PRO-CARBO PROTOCOL

Multicenter, open-label phase 2 trial evaluating the efficacy of CARBOPLATIN in metastatic prostate tumors with alterations in homologous recombination pathway genes.

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TRIAL CLASSIFICATION: Interventional research involving humans relating to a health product

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REGULATORY AUTHORIZATIONS	National Medicines Safety Agency (ANSM)	Authorization date: 07/24/2018
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PRIVACY STATEMENT

PEOPLE INVOLVED IN THE PREPARATION AND CONDUCT OF RESEARCH

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1 SYNOPSIS

TITLE	**Multicenter, open-label phase 2 trial evaluating the efficacy of CARBOPLATIN in metastatic prostate tumors with alterations in homologous recombination pathway genes.**
ACRONYM	**PRO-CARBO**
Coordinator	**Dr Elodie COQUAN**
Indication	Metastatic castration-resistant prostate carcinoma with somatic abnormality of the homologous recombination pathway.
Methodology	Multicenter prospective open-label phase 2 trial
Goals	**Objective main** To evaluate the response rate efficacy of CARBOPLATIN monotherapy in patients with castration-resistant metastatic prostate carcinoma with somatic abnormality of the homologous recombination pathway. **Secondary objectives** - Assess survival without radiographic progression - Evaluate survival without biological progression - Evaluate the duration of the tumor response - Assess overall survival - To assess the safety and safety data of carboplatin in this population **Exploratory objectives** - Correlate the response to carboplatin according to the type of abnormality of the homologous recombination pathway found. - Detect mechanisms of new resistance on circulating tumor DNA
Judgment criteria	**Main criterion** **The main criterion of the study** is the response rate (TR) defined according to the PCWG3 recommendations as one of the following 2 points: • Objective radiological response (Complete or partial response according to modified RECIST 1.1 criteria and no bone progression) and/or • Decrease in PSA ≥ 50%, measured twice 3 to 4 weeks apart. **Secondary criteria** - Radiographic progression-free survival (RPS) defined by the time between the start date of treatment and the first date of documented radiographic progression or the date of death regardless of the cause - Survival without biological progression defined by the time between the start date of treatment and the first date of documented biological progression or the date of death regardless of the cause - Duration of tumor response (radiographic/biological) defined by the time between the date of best response (objective/stable) and the first date of documented progression (radiographic/biological) or the date of death whatever the cause - Overall survival defined by the time between the start date of treatment and the date of death regardless of the cause - THE toxicities : type, frequency and grade of adverse events according to CTCAE version 4.0 - Dose-intensity of Carboplatin - Presence of an anomaly of the homologous recombination pathway found - Mechanisms of new resistance on circulating tumor DNA

Inclusion criteria	- Patients > 18 years old - Patients with adenocarcinoma or poorly differentiated carcinoma prostate, histologically confirmed (pure small cell histologies or pure high-grade neuroendocrine histologies are excluded) - Tumor presenting a pathogenic somatic variant likely to alter the homologous recombination pathway previously detected on a tumor biopsy or on circulating tumor DNA, or germline mutation among the defined list of genes (Appendix 1) - Castration-resistant tumor defined by progression despite well-conducted androgen deprivation therapy: testosterone ≤ 50ng/dL under luteinizing hormone releasing hormone (LHRH) agonist/antagonist or surgical castration. The patient must agree to continue concomitant treatment with an analogue (agonist or antagonist) of LHRH for the duration of administration of the study treatment for patients without a history of surgical castration. - Patients must have completed at least one line of taxane chemotherapy in a castration resistance situation: o patients who have received treatment with docetaxel in a situation of hormone sensitivity must have received at least one treatment with cabazitaxel in a situation of resistance to castration o Patients who have not received chemotherapy in a hormone-sensitive situation must have received treatment with docetaxel AND cabazitaxel or have a contraindication justifying non-administration of the treatment - Patients must have been treated with at least 2 hormonal therapiesth generation (e.g. abiraterone acetate or enzalutamide) - Patients may have been treated with a poly(ADP-ribose) polymerase (PARP) inhibitor - Performance Status $\leq$ 2 - Disease metastatic in current progression defined by one or more of the criteria below: • Progressive disease measurable according to RECIST 1.1 criteria: Increase of at least 20% in the sum of the diameters of the measurable lesions compared to the smallest sum observed, or appearance of one or more new lesions observed by CT. • Progression noted by bone scintigraphy: appearance of two or more new lesions on the bone scintigraphy • Increased serum PSA levels: It is necessary to have two consecutive documented increases in PSA levels at intervals of at least one week from a previous baseline. If the third PSA level value is less than the second, then a fourth additional test is recommended to confirm the increase in PSA level. For patients whose progression is only documented by an increase in PSA level, the minimum baseline value is 5.0 ng/ml to be eligible for inclusion in the study. - Function normal organ and sufficient bone marrow reserve, measured within 28 days prior to administration of study treatment, as defined below: o Hemoglobin ≥ 9.0 g/dL without blood transfusion in the last 28 days o Neutrophils ≥ 1.5 x 10^9/L o Pads ≥ 100 x 10^9/L o Total bilirubin ≤ 1.5 x upper limit of normal (ULN) o Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal, or ≤ 5 x ULN if there are liver metastases o Creatinine clearance according to MDRD > 40 ml/min. - Concomitant treatment with authorized bisphosphonates or denosumab - Patient affiliated to a social security system - Patient who has given written consent

