4 dermatitis present 6 weeks or more after the end of treatment.
- Grade 3 pain due to dermatitis present 6 weeks or more after the end of treatment.
- Grade 3 breast edema in presence of maximal support/treatment.
- Grade 3 or 4 esophagitis.
- Soft tissue necrosis.
- Febrile neutropenia (grade 3/4 neutropenia associated with >38.3 fever).
- Grade 4 neutropenia lasting more than 7 days.
- Grade 4 thrombocytopenia or grade 3 with bleeding.
- Grade 3 or 4 anaemia in presence of maximal support/treatment.
- Grade 3 or 4 nausea in presence of maximal support/treatment.
- Grade 3 or 4 vomiting in presence of maximal support/treatment.
- Grade 3 or 4 diarrhea in presence of maximal support/treatment.
- Any other grade 3/4 non hematological adverse events except non-clinically significant lab abnormalities (i.e. GGT increase).
- Inability to receive more than 4 weeks of Olaparib.
- Radiotherapy discontinuation, for toxicity reasons, longer than 7 successive radiotherapy fractions.

However, dysphagia and skin disorders grade 2 or 3 are part of the well-known safety profile observed in relationship to locoregional radiotherapy. Therefore, only unusual severity and precocity may be considered as early DLT.

Local adverse events of unusual duration whatever the severity may be also considered as DLT after evaluation of its clinical course and unusual outcome.

Any other toxicity that the investigator or the sponsor medical expert deems to be dose-limiting, regardless of the grade, may be considered as a DLT.

Early DLT assessment period will end, for every patient, 6 weeks after the last radiation fraction.

Study treatment must be withheld for any patient who experiences an early DLT.

Study treatment may be resumed at fewer radiation fractions after the toxicity has resolved to acceptable grade or baseline level, following discussion between the investigator and the sponsor. Radiotherapy fraction treatment may be delayed to permit resolution of any product/radiation-related toxicity.

6.3.3 Dose escalation rules.

Phase I dose-finding based on toxicity will be conducted in a sequential and adaptive Bayesian scheme, using the method of Time-to-event Continual Reassessment Method **[15-16]** to determine the Maximum Tolerated Dose (MTD) of Olaparib associated with radiotherapy. The primary endpoint is Dose-Limiting Toxicity (DLT) occurring during the treatment and until 6 weeks after the end of the radiotherapy. Dose allocation will be centrally defined, based on DLT observed in all patients already evaluated, by modeling the probability of DLT. An empiric model will be used for the dose-toxicity relationship. The working model is obtained with the R dfcrm package, assuming expected DLT probabilities for the five dose levels to be explored: (0.03, 0.06, 0.11, 0.17, **0.25**).

No intra-patient dose-escalation is permitted. No dose skipping in escalation is permitted. The MTD is defined as the dose associated with a probability of DLT the closest, but inferior or equal, to 25% of DLT.

As the expected number of patients to be enrolled per month is equal to 2, this method allows the registration of patients continuously without stopping registrations. Indeed, patients with partial follow-up at the time of a new enrollment will be weighted by the proportion of the observation period completed. So, this method allows taking into account the full information available regarding patients included without waiting 6 weeks after the end of the radiotherapy. This method will shorten the duration of the trial **[15-16]**. A safety period of three weeks is requested between two consecutive patients of the first cohort (i.e. the first three patients) at each new explored dose level.

Four dose levels are considered (50 mg bid, 100 mg bid, 150 mg bid and 200 mg bid daily). For a safety reason, a dose level of 25 mg bid (dose level -1) is included in case that the first dose level at 50 mg bid is found to be toxic. Cohort of size 3 is used with the TITE-CRM design. So, three patients will be included at the first dose level (50 mg bid daily). Prior to escalation, at least three patients fully observed by completing all the observation period at the previous dose level are requested. Every new patient will be treated at the best current recommended dose proceed (50 mg bid, 100 mg bid, 150 mg bid and 200 mg bid daily), i.e. the dose associated with an estimated level of toxicity that is judged acceptable (the highest dose with a DLT probability $\leq$25% DLT).

Given the number of pre-specified dose levels in the study, it is planned to include a maximum of 30 patients if no stopping rule is reached earlier. A stopping rule will advise the dose escalation termination in case of a high probability (>90%) for the next 6 patients to be assigned to the same dose level, *O'Quigley and Reiner (1998).*

Patients who receive reduced dose of study drugs (<80% of the planned dose of the systemic treatment) for a reason other than toxicity related to the study drugs will be considered as not evaluable for the primary toxicity endpoint assessment. Those patients must be replaced. In the

other hand, a patient who would not receive the protocol dose due to toxicity possibly related to the study drug will be classified as evaluable and “with a DLT”. Patient with metastatic progression during the DLT window will be considered to be non-evaluable for DLT evaluation of the dose level.

The sample size in TITE-CRM Phase I studies is fixed in advance. There are no explicit rules built into the approach. TITE-CRM trials generally recruit between 24 and 36 participants *(Daniel Normolle JCO 2006)*. Simulation studies demonstrated that 30 patients lead to good operating characteristics of the method in terms of correct selection of the MTD.

A maximum of 30 patients will be treated. The expected length of accrual is 2 years.

Specific rules

a. No dose skipping in escalation.

b. No escalation if $\geq$ 1 DLT observed among < 3 patients.

c. A safety period of three weeks is requested between two consecutive patients of the first cohort (i.e. the first three patients) at each new explored dose level.

6.3.4 Efficacy and Safety Evaluation committee

An efficacy and safety evaluation committee will be requested to give their agreement before the inclusion of the next patient of the waiting list.

This committee is composed of:

- A medical oncologist specialist in phase I area
- A medical oncologist used to manage Olaparib
- A radiotherapist specialized in breast cancer treatment
- The coordinating investigator
- The methodologist and biostatistician
- The project manager
- The site coordinator

7. EFFICACY ASSESSMENT

7.1 Response to study Treatment

In this Phase I study, efficacy assessment is secondary objective.

For operated patients, efficacy will be evaluated with the pathological response according to Symmans *et al* to determine the Residual Cancer Burden (JCO, 2007).
For adjuvant breast cancer patient, response will be assessed by imaging (residual disease evaluation or not using MRI): Objective Response Rate (ORR) and Complete Response (CR) by imaging according to RECIST 1.1 criteria and Tumor Volume estimation (Lenght×Width×Depth) (WHO criteria).

Loco-regional Progression Free Survival (lPFS) at one year, defined as the time between any loco-regional recurrence (either at the site of the primary tumor and/or lymph nodes) and patient inclusion date.

- Patient outcome will be assessed using :
  - Progression Free Survival (PFS) or Disease Free Survival (DFS) (according to disease staging) rate at one year, defined as the time from patient inclusion to the first radiologic confirmation of disease progression or death from any cause, whichever comes first.
  - Distant relapse rate at one year.
  - Overall Survival (OS) defined as the time from patient inclusion to death from any cause.

7.2 Ancillary analyses

- **Determination of the HR status from genomic profiling**

Frozen tissues from biopsies are preferred but not mandatory.
500 ng of DNA are necessary for the SNP-array.
Cytoscan array will be performed for frozen samples whereas Oncoscan (both from Affymetrix) is used for FFPE, if no frozen sample was preserved.
Bioinformatics analysis will be performed in Inserm U830 “Genetics and Biology of Cancers”.

- **Determination of the causes of HRD (BRACness)**

Approximately half of patients included in the study are anticipated to have tumors with a HRD status.
We propose to test them for BRCA1 and BRCA2 alterations, in the constitutional and tumor DNA. This study should be completed by a methylation study of BRCA1 and RAD51C promoters.