Non-inclusion criteria	- Absence of previous treatment with taxane in situations of sensitivity or resistance to castration. - Absence of previous treatment with cabazitaxel in a situation of resistance to castration (unless contraindicated justifying non-administration of the treatment) - Absence of treatment with 2nd generation hormonal therapy (for example abiraterone acetate or enzalutamide) unless contraindicated justifying non-administration of treatment - Previous treatment with platinum salt - Previous anti-tumor treatment stopped less than 21 days ago. For treatments with short half-lives, it will be possible to initiate study treatment at the end of the 5 elimination half-lives of the previous treatment (i.e. before 21 days) - Symptomatic and untreated central nervous system (CNS) metastases. Patients with asymptomatic and previously treated CNS metastases are included if they are clinically stable (not requiring corticosteroid therapy for 28 days) and must have a brain MRI assessment during screening and during follow-up. - Spinal cord compression not treated with radiotherapy or surgery. Patients with previously treated spinal cord compression are included if they are clinically stable (not requiring corticosteroid therapy for 28 days). - Symptomatic metastases candidates for palliative radiotherapy or surgery (for example, painful bone metastases or at risk of fracture) should be treated before initiating study treatment. - History of malignancy within the last 3 years, except non-melanoma skin cancer, carcinoma in situ or superficial bladder tumor. Any other solid tumor or lymphoma (without spinal cord involvement) must have been treated and not show signs of recurrence for at least 3 years. - Radiotherapy treatment within 14 days before inclusion - Uncontrolled pathology such as diabetes mellitus, congestive heart failure, angina, severe cardiac arrhythmia, severe hypertension, or active infection requiring systemic treatment with antibiotics, or any event such as myocardial infarction, stroke or symptomatic pulmonary embolism, within 3 months preceding inclusion, or any significant concomitant pathology that would, according to the investigator, prevent protocol therapy. - Any associated geographic, social, or psychopathological conditions that could compromise the patient's ability to participate in the study - Patient deprived of liberty or under guardianship - Known allergy to platinum salts.
Progress of the study	After signing informed consent and inclusion in the study, the patient will benefit from chemotherapy treatment by: **CARBOPLATIN intravenously, AUC 5 according to Calvert, every 3 weeks, for a duration of 6 to 9 cycles, depending on the tolerance observed.** The therapeutic response will be assessed by a clinical examination, a PSA assay and a radiological assessment (thoraco-abdomino-pelvic scan or MRI, bone scintigraphy, CT scan or brain MRI if necessary) every 3 cycles during treatment then every 3 months until progression. The tolerance of the treatment will be evaluated at each treatment, according to the NCI-CTAE v.4 criteria.
Number of patients needed	Treatment with CARBOPLATIN monotherapy in patients in this study will be considered insufficiently effective if the response rate is less than 20%, and effective if this rate is greater than 40%. According to an optimal Simon design, the number of patients to include is 43 patients in total, including 13 patients in the first stage, considering an alpha risk of 5% and a potency of 80%. At the end of the interim analysis, the study will be stopped for futility if less than 4 responses are observed. Otherwise, carboplatin treatment will be considered effective after observing at least 13 responses out of the 43 evaluable patients. An increase of 10% to take into account non-evaluable patients increases the number of patients to be included to 47 patients.
Participating centers	Number of centers: approximately 3

Duration of the study	The expected duration of recruitment is 36 months. Approximate start of inclusion period: September 2018 The duration of treatment is 9 cycles maximum, i.e. 27 weeks. The duration of the follow-up period is estimated at approximately 12 months

2 SUMMARY OF EXAMINATIONS TO BE CARRIED OUT

	Before Inclusion	**TREATMENT WITH CARBOPLATIN (6 to 9 cycles every 21 days)**		**End of treatment visit (4 weeks after the end of treatment +/- 2 weeks)**	**Post-treatment follow-up visits:** *every 3 months until progression*
	D-28 to D0	**Before each cycle**	**Every 3 cycles**		
Information and signing of informed consent	✓				
Clinical examination – History of illness, medical history – Complete clinical assessment weight, height, PS)	✓ ✓	✓	✓	✓	✓
Biological assessment	✓[1]	✓[2]		✓[2]	✓[3]
Assessment of toxicities		✓	✓	✓	
Evaluation tumor[6] - Thoraco-abdomino-pelvic scan (or MRI) - Bone scintigraphy - Brain scan or MRI	✓ ✓ ✓[4]		✓ ✓ ✓[4]	✓ ✓ ✓[4]	✓ ✓ ✓[4]
Pain assessment QCD/BPI questionnaire	✓	✓		✓	✓
Assessment of quality of life QLQ-C30 and PR-25 questionnaires	✓		✓	✓	✓
Blood sample for research[5]	✓		✓	✓ To do during 1[era] progression after Carboplatin	

[1] Biological assessment to be carried out within 14 days before inclusion and including:
NFS-platelets, sodium, potassium, calcium, creatinine, and clearance (according to MDRD), albumin, AST, ALT, PAL, Gamma GT, total bilirubin, LDH, PSA, Testosterone

[2] Biological assessment including:
NFS-platelets, sodium, potassium, calcium, creatinine, and clearance (according to MDRD), albumin, AST, ALT, PAL, Gamma GT, total bilirubin, LDH, PSA,

[3] PSA only

[4] Brain scan or MRI if known brain metastases or symptoms

[5] On specific tubes: 1 Streck Cell Free DNA BCT tube at each sampling point

[6] Centralized proofreading of bone scans and scanners will be performed in the study. Each exam will thus be sent to the promoter.

3 SCIENTIFIC JUSTIFICATION FOR THE STUDY

3.1 MANAGEMENT OF PROSTATE CANCER

Prostatic carcinoma is the most common cancer in men with an estimated incidence of 48,000 new cases in France in 2017 and 8,200 deaths (INCA, www.e-cancer.fr).

In the metastatic phase, the first-line treatment is androgen deprivation carried out by LHRH agonist or antagonist or by surgical castration. When prostate carcinoma becomes resistant to castration (mCRPC for "metastatic castration resistant prostate cancer"), the therapeutic options are mainly hormone therapies of 2th generation targeting the androgen receptor pathway and taxane chemotherapy. (Rozet, Progress in Urology, 2016)

In the 1990s, randomized phase III clinical trials comparing mitoxantrone corticosteroids to corticosteroids alone showed that mitoxantrone significantly increased the palliative effect of corticosteroid therapy (p = 0.01) (Tannock, J Clin Oncol, 1996; Berry, J Urol, 2002). Mitoxantrone thus became number 1^{era} chemotherapy authorized for the treatment of prostate cancer. However, no difference was observed between the treatment arms in terms of survival.

Subsequently, a randomized phase III study (Tannock, NEJM, 2004) comparing docetaxel combined with prednisone versus mitoxantrone combined with prednisone in 1006 men with mCRPC (TAX 327), showed an increase in overall survival (OS) in favor of the docetaxel arm at a dose of 75 mg/m^2 administered intravenously (IV) every 3 weeks, compared to the mitoxantrone arm (HR = 0.761 [0.619-0.936], p=0.0094). Median overall survival was 18.92 months in the docetaxel group every 3 weeks and 16.49 months in the mitoxantrone group every 3 weeks. This was the first study demonstrating the effectiveness of chemotherapy in terms of overall survival in prostate carcinoma. In a metastatic hormone-sensitive situation, the introduction of docetaxel improves overall survival in the event of a large tumor volume, as documented by CHAARTED studies (Sweeney CJ,, N Engl J Med.,2015) and STAMPEDE (Gandaglia G, Lancet Lond Engl., 2016). Therefore, patients can now receive docetaxel in a hormone-sensitive situation.

The second chemotherapy treatment that has shown benefit in meatastatic prostate carcinoma is cabazitaxel. A randomized phase III study (De Bono, Lancet, 2010) comparing cabazitaxel at a dose of 25 mg/m² IV every 3 weeks plus prednisone, to mitoxantrone at a dose of 12 mg/m² IV every 3 weeks, in 755 patients with mCRPC after treatment with docetaxel, showed an increase in overall survival in favor of cabozantinib compared to mitoxantrone (HR = 0.70 [0.59-0.83], p < 0.0001) This study confirmed the benefit of chemotherapy in mCRPC, demonstrating for the first time the benefit of second-line chemotherapy.