- **Determination of the therapeutic response by liquid biopsy**

We have previously shown that almost all TNBCs are bearing TP53 mutations. We used these mutations to follow circulating tumor DNA (ctDNA) in metastatic TNBCs, and shown the feasibility of such study **[21]**. We propose to follow patients included in the RadioPARP study by this approach, to better and more objectively quantify the tumor burden, therapeutic response, and relapse.
This would include TP53 sequencing in the tumors, sampling the patient before treatment, every week during Olaparib/radiotherapy, and at the first timepoint during the follow-up (2 weeks).
Tumor sampling will be performed prior to treatment. Formalin-fixed as well as frozen specimen will be obtained in order to assess biomarker status before treatment.
We have compared two detection techniques, by droplet digital PCR and by NGS, which had similar performances. We propose to use the most efficient technique available by the time the protocol is on-going.

- **Angiogenesis assay and Immune markers analysis on biopsies and mastectomy pieces**

Tissue samples will be fixed in 10% formalin and routinely processed for paraffin embedding. Histologic sections cut with 4-µm thickness will be stained with hematoxylin, eosin, and safran.
Tumors will be classified according to the method of the World Health Organization for carcinomas of the breast, and tumor grading will be done in accordance with Elston and Ellis.
Immunohistochemistry will be performed on 4-µm paraffin-embedded sections with an indirect immunoperoxidase method, using antibodies directed against CD31 protein, and CD105 protein.
The number of vessels staining positively for CD31 or CD105 will be counted on 10 consecutive fields at ×400 magnification in the area with carcinoma invasion. Vessels with a clearly defined lumen or well-defined linear vessel shape, but not single endothelial cells, will be considered for microvessel assessment.
Immune cell biomarkers such as CD8, FOXP3, CD68, PD1-PDL1, and other markers of macrophages will be also explored on same tissue samples.

These analyses are related to the every patient's situation (neo adjuvant or adjuvant setting).
We expect to have in the global population targeted in this study, 24 to 30 patients with an estimated proportion of preoperative about 18 patients and postoperative about 6 patients.

8. SAFETY ASSESSMENT

8.1 Safety

Safety will be monitored by evaluating adverse events and laboratory data. The NCI CTC-AE version 4.03 will be utilized for grading the severity of adverse events as well the early and late toxicity.
DLTs are defined in section 6.3.2.

8.2 Methods and timing of safety assessments

Serial measurements of safety will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in appendix 1: Flow-Chart.

Abnormalities will be captured as adverse events. Clinically significant laboratory abnormalities will be captured as AEs rather than capturing the raw laboratory values. Cause of death is to be recorded in the eCRF and the patient's medical record.

A "Patient diary" will be given at the beginning of the study and controlled each week by the investigator. Patient will record drug intake and adverse events (AE) experienced.

8.3 Adverse Event(s)

An adverse event is defined as any medical event, or any event requiring clinical investigation, occurring during treatment, whether or not it is attributable to the study drugs (especially: abnormal biological exams, symptoms, new or impaired concomitant diseases…). Any variation of the studied disease, except for serious impairment, is not considered an adverse event. Any event occurring during the trial (from signature of informed consent to 28 days after the last study treatment intake) must be reported in the eCRF.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to study treatment should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study treatment dose, or any other therapeutic intervention; or

- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- induces a congenital anomaly or birth defect or abortion
- is medically relevant

These AE Must be considered as SAE:

- MDS/AML,
- new primary malignancy
- and inflammatory pneumonitis (whatever the severity graduation).

Are not considered SAE:

- hospitalization < 24 hours,
- hospitalization that was planned prior to the trial's beginning and/or scheduled by the protocol (biopsy, first Olaparib intake, surgery,…).
- hospitalization for progressive disease
- death for progressive disease

8.4 Definition of Expected Serious Adverse Event (E-SAE)

The event is expected when it is mentioned in the most recent version of the Investigator's Brochure (IB).

8.5 Definition of Suspected Unexpected Serious Adverse Event (SUSAR)

A SUSAR is an event that is not mentioned in the IB or differing from the Brochure's description in its nature, intensity, evolution or frequency.

8.6 Intensity Criteria

The intensity criteria must not be confused with the seriousness criterion that is utilized to define the obligations of declaration.
The events intensity is to be estimated according to the NCI CTC-AE version 4.03 classification. The intensity of the AE not listed in this classification will be evaluated according to the following scale:

Mild (grade 1): does not affect the usual daily activity of the patient
Moderate (grade 2): perturbs the usual daily activity of the patient
Severe (grade 3): hampers the usual daily activity of the patient
Life threatening or disabling (grade 4): requires intensive cares / is life-threatening
Lethal (grade 5): results in death

8.7 Reporting SAE

All SAE, Expected (E-SAE) or unexpected (SUSAR) related or not to the study treatment, occurring during the treatment phase and within 30 days after the last study treatment administration (except for second cancer which must be reported during 5 years), must be reported to the R&D UNICANCER Safety Department.
Any late Serious Adverse Drug Reaction (SAE related to the study treatment), occurring after the 30-day period also must be reported to the R&D UNICANCER Safety Department.
The SAE declaration must be faxed to the R&D UNICANCER Safety Department within 24 working hours of the initial observation of the event using a **SAE notification form:**

R&D UNICANCER - PharmacoVigilance
Tel. : 01 44 23 04 16 – Fax : 01 44 23 55 70
Email : pv-rd@unicancer.fr

More information might be requested by the R&D UNICANCER Safety Department or by the study Clinical Research Associate (CRA) through a SAE Query Form to the investigator site.

For each event, the investigator will report:

- the patient identification
- the event's description, as clearly as possible and in accordance with the medical terminology
- the intensity
- the date of the event's onset and recovery
- the seriousness criteria
- the measures undertaken and necessity to use corrective treatments
- if the study treatment was interrupted or reduced

- the outcome (the event will be followed until remission or recovery of the baseline status or stabilization of possible sequelae)
- the relationship to the study schedule or to a protocol procedure (e.g. treatment schema, additional examinations specifically requested by the protocol, etc.)
- the relationship to the study treatment, to the treated pathology, to another concomitant pathology, or another treatment

Whenever possible, the investigator should also provide:

- a copy of the hospitalization or prolonged hospitalization report
- a copy of the autopsy report
- a copy of all complementary examinations results, including the relevant negative results (with normal laboratory values)
- any other document that is relevant in the investigator's opinion

All these documents must be made anonymous. More information might be requested by the R&D UNICANCER Safety Department or the study CRA.

However, an expected event different by its nature, intensity, outcome or frequency from the IB description could be considered as unexpected by the R&D UNICANCER Safety Department.

8.8 Serious Adverse Event Follow-up

The investigator is responsible for the appropriate medical follow-up of the patients until the recovery, the stabilization or the death of the patient. **If required, follow-up might be maintained beyond the end of the protocol.**
The investigator provides complementary information to the R&D UNICANCER Safety Department using a SAE declaration form (ticking the box: Follow-up **# X** will specify that it is not an initial report) within 48 hours. The last follow-up form is sent once recovery or stabilization is observed.
The investigator keeps all the documents regarding the SAE in order to answer further information demands from the R&D UNICANCER Safety Department.

8.9 Pregnancy management

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug or within 28 days of the subject's last dose of study drug are considered immediately reportable events to the R&D UNICANCER Safety Department using the **Pregnancy Reporting Form**.

If the subject is on study drug, the study drug is to be discontinued immediately (please refer to section 6.1.3) and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Sponsor who will inform AstraZeneca.

The Investigator will follow the subject until completion of the pregnancy, and must notify the Sponsor immediately of the outcome of the pregnancy (either normal or abnormal outcome) as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects as related to the in utero exposure to the study drug should also be reported within 24 hours of the investigator's knowledge of the event.
Any suspected foetal exposure to study drug must be reported to the sponsor within 24 hours of being made aware of the event.

9. STATISTICAL CONSIDERATIONS

9.1 Study design

Phase I dose-finding based on toxicity will be conducted in a sequential and adaptive Bayesian scheme, using the method of Time-to-event Continual Reassessment Method **[15-16]** to determine the Maximum Tolerated Dose (MTD) of Olaparib associated with radiotherapy. The primary endpoint is Dose-Limiting Toxicity (DLT) occurring during the treatment and until 6 weeks after the end of the radiotherapy. Dose allocation will be centrally defined, based on DLT observed in all patients already evaluated, by modeling the probability of DLT. An empiric model will be used for the dose-toxicity relationship. The working model is obtained with the R dfcrm package, assuming expected DLT probabilities for the five dose levels to be explored: (0.03, 0.06, 0.11, 0.17, **0.25**).