Studies using platinum salts as monotherapy in mCRPC are few in number and have been carried out on small numbers of patients. Toxicity, essentially hematological, remains manageable despite the profile of patients (often elderly patients with metastatic bone damage). They find fairly low response rates varying between 4 and 23% and a regression of PSA of more than 50% for 11 to 33% of patients (Hager, Ann Oncol Off J Eur Soc Med Oncol. 2016). A phase III study with Satraplatin (SPARC trial), an oral derivative of platinum salts, associated with prednisone versus placebo plus prednisone, has not demonstrated a benefit of chemotherapy in terms of overall survival (Sternberg, JCO, 2009). Platinum salts are therefore not used in clinical practice for mCRPC.

However, recent tumor genomic data suggest that certain tumor profiles may respond more favorably to platinum salts.

It therefore seems relevant to evaluate more precisely the place of second-line chemotherapy for mCRPC, which could differ depending on certain tumor characteristics.

3.2 GENOMIC RESEARCH IN PROSTATE CARCINOMA

Recently, genomic analyzes have demonstrated the presence of alterations in DNA repair on the homologous recombination (HR) pathway in approximately 20% to 30% of mCRPCs (Robinson, Cell, 2015). These observations are consistent with what is documented for breast, ovarian, pancreatic and stomach cancers, for which mutations in the RH pathway are found for

approximately 20% of patients.

These are classically anomalies found on genes *BRCA* and *ATM,* but also *CHEK2*. These alterations are associated with a poorer prognosis with a greater risk of lymph node invasion, metastases or even a reduction in overall survival (Annala, Eur Urol, 2017; Mateo, Eur Urol, 2017, Castro, JCO, 2013).
The predictive impact of these abnormalities on responses to second-generation taxane or hormone therapy chemotherapy treatments is being investigated in prostate carcinoma because current studies are contradictory and carried out on a small number of patients, retrospectively: Antonarakis, Eur Oncol, 2018, Annala, Eur Urol, 2017, Mateo, Eur Urol, 2018. Castro, Eur oncol, 2015, Gallagher, BJU int, 2012.

In contrast, these alterations on the RH pathway are associated with increased sensitivity to poly(ADPribose) polymerase (PARP) enzyme inhibitors. Indeed, PARP is a molecular detector of breaks in DNA and plays an essential role in their repair, thus contributing to the maintenance of genome integrity and cell survival. PARP inhibitors are particularly effective in cells with abnormalities of the RH pathway. This phenomenon is called synthetic lethality, that is, a lethal combination of two effects which, taken in isolation, are not fatal. The synthetic lethality created by the combination of PARP inhibitor and RH pathway anomaly was interpreted as resulting from the repair inefficiency of spontaneous single-strand breaks in cells treated with a PARP inhibitor, inducing the conversion of these breaks single-stranded to double-stranded breaks during replication. These double-strand breaks are fatal in cells mutated for BRCA1/2, because they cannot be repaired, due to the non-functionality of RH. Thus, olaparib has demonstrated its effectiveness as a maintenance treatment versus placebo after response to platinum chemotherapy in patients with a BRCA mutation (germinal or somatic) in late relapse (> 6 months) of their serous ovarian cancer high grade, tube or primary peritoneum (Ledermann J, Lancet oncol, 2014). More recently, niraparib has demonstrated its effectiveness in the same indication on ovarian tumors not selected according to their genetic profile but the benefit remains greater in patients with a germline BRCA mutation or for tumors presenting an anomaly of the homologous recombination pathway (Mirza, NEJM, 2016).

Olaparib also demonstrated its effectiveness in a phase III study versus standard chemotherapy in patients with a germline BRCA mutation and metastatic breast carcinoma (Robson, NEJM, 2017).
Furthermore, olaparib was evaluated in prostate carcinoma as monotherapy in a non-randomized phase II study (Mateo, NEJM, 2015). Among the 50 patients included, a partial response was observed for 16 patients (33%), with a treatment duration of more than 6 months for 12 of them. Somatic tumor abnormalities in the HR pathway were found in 16 patients, including 14 patients (88%) who achieved a response to treatment with olaparib. Abnormalities of the HR pathway therefore appear to be biomarkers of the effectiveness of PARP inhibitors in prostate carcinoma. Several phase II and III studies are underway with olaparib and other PARP inhibitors in CPRC selected for abnormalities of the homologous recombination pathway (ClinicalTrial references: NCT02987543, NCT03434158, NCT02893917...).

In breast and ovarian cancers, literature data show the particular sensitivity of tumors with alterations in DNA repair on the RH pathway to platinum salts (ZHAO, Clinical Cancer Research, 2017; Telli, Breast Cancer Res Treat 2018; XU Kai, Oncotarget 2017). Indeed, platinum salts form covalent bonds on the deoxyribonucleic acid (DNA) molecule either the same helix, or between the 2 strands of the DNA double helix called intra and interstrand bridges: the first are in the vast majority, representing more than 90% of the adducts formed. The formation of these platinum adducts will cause distortion of the DNA double helix and these adducts will disrupt the DNA replication and transcription phenomena. In cells with an abnormality of the RH pathway, DNA repair is not possible, leading to cell death.

Studies with carboplatin in prostate carcinoma in unselected tumors are inconclusive. However, recently, Cheng et al (Cheng, Eur Urol, 2016) reported a clinical benefit of Carboplatin for 3 patients with BRCA 2 mutated prostate carcinoma, retrospectively. Similarly, retrospective analysis of the cohort of patients with castration-resistant prostate carcinoma mutated for BRCA 2 and treated with carboplatin in Dana-Farber Cancer Institute finds an encouraging response rate since 6 of the 8 patients (75%) obtained a 50% reduction in their PSA level at 12 weeks (compared to only 17% in patients without a mutation) (Pomerantz, Cancer, 2017).

Empirically, several medical teams are starting to use it in the specific subgroup of tumors presenting an abnormality on the RH pathway which would confer particular sensitivity to platinum salts.
It therefore seems important to rigorously and prospectively evaluate the benefit of Carboplatin in this type of patient an anomaly on the path to HR.