No intra-patient dose-escalation is permitted. No dose skipping in escalation is permitted. The MTD is defined as the dose associated with a probability of DLT the closest, but inferior or equal, to 25%.

As the expected number of patients to be enrolled per month is equal to 2, this method allows the registration of patients continuously without stopping registrations. Indeed, patients with partial follow-up at the time of a new enrollment will be weighted by the proportion of the observation period completed. So, this method allows taking into account the full information available regarding

patients included without waiting 6 weeks after the end of the radiotherapy. This method will shorten the duration of the trial **[15-16]**. A safety period of three weeks after the beginning of the systemic treatment is requested between two consecutive patients of the first cohort (i.e. first three patients) at each new explored dose level.

Four dose levels are considered (50 mg bid, 100 mg bid, 150 mg bid and 200 mg bid daily). For a safety reason, a dose level of 25 mg bid (dose level -1) is included in case that the first dose level at 50 mg bid is found to be toxic. Cohort of size 3 is used with the TITE-CRM design. So, three patients will be included at the first dose level (50 mg bid daily). Prior to escalation, at least three patients fully observed by completing all the observation period at the previous dose level are requested. Every new patient will be treated at the best current recommended dose proceed (50 mg bid, 100 mg bid, 150 mg bid and 200 mg bid daily), i.e. the dose associated with an estimated level of toxicity that is judged acceptable (the highest dose with a DLT probability $\leq$25% DLT).

Given the number of pre-specified dose levels in the study, it is planned to include a maximum of 30 patients if no stopping rule is reached earlier. A stopping rule will advise the dose escalation termination in case of a high probability (>90%) for the next 6 patients to be assigned to the same dose level, *O'Quigley and Reiner (1998).*

Patients who receive reduced dose of study drugs (<80% of the planned dose of the systemic treatment) for a reason other than toxicity related to the study drugs will be considered as not evaluable for the primary toxicity endpoint assessment. Those patients must be replaced. In the other hand, a patient who would not receive the protocol dose due to toxicity possibly related to the study drug will be classified as evaluable and "with a DLT". Patient with metastatic progression during the DLT window will be considered to be non-evaluable for DLT evaluation of the dose level.

The sample size in TITE-CRM Phase I studies is fixed in advance. There are no explicit rules built into the approach. TITE-CRM trials generally recruit between 24 and 36 participants *(Daniel Normolle JCO 2006)*. Simulation studies demonstrated that 30 patients lead to good operating characteristics of the method in terms of correct selection of the MTD.

A maximum of 30 patients will be treated. The expected length of accrual is 2 years.

Specific rules

a. No dose skipping in escalation.

b. No escalation if $\geq$ 1 DLT observed among < 3 patients.

c. A safety period of three weeks after the beginning of Olaparib treatment (corresponding to the peak in toxicity risk when around 40 Gy are delivered) is requested between two consecutive patients of the first cohort (i.e. the first three patients) at each new explored dose level.

9.2 Statistical analysis

9.2.1 Safety analysis (primary analysis)

The Phase I main analysis set will include only patients deemed evaluable for the DLT evaluation (DLT population). Patients who received a reduced dose of study drugs (<80% of the planned dose) for a reason other than DLT will be considered as not evaluable for the primary toxicity endpoint assessment.

9.2.2 Secondary efficacy and safety objectives analyses

Efficacy and safety analyses will be done on efficacy and safety population.

Safety analyses:
The safety analysis will be performed on the subset of patients receiving at least one dose of Olaparib.
Safety analyses will include:

- Maximum CTCAE grade (Version **CTCAE v4.03**) for adverse events,
- Serious adverse events during the treatment period or within 6 weeks of the last dose of study treatment (DLT period),
- Study discontinuation due to adverse event,
- Death occurring during the study treatment period or within 6 weeks of the last dose of study treatment (DLT period).

Analyses of efficacy:
Analyses of efficacy will be exploratory and descriptive. They will be performed on all patients who received at least one dose of Olaparib on MTD and MTD-1 levels, evaluable or not for DLT, in order not to overestimate response rate or long term criteria as survival, PFS, by excluding patients progressing or dying in the DLT window.

Progression free survival (PFS) and Disease Free Survival (DFS) (according to disease staging) rate will be calculated according to Kaplan Meier method. .

10. DATA PROTECTION AND CONFIDENTIALITY MANAGEMENT

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by him and all other individuals involved in the course of the trial. This obligation holds neither for the information that the investigator may communicate to the patients within the context of the trial nor for the already published information.

Nevertheless, in conformity with the article R. 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:

- to the Health Minister,
- to the public health inspectors,
- to the ANSM General Director and inspectors.

11. QUALITY ASSURANCE AND QUALITY CONTROL

In order to guaranty the authenticity and credibility of the data in accordance with the Good Clinical Practices (GCP), the sponsor will set up an insurance quality program that includes:

- management of the trial according to the Institut Curie procedures,
- quality control of the data provided by the investigation site is performed by the study monitor whose role is to match and check the consistency of the data reported in the CRF with respect to the source-documents,
- possible audit of investigational sites,
- centralized review of selected criteria of the protocol.

12. ETHICAL AND REGULATORY ISSUES

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women. TNBC is a particular subset of breast cancer and patient have generally poor prognosis in particular when locoregional disease control cannot be obtained.

In addition to surgery and radiotherapy, chemotherapy remains the ultimate treatment option for those patients with varied impact on long-term prognosis. TNBC patient treated with neoadjuvant chemotherapy without complete pathological response at surgery experience poor outcome **[22]**. Currently, after failure of neoadjuvant chemotherapy for all non-operable patients with metastatic,

locally advanced or inflammatory breast cancer, the treatment option is association of radiotherapy with or without chemotherapy in order to obtain locoregional disease control. This therapeutic option is used also in case of patients with poor response (residual disease in the breast and the lymph nodes) **[22]**.

No targeted treatment has been developed for TNBC in a curative strategy.

A new strategy with preoperative radiotherapy in combination with new drugs could increase breast conservation approach and could improve locoregional outcome. For patients with triple negative metastatic breast cancer in progression after initial treatment, radiotherapy in combination with new drugs could also increase breast conservation approach and could improve locoregional outcome.

The clinical trial will be conducted in accordance with:

- the principles of ethics as stated in the last version in use of the Declaration of Helsinki,
- Good Clinical Practices defined by the International Conference on Harmonization (ICH–E6, 17/07/96),
- European directive 2001/20/CE on the conduct of clinical trials,
- the law on 'informatics and freedom' (Informatique et Libertés n° 78-17) of January 6th,1978 modified notably by the law n° 2016-41 of January 26th 2016 of modernization of our Health System,
- Bioethic law n° 2004-800 of August 6th, 2004,
- the law n° 2012-300 of March 5th 2012 relating to the researches involving the human person.
- Regulation of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

12.1 Ethics Committee (CPP)

Before starting a biomedical research on human patients, the sponsor must submit its project to the opinion of one of the competent Ethics Committee in the region where the principal investigator is practicing.

A request for opinion on the biomedical research project is addressed to the CPP by the sponsor.

Request of substantial modifications to initial projects are submitted for the CPP's opinion by the sponsor as well.

12.2 Competent authority

Before carrying out or letting a biomedical research to be carried out on its behalf, the sponsor must file a request with the competent authority.

12.3 Information and consent of the participants

Prior to carrying out biomedical research on human patients, a free and written informed consent form must be signed by each individual participating in the trial after she has been informed by the investigator during a physician-patient consult and after sufficient time for reflection has been allowed.

Information given to the trial participants must cover all of the elements defined by the public health law of August 9th, 2004 and must be written in a simple and comprehensible patient-appropriate manner. Once the participant is acquainted with the information, she must sign the information sheet.