3.3 ASSUMPTIONS AND EXPECTED RESULTS

To date, there are no prospective data on the benefit of platinum salts for prostate carcinomas presenting an alteration of the RH pathway.
The Laboratory of Cancer Biology and Genetics (INSERM U1245) of the François Baclesse Center has expertise in the study by NGS and its bioinformatics analysis of constitutional mutational events at the origin of genetic predispositions to breast and ovarian cancers and tumor mutational events of prognostic or therapeutic interest. He developed a panel of genes as part of the search for abnormalities in the HR pathway. These genetic alterations are sought on tumor tissue by the simultaneous study of a panel of 33 genes involved in the HR pathway by Next-Generation Sequencing (NGS) and an adapted bioinformatics analysis, in particular for the detection of variations in copy number (CNV) (Knijnenburg, Cell Reports, 2018).

In this context, we propose a phase II study aimed at prospectively evaluating the effectiveness of Carboplatin monotherapy in the tumor subgroup of metastatic castration-resistant prostate carcinomas presenting a somatic abnormality on the RH pathway. This study could also make it possible to better characterize the molecular abnormalities of tumors necessary for the response to carboplatin.

3.4 BIOLOGICAL ANCILLARY STUDY

Circulating tumor DNA (ctDNA: Circulating Tumor DNA), a fraction of circulating DNA (cfDNA: Cell Free DNA) today constitutes a biomarker of choice for evaluating tumor progression as well as response and resistance to treatments, in particular due to its ease of access and its minimally invasive nature (sampling from a simple blood test: "liquid biopsy"). The TOPARP-A clinical trial, evaluating olaparib in mCRPC, was able to show that a drop in cfDNA concentration of more than 50% after 8 weeks of treatment was correlated with better overall survival and better progression-free survival (Goodall, Cancer Discov., 2017). In the same study, cfDNA genotyping also made it possible to highlight the appearance of reversion variants during treatment, restoring the reading framework and possibly being the cause of resistance mechanisms to PARP inhibitors.
The objective of this ancillary study is to evaluate the relevance of ctDNA and cfDNA as a biomarker of disease progression and response to Carboplatin.
Thus, at the inclusion of patients and at each tumor evaluation (every 3 cycles of carboplatin chemotherapy), a dedicated blood sample will be taken for extraction and evaluation of the cfDNA concentration, in order to study variations in concentration over time. time. The material will be retained for genotyping at the end of the study of selected cases that showed progression, looking for resistance variants.
Genotyping of cfDNA will be carried out by high-throughput sequencing of a panel of 33 genes involved in HR, in the same way as the initial molecular characterization of the tumor.

4 OBJECTIVES OF THE STUDY

4.1 MAIN OBJECTIVE

The main objective is to evaluate the effectiveness in terms of response rate of Carboplatin monotherapy in patients with metastatic castration-resistant prostate carcinoma and presenting a somatic abnormality of the homologous recombination pathway.

4.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate progression-free survival (radiographic and biological) in patients treated with carboplatin for a prostate tumor presenting abnormalities of the homologous recombination pathway.
- Evaluate the duration of the tumor response
- Assess overall survival
- To evaluate the safety and safety data of carboplatin in this population

4.3 GOALS EXPLORATORY

- Correlate the response to carboplatin according to the type of abnormality of the homologous recombination pathway found.
- Detect mechanisms of new resistance on circulating tumor DNA

5 JUDGMENT CRITERIA

5.1 MAIN CRITERION

The main criterion of the study is the response rate (TR) defined according to the recommendations of the PCWG3 (Prostate Cancer Clinical Trials Working Group 3, Scher et al, J Clin Oncol, 2016) as one of the following 2 points:

- Objective radiological response (Complete or partial response according to RECIST 1.1 modified criteria and no bone progression).
- Decrease in PSA ≥ 50%, measured twice 3 to 4 weeks apart.

Response rate is the proportion of patients for whom an objective response was observed during tumor assessments.

5.2 SECONDARY CRITERIA

The secondary criteria are:

- Radiographic progression-free survival (RPS) defined by the time between the start date of treatment and the first date of radiographic progression or the date of death regardless of the cause
- Survival without biological progression defined by the time between the start date of treatment and the first date of documented biological progression or the date of death regardless of the cause
- The duration of the tumor response (radiographic/biological) defined by the time between the date of best response (objective/stable) and the date of progression (radiographic/biological) or death whatever the cause
- Overall survival defined by the time between the start date of treatment and the date of death regardless of the cause
- Toxicities: type, frequency and grade of adverse events according to CTCAE version 4.0
- The dose-intensity of Carboplatin
- The presence of an anomaly of the homologous recombination pathway found
- Mechanisms of new resistance on circulating tumor DNA

6 STUDY PLAN

6.1 METHODOLOGY

This is a multicenter, open-label, prospective phase 2 trial.

6.2 DURATION OF STUDY

The expected duration of recruitment is 36 months.

The duration of treatment with carboplatin is a maximum of 9 cycles or 27 weeks.

The duration of the follow-up period which will be carried out until the last patient progresses is estimated at approximately 12 months.

6.3 PATIENT SELECTION

6.3.1 Inclusion criteria

- Patients > 18 years old
- Patients with adenocarcinoma or poorly differentiated carcinoma prostate, histologically confirmed (pure small cell histologies or pure high-grade neuroendocrine histologies are excluded)
- Tumor presenting a pathogenic somatic variant likely to alter the homologous recombination pathway previously detected on a tumor biopsy or on circulating tumor DNA, or germline mutation among the defined list of genes (appendix 1)
- Tumor resistant to castration defined by progression despite well-conducted androgen deprivation treatment: testosteroneemia ≤ 50ng/dL sub-luteinizing hormone releasing hormone (LHRH) agonist/antagonist. The patient must agree to continue concomitant treatment with an analogue (agonist or antagonist) of LHRH or surgical castration for the duration of administration of the study treatment for patients without a history of surgical castration.
- Patients must have completed at least one line of taxane chemotherapy in a castration resistance situation:
    - patients who have received treatment with docetaxel in a situation of hormone sensitivity must have received at least one treatment with cabazitaxel in a situation of resistance to castration
    - Patients who have not received chemotherapy in a hormone-sensitive situation must have received treatment with docetaxel AND cabazitaxel or have a contraindication justifying non-administration of the treatment
- Patients must have been treated with at least 2 hormonal therapiesth generation (e.g. abiraterone acetate or enzalutamide)
- the patients may have been treated with an inhibitor poly(ADP-ribose) polymerase **(**PARP)
- Performance Status $\underline{<}$ 2
- Current progressive metastatic disease defined by one or more of the criteria below:
    - Progressive disease measurable according to RECIST 1.1 criteria: Increase of at least 20% in the sum of the diameters of the measurable lesions compared to the smallest sum observed, or appearance of one or more new lesions observed by CT.
    - Progression noted by bone scintigraphy: appearance of two or more new lesions on the bone scintigraphy
    - Increased serum PSA levels: It is necessary to have two consecutive documented increases in PSA levels at intervals of at least one week from a previous baseline. If the third PSA level value is less than the second, then a fourth additional test is recommended to confirm the increase in PSA level. For patients whose progression is only documented by an increase in PSA level, the minimum baseline value is 5.0 ng/ml to be eligible for inclusion in the study.
- Normal organ function and sufficient bone marrow reserve, measured within 28 days prior to administration of study treatment, as defined below:
    - Hemoglobin ≥ 9.0 g/dL without blood transfusion in the last 28 days
    - Neutrophils ≥ 1.5 x 10^9/L
    - Pads ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)

- Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal, or ≤ 5 x ULN if there are liver metastases
- Creatinine clearance according to MDRD > 40 ml/min.