The consent form must be dated and signed by both the participant in research and the investigator. The original sheet will be kept in the investigator's folder and the duplicate copy will be returned to the participant.

The information sheet and informed consent form must be associated within the same document to insure that the whole information is given to the participant.

12.4 Sponsor responsibilities

The sponsor (Institut Curie) of the trial is the natural or moral person that takes the initiative of conducting biomedical research on human patients, and is therefore accountable for the research management and for verifying the financing schedule.

The main sponsor responsibilities are:

- to subscribe a civil-responsibility insurance,
- to register the trial in the ANSM (French competent authority for clinical trials) data base,

- to request the opinion of the Committee for the Protection of Persons (CPP) on the initial project and the substantial amendments,
- to file the demand of authorization for the initial project and all substantial amendments with the competent authority,
- to provide information on the trial to the heads of the health care centers, the appropriate investigators and the pharmacists,
- to declare to the competent authorities, i.e. the ANSM and the EMA (the European pharmacovigilance data bank, Eudravigilance) any suspicion of unexpected serious adverse events (SUSAR) related to any of the treatments used in the trial and communicate the information to the CPP and the investigators of the trial,
- the annual declaration of the security report to the competent authority and the CPP,
- the declaration of the beginning and the end of the trial to the competent authority,
- editing the final report on the trial,
- communicating the information on the trial's results to the competent authority, the CPP and the research participants,
- archiving the trial's essential documents in the sponsor folder for a minimal duration of 15 years after the research is ended.

12.5 Investigators responsibilities

The main investigator of each concerned health care center commits to conducting the clinical trial in compliance with the protocol that has been approved by the CPP and the competent authority.
The investigator must not bring any modification to the protocol without having obtained written authorization of the sponsor and the proposed modifications have been authorized by the CPP and the competent authority.

It is the responsibility of the principal investigator:

- to provide the sponsor with its own curriculum vitae and co-investigators' curriculum vitas,
- to identify the members of its team that participate in the trial and to define their responsibilities,
- to insure patient recruitment after the sponsor has issued its authorization.

It is the responsibility of each investigator:

- to collect the informed consent form, dated and signed personally by each individual research participant before any selection procedure specific to the trial may start,
- to regularly fill in the CRF for each patient included in the trial and to allow the clinical research assistant mandated by the sponsor to have direct access to the source-documents in order to validate the data collected in the observation handbook,

- to date, correct and sign the corrections brought to the observation handbook for each patient included in the trial,
- to accept regular visits of the study monitor and possibly the auditors mandated by the sponsor or the inspectors of the legal competent authorities.

12.6 Federation of the Patient Committees for Clinical Research in Cancerology

The creation of the Federation of the Patient Committees for Clinical Research in Cancerology (FCPRCC) is the initiative of the UNICANCER and the LNCC (National League for Treating Cancer). Its dedicated task is to make a second read of the clinical trial protocols in cancerology. The patient committees' federation is coordinated by the BECT (Clinical and Therapeutic Trials Offices), a department of the UNICANCER. It gathers both the patient committees of the LNCC and other health care centers. It commits to rereading the protocol and proposing improvements dealing principally with the quality of the letter of information to the patients, the setting up of a treatment and monitoring plan, suggesting measures aimed at ameliorating the comfort of the patients.

13. DATA REVIEW AND DATA MANAGEMENT

Data analysis will be performed by the biostatistics service of Institut Curie under the supervision of Alexia Savignoni (head of the Institut Curie D.R.C.I. Biometry Unit) and Youlia Kirova, coordinator of the study. DLTs data will be verified continuously by the investigators and monitored if possible in real-time in order to facilitate the inclusions with reliable information from previous patients.

Nevertheless, in conformity with the article R. 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:

- to the Health Minister,
- to the public health inspectors,
- to the ANSM General Director and inspectors.

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by him and all other individuals involved in the course of the trial. This obligation holds neither for the information that the investigator may communicate to the patients within the context of the trial nor for the already published information.