- Concomitant treatment with authorized bisphosphonates or denosumab
- Patient affiliated to a social security system

6.3.2 Non-inclusion criteria

- Absence of previous treatment with taxane in a sensitive situation or resistance to castration.
- Absence of previous treatment with cabazitaxel in a situation of resistance to castration (unless contraindicated justifying non-administration of the treatment)
- Absence of treatment with hormonal therapy of 2th generation for example abiraterone acetate or enzalutamide unless contraindicated justifying non-administration of the treatment
- Previous treatment with platinum salt
- Previous anti-tumor treatment stopped less than 21 days ago. For treatments with short half-lives, it will be possible to initiate study treatment at the end of the 5 elimination half-lives of the previous treatment (i.e. before 21 days)
- Symptomatic and untreated central nervous system (CNS) metastases. Patients with asymptomatic and previously treated CNS metastases are included if they are clinically stable (not requiring corticosteroid therapy for 28 days) and must have a brain MRI assessment during screening and during follow-up.
- Medullary compression not treated with radiotherapy or surgery. Patients with previously treated spinal cord compression are included if they are clinically stable (not requiring corticosteroid therapy for 28 days).
- Symptomatic metastases candidates for palliative radiotherapy or surgery (for example, painful bone metastases or at risk of fracture) should be treated before initiating study treatment.
- History of malignancy within the last 3 years, except non-melanoma skin cancer, carcinoma in situ or superficial bladder tumor. Any other solid tumor or lymphoma (without spinal cord involvement) must have been treated and not show signs of recurrence for at least 3 years.
- Radiotherapy treatment within 14 days before inclusion
- Pathology uncontrolled such as diabetes mellitus, congestive heart failure, angina, severe cardiac arrhythmia, severe hypertension, or active infection requiring systemic treatment with antibiotics, or any event such as myocardial infarction, stroke, or symptomatic pulmonary embolism, within 3 months preceding inclusion, or any significant concomitant pathology that would, according to the investigator, prevent protocol therapy.
- Any associated geographic, social, or psychopathological conditions that could compromise the patient's ability to participate in the study
- Patient deprived of liberty or under guardianship
- Known allergy to platinum salts

6.4 PROGRESS OF THE STUDY

6.4.1 Signing of study consent

The study will be offered by oncologists to patients meeting the eligibility criteria. They will be given an information note and an informed consent form. Patients will have a reflection period of the duration of their choice.

After obtaining the patient's consent by signing the study consent, the selection criteria will be verified before inclusion in the trial.

6.4.2 Inclusion procedure

After obtaining the patient's agreement by signing the study consent, the selection criteria will be verified before inclusion.
The inclusion will be recorded before the administration of the treatment on the software dedicated to the study via an internet portal.
An identification number will be assigned to the patient and will be used throughout the study.

6.4.3 Administration of Carboplatin

After inclusion in the trial, **chemotherapy treatment with intravenous CARBOPLATIN, AUC 5, will then be carried out every 3 weeks, for a duration of 6 to 9 cycles, depending on the tolerance observed.**

The dose to be administered will be calculated according to the Calvert formula which determines a total dose in mg. Calvert's formula takes into account the glomerular filtration rate (GFR in ml/min) and the area under the curve (AUC in mg/ml x min.):

Total dose (mg) = AUC X (GFR +25)

The AUC is set at 5 in this study for all patients. The maximum dose of Carboplatin allowed for a cycle is 750 mg.

6.5 EVALUATIONS OF THE STUDY

A summary table of the requested investigations is present at the start of the protocol.

6.5.1 Inclusion report

Patients eligible for the trial and having signed their consent to participate must carry out an initial assessment within 28 days before the start of chemotherapy treatment.

This assessment will understand:

- Clinical examination with Performance Status and weight
- Thoraco-abdomino-pelvic scan or MRI
- Bone scintigraphy
- Brain scan or MRI if known brain metastases or symptoms
- Pain questionnaire: BPI
- Quality of life questionnaires: QLQ-C30 and module PR-25
- Biological assessment to be carried out within 14 days preceding the start of treatment and including:
    - NFS-platelets, sodium, potassium, calcium, creatinine, and clearance (according to MDRD) albumin, AST, ALT, PAL, Gamma GT, total bilirubin, LDH, PSA, testosterone
- Blood sample for ancillary study: 1 tube Streck Cell Free DNA BCT

6.5.2 Assessments during treatment

❖ **Before each cycle**

- Clinical examination with Performance Status and weight
- Pain questionnaire: BPI
- Biological assessment including
    - NFS-platelets, sodium, potassium, calcium, creatinine, and clearance (according to MDRD) albumin, AST, ALT, PAL, Gamma GT, total bilirubin, LDH, PSA
- Monitoring of treatment tolerance according to NCI-CTAE v.4 criteria.

❖ **Every 3 cycles**

A tumor assessment will be carried out every 3 cycles, approximately every 9 weeks during treatment and will include:

- Thoraco-abdomino-pelvic scan or MRI
- Bone scintigraphy
- Brain scan or MRI if known brain metastases or symptoms

It will also be carried out:

- Quality of life questionnaires: QLQ-C30 and module PR-25
- Blood sample for ancillary study: 1 tube Streck Cell Free DNA BCT

The assessment will be carried out every 3 cycles. In the event of a cycle postponement, the assessment will also be postponed in order to comply with the protocol.

6.5.3 End of treatment assessment

The end-of-treatment assessment will be carried out approximately 4 weeks after the end of treatment (+/- 2 weeks)

- Clinical examination with Performance Status and weight
- Monitoring of treatment tolerance according to NCI-CTAE v.4 criteria.
- Thoraco-abdomino-pelvic scan or MRI
- Bone scintigraphy
- Brain scan or MRI if known brain metastases or symptoms
- Pain questionnaire: BPI
- Quality of life questionnaires: QLQ-C30 and module PR-25
- Biological assessment including
    - NFS-platelets, sodium, potassium, calcium, creatinine, and clearance (according to MDRD) albumin, AST, ALT, PAL, Gamma GT, total bilirubin, LDH, PSA
- If progression: blood sample for ancillary study on 1 Streck Cell Free DNA BCT tube

6.5.4 Follow-up visits

Follow-up visits will be carried out every 3 months until progress.