14. FINANCIAL INFORMATION AND TRIAL INSURANCE

This study is financially supported by AstraZeneca which also agreed to provide Olaparib to the sponsor. Notwithstanding this support, Institut Curie takes full responsibility for conducting this trial and has subscribed specific civil-responsibility insurance.

15. PUBLICATION OF RESULTS

All information resulting from this trial is considered to be confidential, at least until first communication and after appropriate analysis and checking has been completed by the sponsor, the investigator coordinator of the project and the statistician of the trial.

Any subsequent publication, abstract or presentation comprising results from the trial must be submitted for examination and approval to the Sponsor (Institut Curie).

The first author and writer of the publication will be the coordinator. She may however designate another person to (co-)write the publication.

The other investigators will appear in the list of co-authors in decreasing order, according to the number of recruited patients regardless of the importance of the cooperating group they belong to. Methodologist and statistician will be cited as well.

In an equal manner, publication of the sub-studies (biological studies) will make mention of the name of the person who has carried out the sub-studies as well as the names of all the individuals who have taken part in carrying out these sub-studies.

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17. APPENDIX

Appendix 1 – Flow Chart

Study Procedure	Screening Period			Treatment period			Follow-up visits		Observational evaluation
	within 28 days before inclusion	within 14 days before inclusion	within 7 days before inclusion	D-7	D1	Each week (D8, D15, D22, D29, +/- D36)	2 weeks after end of treatment	6 weeks after end of treatment	Each year (up to 5 years after the end of treatment)
Study inclusion assessments									
Inclusion/exclusion criteria assessment(1)	x	x							
Patient information & Informed consent	x								
Clinical and Laboratory exams									
Medical history	x								
Clinical examination	x			x	x	x	x	x	
Hematology and biochemistry		x		x	x	x	x	x	
Electrocardiogram			x						
Pregnancy test(2)		x		x					
Olaparib administration (according to assignated dose level, BID)				x	x	x			
Concomitant medication	x	x	x	x	x	x	x	x	
Tissue sampling for ancillary studies									
Tumor sampling		x(3)						x(4)	
Blood sampling		x		x	x	x	x	x	
Assessments									
Safety assessment (including DLT assessement)	x	x	x	x	x	x	x	x	x(5)
Pathological assessment (pathological parameters and response assessment)	x(6)							x(7)	
Breast imaging assessment : breast mammogram and/or ultrasound and/or breast MRI and/or CT-scan	x						x(8)	x(8)	x(8)
Post-study Patient outcome evaluation (according to local standard practices)							x	x	x
Post study Loco-regional and metastatic control evaluation (according to local standard practices)								x	x

(1) Some of the criteria must be checked with 28 days before patient inclusion and some other within 14 days.
(2) For non-postmenopausal patients. Should be done within 14 days and repeated within 1-2 days prior to first Olaparib intake.
(3) Archived tumor sample (from biopsy or surgery piece) according to disease status.
(4) Surgery sample if applicable.
(5) Late toxicities assessments (during 2 years as of initiation of radiation therapy).
(6) Should be done on diagnosis biopsy.
(7) Should be done on surgical sample: Breast and lymph nodes surgery is performed according to standard guidelines in this indication.
(8) According to disease status. Must be done if no surgery planned after Olaparib and irradiation treatment.

Appendix 2 – ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office 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.
5	Dead.

Appendix 3 – Toxicity criteria (NCI CTC-AE)

http://ctep.cancer.gov/

NCI Common Terminology Criteria for Adverse Events v4.03 (NCI CTC-AE)

Appendix 4 – Contraception requirements

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

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 their participation in the study and for 3 months after last dose of study drug.

Acceptable non-hormonal birth control methods are:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom with spermicide. Provided coils are copper-banded.

Acceptable hormonal methods are:

- Etonogestrel implants (eg, Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Non acceptable methods of contraception are:

- Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal.

Appendix 5 – Resting 12-lead ECG

Electrocardiographies are required within 7 days prior to starting study treatment.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF.

The original ECG traces must be stored in the patient medical record as source data.