This assessment will understand:

- Clinical examination with Performance Status
- Thoraco-abdomino-pelvic scan or MRI
- Bone scintigraphy
- Brain scan or MRI if known brain metastases or symptoms
- Pain questionnaire: BPI
- Quality of life questionnaires: QLQ-C30 and module PR-25
- Biological assessment including a PSA assay
- During progression: Blood sample for ancillary study on 1 Streck Cell Free DNA BCT tube

6.5.5 Follow-up after progression with Carboplatin

No protocol monitoring will be imposed. Only survival and anti-tumor treatments administered after carboplatin will be collected.

6.6 PREMATURE DISCONTINUATION OF TREATMENT

Treatment will be interrupted at any time in the following circumstances:

- Disease progression (clinical or radiological)
- Need to initiate another anti-tumor treatment such as radiotherapy. Analgesic radiotherapy is also a criterion for stopping treatment in the study
- Unacceptable toxicity, not compatible with continued treatment, particularly in the event of abnormal myelosuppression or abnormal impairment of renal or hepatic function

- Patient decision (data already collected during research may be retained and used unless the patient objects''to it)
- Intercurrent illness or other reason that requires stopping study treatment
- Patient lost to follow-up
- Investigator's decision

6.7 CONCOMITANT TREATMENTS

The following treatments/procedures are permitted:

- Antiemetic treatments are authorized and are prescribed according to the habits of the investigators.
- Biphosphonates may be prescribed at the discretion of the investigator in accordance with local practices.
- EPO and G-CSF may be prescribed at the discretion of the investigator in accordance with local practices.

The following treatments/procedures are not permitted:

- Systemic treatments such as chemotherapy, hormone therapy, immunotherapy or other anti-cancer treatments (including bone radiotherapy)
- Administration of yellow fever vaccine (risk of fatal generalized vaccine disease)
- Administration of live attenuated vaccines (risk of possibly fatal generalized vaccine disease

The following treatments will be subject to precautions for use:

- Phenytoin (risk of occurrence of convulsions due to reduced digestive absorption of phenytoin by the cytotoxic agent. Temporarily combine an anticonvulsant benzodiazepine)
- Cyclosporine (excessive immunosuppression with risk of lymphoproliferation), Tacrolimus
- Loop diuretics should be considered due to cumulative nephrotoxicity and ototoxicity

7 TREATMENT OF THE STUDY: CARBOPLATIN

Carboplatin will be the responsibility of the Promoter.

7.1 Description of carboplatin

Carboplatin is a cytostatic with biochemical properties similar to cisplatin.

Carboplatin binds to the DNA molecule by producing alkyl bonds responsible for forming bridges between the two chains of the molecule or between the chains of two adjacent DNA molecules. Replication synthesis and subsequent separation of DNA are thus inhibited, as are, secondarily, syntheses of RNA and cellular proteins.

7.2 Carboplatin packaging

The carboplatin is packaged as a solution for infusion.

7.3 Storage methods for carboplatin

There conservation carboplatin is made at a temperature not exceeding 25°C, in the original packaging and protected from light.

After dilution: immediate use is recommended.

The storage methods are in line with the manufacturer's recommendations as specified in the SmPC of carboplatin used in the investigating center.

7.4 Method of administration of carboplatin

There route of administration of carboplatin is by intravenous infusion.

The different dosages of carboplatin can be administered as is at a concentration of 10 mg/ml as a diversion from an infusion of 5% glucose solution. They can also be diluted before administration

using a 5% glucose solution, up to a minimum concentration of 0.5 mg/ml. In all cases, it is recommended after infusion of Carboplatin to rinse the vein with a 5% glucose solution.

Note:
None of the components necessary for intravenous infusion administration of Carboplatin should contain all or part aluminum. Indeed, an interaction between aluminum and platinum would be responsible for a black precipitate that could be observed after reconstitution of the solution.
In case of extravasation, administration will be stopped immediately.

8 DOSE ADJUSTMENTS

8.1 General conditions of administration

The following conditions must be met for the prescription of carboplatin before each cycle:

- PNN $\geq$ 1500 /mm^3
- Brochures $\geq$ 100,000/mm^3

If cycles are postponed for more than 21 days, treatment will be permanently interrupted.

8.2 Adaptation of treatment

The treatment and dose levels will have to be adapted according to the SmPC of carboplatin.

9 ANCILLARY STUDY

In the event of progression to carboplatin treatment, targeted sequencing of circulating DNA will be carried out by Next-Generation Sequencing (NGS) on an Illumina platform, after simultaneous capture enrichment (Superect XT, Agilent) of the coding regions of a expanded panel of 33 genes involved in homologous recombination. It will be produced with a reading depth objective of 1000x average.

An adapted bioinformatics analysis allowing the detection of variants such as point mutations (Single Nucleotide Variation), insertions-deletions and copy number variation (Copy Number Variation) will be implemented. It will also make it possible to highlight the weakly represented variants (low fraction of mutant alleles) in the tumor sample which can indicate the heterogeneity of the tumors. This pipeline will be based on BWA (alignment) then HapotypeCaller, Lofreq2 and OutLyzer ("variant calling" of SNV and Indels) and CNVkit (analysis of CNVs in "read count").

10 CENTRALIZED RADIOLOGICAL PROOFREADING

Centralized proofreading of bone scans and scanners will be performed in the study.
An anonymized copy of the imaging examinations will thus be sent to the promoter.

11 EVALUATION OF EFFECTIVENESS AND SAFETY

11.1 Efficacy evaluation parameters

Response to treatment will be assessed according to the recommendations of the PCWG3 (Scher et al, J Clin Oncol, 2016) and defined as one of the following 2 points:

- Objective radiological response (Complete or partial response according to RECIST 1.1 modified criteria and no bone progression).
- Decrease in PSA ≥ 50%, measured twice 3 to 4 weeks apart.

11.2 Security assessment settings

Safety assessment will be carried out by assessing the general (PS, weight) and clinical condition of patients, and by collecting events occurring during and after irradiation during consultations.

The intensity of events will be estimated according to the NCI-CTCAE version 4.0 classification (toxicity grades 1 to 5). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Light (grade 1):	does not affect the patient's usual daily activity
Moderate (grade 2):	disrupts the patient's usual daily activity
Severe (grade 3):	prevents the patient's usual daily activity
Very Severe (grade 4):	imposes resuscitation measures/threatens the vital prognosis
Death (grade 5):	Death

12 VIGILANCE FOR RESEARCH

12.1 GENERAL RULES - INSTRUCTIONS

Vigilance will be conducted in accordance with the regulations in force on research involving so-called category 1 humans.

12.2 DEFINITIONS

12.2.1 Adverse event

Any harmful manifestation occurring in a person who is involved in research involving humans, whether or not this manifestation is linked to the research or to the product to which this research relates.

12.2.2 Undesirable effect

Any harmful manifestation occurring in a person who is involved in research involving humans **related to the research or product** which this research focuses on.
Any harmful and unwanted reaction to an investigational drug regardless of the dose administered.

12.2.3 SERIOUS Adverse Event or Effect

An adverse event or adverse reaction is considered serious when it:

- causes death.
- endangers the life of the person who undertakes the research,
- requires hospitalization or extension of hospitalization,
- causes significant or lasting incapacity or handicap,
- results in a congenital anomaly or malformation,
- *is considered medically significant**

Is considered " *medically significant* any clinical event or laboratory result considered serious by the investigator and not corresponding to the other severity criteria defined above. This type of adverse event can put the patient at risk and requires medical intervention to prevent an outcome corresponding to one of the severity criteria mentioned above (examples: overdoses, second cancers, pregnancies and new facts can be considered medically significant and must be brought to the attention of the sponsor).

Some "hospitalization/extension of hospitalization" are not considered serious adverse events:

- **admission for social or administrative reasons**
- **hospitalization predefined by the protocol**
- **hospitalization for medical or surgical treatment scheduled before the research**
- **passage to day hospital**
- **hospitalizations for pre-existing, non-aggravated signs and symptoms**

It is therefore not necessary to notify them as SAEs

12.2.4 UNEXPECTED side effect

Any adverse effect of the product whose nature, severity, frequency or evolution do not agree with **safety reference information** mentioned in the summary of product characteristics or in the brochure for the investigator when the product is not authorized.
It is the promoter who determines the expected/unexpected nature of an event with regard to the pharmacovigilance reference document

12.2.5 New security development

Any new data that may lead to a reassessment of the ratio of benefits and risks of the research or the product subject to the research, to modifications in the use of this product, in the conduct of the research, or to documents relating to the research, or to suspend or interrupt or modify the research protocol or similar research.

12.3 RESPONSIBILITIES OF THE INVESTIGATOR

12.3.1 Methods for detecting and collecting adverse events

All adverse events should be investigated, reported and recorded, treated and evaluated.
Adverse events **occurring from the signing of the consent will be collected in the CRF, up to 30 days after the last one** administration of the investigational drug.
Each adverse event observed will be the subject of an individual collection. The intensity of adverse events will be estimated according to the NCI-CTCAE version 4.0 classification (toxicity grades 1 to 5). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Mild (grade 1): does not affect the patient's usual daily activity

Moderate (grade 2): disrupts the patient's usual daily activity

Severe (grade 3): prevents the patient's usual daily activity

Very Severe (grade 4): imposes resuscitation measures/threatens the vital prognosis

Death (grade 5): Death

The nature of each adverse event and the severity will be established *(see 1.2.3)*, date of occurrence/end, duration, severity, relationship to treatment and course.
The investigator will need to clarify whether the events are related to research, the products being tested, associated medications, an underlying pathology, disease progression or another cause.

If an adverse event meets the definition of serious adverse event, it must also be notified to the promoter without delay on the dedicated form according to the procedures described in paragraph 1.3.2.

12.3.2 Notification of Serious Adverse Events

The investigator informs the Clinical Research Unit of all serious adverse events **which occur during the study or within 30 days of the last administration of the product.**

All Serious Adverse Events Delayed (**occurring after this 30 day period)** considered reasonably **related** protocol processing(s) or research must be declared without time limit.

The investigator must **notify the promoter without delay from the day he becomes aware of it**, all serious adverse events occurring in the trial, except those identified in the protocol or in the investigator's brochure as not requiring immediate notification.

This notification is the subject of a written report and must be followed if necessary by one or more detailed written report(s)).

The investigator will note for each event

- ✓ Its description as clearly as possible according to medical terminology.
- ✓ Intensity,
- ✓ The start and end date of the event,
- ✓ The measures taken and the need or not for corrective treatment,

- ✓ If trial processing has been interrupted,
- ✓ Its evolution. In the event of a non-fatal event, the progress must be followed until recovery or return to the previous state or stabilization of possible after-effects
- ✓ There **causal relationship** with the product(s) of the trial, the research procedures, the pathology treated, another pathology, another treatment.
- ✓ Its description as clearly as possible according to medical terminology.
- ✓ Intensity,

To do this, he uses the dedicated study form made available in the Investigator binder, which he completes, dates and signs. He must also attach laboratory results or examination or hospitalization reports providing information on the serious event, including relevant negative results without failing to report these ***anonymous documents,*** so that it does not appear that the patient's initials (1st letter of the last name and 1st letter of the first name), their gender and their date of birth***.*** If necessary, he may also send the promoter a copy of the autopsy report.
All these documents will be sent to the vigilance service, mandated by the promoter, according to the procedures listed on the dedicated research form.

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

The investigator must document the event as best as possible, if possible give it **medical diagnosis** and establish one causal link between the serious adverse event and research, the products under test, associated medications, underlying pathology, disease progression or other cause.

The investigator immediately communicates to the sponsor additional information concerning serious adverse events as he becomes aware of them.

The investigator must monitor the patient who has experienced a serious adverse event **until resolved**, stabilization at a level deemed acceptable by the investigator or return to the previous state, **even if the patient has exited the trial and inform the sponsor of the progress of the serious adverse event**.

12.3.3 Special cases

12.3.3.1 Adverse Event of Special Interest (AESI)

Any serious or non-serious adverse event that requires special attention and will be specifically investigated. These AESIs must be notified and monitored in the same way as serious adverse events.
There is no AESI for this research.

12.3.3.2 Serious adverse event not to be reported immediately

Any event that is part of the natural history of the disease (progression of the disease or hospitalization for progression of the disease) should not be reported immediately to the sponsor but should be reported in the research FIU.
Certain "hospitalization/extension of hospitalization" are not considered serious adverse events and do not require immediate notification (see last paragraph of 11.2.3)

12.3.3.3 Pregnancy case

If a woman begins a pregnancy as part of research or in certain cases if it is her partner who participates in research (medication that can reach the man's seminal lineage), the pregnancy must be declared to the sponsor.
The investigator informs the sponsor (by telephone, fax or email) who will send him a "collection of initial pregnancy data" form. This form must contain the expected date of delivery, contact details of the obstetrician and the maternity ward planned for delivery if the pregnancy continues.

The investigator must follow the patient until the end of the pregnancy or its termination and notify the outcome to the sponsor.

If the outcome of pregnancy falls within the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, ...) the investigator must follow the IGE reporting procedure.

If it is a paternal exposure, the investigator must obtain the consent of the party to collect information on the pregnancy.

13 STATISTICAL CONSIDERATIONS

13.1 NUMBER OF SUBJECTS NEEDED

Treatment with CARBOPLATIN monotherapy in patients in this study will be considered insufficiently effective if the response rate is less than 20%, and effective if this rate is greater than 40%. According to an optimal Simon design, the number of patients to include is 43 patients in total, including 13 patients in the first stage, considering an alpha risk of 5% and a potency of 80%. At the end of the interim analysis, the study will be stopped for futility if less than 4 responses are observed. Otherwise, carboplatin treatment will be considered effective after observing at least 13 responses out of the 43 evaluable patients.
An increase of 10% to take into account non-evaluable patients increases the number of patients to be included to 47 patients.

13.2 STATISTICAL ANALYSIS

Qualitative variables will be described using numbers and percentages, quantitative variables using mean (+/- standard deviation) or median and extent if the assumption of normality is not not verified.

The statistical significance threshold is set at 5% for each statistical analysis and confidence interval.

For the evaluation of the primary endpoint, the effectiveness of carboplatin monotherapy in the patients studied will be proven if an objective response is observed for a minimum of 14 patients. Otherwise, the use of carboplatin will be considered ineffective.

Survival curves will be estimated using the Kaplan-Meier method. Medians of survival as well as survival rates will be estimated with their 95% confidence interval.

Toxicities occurring during and within one month of the end of chemotherapy will be described in terms of type, frequency and grade (according to the NCI CTCAE v.4.0 classification).

14 TEST MONITORING

14.1 QUALITY ASSURANCE

In order to guarantee the authenticity and credibility of the data in accordance with the GCPs, the promoter will put in place a quality assurance system which includes:

- management of the trial according to the procedures of the Clinical Research Unit,
- quality control of data from the investigating site by the monitor whose role is to verify the concordance and consistency of the data in the observation notebook in relation to the source documents,
- the provision, if funding provides, of dedicated staff in the department to help the investigator with the logistics of the study and the collection of data in the observation notebooks.

15 ETHICAL AND REGULATORY CONSIDERATIONS

The research will be conducted in compliance with current French regulations, in particular the provisions relating to research involving biomedical humans of the Public Health Code, articles L1121-1 et seq. (law n° 2012-300 of 03/05/2012), bioethics laws, the Data Protection Act, the Declaration of Helsinki, and Good Clinical Practices.

15.1 REGULATORY AUTHORIZATIONS

A request for authorization will be sent by the Promoter before the start of the study to the competent authorities:

- to the Committee for the Protection of Persons (CPP)
- to the Competent Authority (ANSM).

This study falls within the framework of the "Reference Methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the amended law of January 6, 1978 relating to data processing, files and freedoms. This change was approved by decision of January 5, 2006.
Any substantial modification of the protocol, concerning the objectives of the study, its plan, the population, the examinations or significant administrative aspects, will require the approval of the coordinating investigator, the sponsor, the favorable opinion of the CPP and the authorization from the competent authority before any implementation.

15.2 PATIENT INFORMATION AND WRITTEN INFORMED CONSENT FORM

Patients will be informed completely and fairly, in understandable terms, of the objectives and constraints of the study, the possible risks involved, the necessary monitoring and safety measures, their rights to refuse to participate in the study or the possibility of withdrawing at any time.
All this information appears on an information and consent form given to the patient. The patient's free, informed and written consent will be obtained by the investigator, or a doctor who represents him before final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient, the other copy will be kept by the investigator. For any substantial modification of the protocol, concerning the objectives of the study, its plan, population, examinations or significant administrative aspects, new consent from the people participating in the research will be obtained if necessary.

15.3 AMENDMENTS TO THE PROTOCOL

Any substantial modification of the protocol, concerning the objectives of the study, its plan, the population, the examinations or significant administrative aspects, will require the approval of the coordinating investigator, the sponsor, the favorable opinion of the CPP and the authorization from the competent authority before any implementation.

15.4 CONDUCT OF THE STUDY AND RESPONSIBILITIES OF INVESTIGATORS

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol which has been approved by the CPP and the ANSM. The investigator must not make any modification to the protocol without the authorization of the sponsor and without the CPP and the ANSM having given a favorable opinion on the proposed modifications.

It is the responsibility of the principal investigator:

- ✓ to provide the promoter with his curriculum vitae as well as those of the co-investigators,
- ✓ to identify the members of your team who participate in the trial and to define their responsibilities,
- ✓ to start patient recruitment after authorization from the sponsor.
- ✓ to do its utmost to include the required number of patients within the established recruitment period.

It is the responsibility of each investigator:

- ✓ to obtain informed consent dated and personally signed by the patient before any trial-specific selection procedure,
- ✓ to regularly complete the observation notebooks (CRF) for each of the patients included in the trial and to give the Clinical Research Assistant (ARC) direct access to the source documents so that the latter can validate the CRF data,

- ✓ to date, correct and sign the corrections of the CRFs for each of the patients included in the study,
- ✓ to accept regular visits from the ARC and possibly those from auditors mandated by the promoter or inspectors from the supervisory authorities.

All documentation relating to the study (protocol, consents, observation notebooks, investigator file, etc....), as well as original documents (laboratory results, radiologies, consultation reports, examination reports clinics performed, etc.) must be held in a secure location and considered confidential material.

The archiving of data will be the responsibility of the investigator and according to current legislation. The latter must keep the data as well as a patient identification list for a minimum period of 15 years after the end of the study.

15.5 DATA OWNERSHIP AND CONFIDENTIALITY

The investigator undertakes, for himself and for all persons required to monitor the progress of the trial, to guarantee the confidentiality of all information relating to the project until the publication of the results of the trial. This obligation of confidentiality will not apply to the information that the investigator will be required to communicate to patients as part of their participation in the trial nor to information already published.

The investigator undertakes not to publish, disclose or use, in any way, directly or indirectly, the scientific or technical information in relation to the trial.

The test cannot be the subject of any written or oral comment without the agreement of the promoter; all information communicated or obtained during the carrying out of the test automatically belongs to the promoter who may freely dispose of it.

16 DATA PROCESSING AND STORAGE

16.1 COLLECTION AND PROCESSING OF DATA

All information required by the protocol must be recorded in the observation notebooks under the responsibility of the principal investigator and an explanation must be provided for each missing data. The data should be collected as it is obtained, and collected in these notebooks.

Data entry and management will be carried out by the Data Processing Center (CTD) of the Cancéropôle Nord-Ouest. The CTD provides a database management software package dedicated to clinical research: EnnovClinical (ClinSight® software; version 7.5.10, ENNOV /CLINSIGHT, 33155 Cenon, France).

This software package, which is based on an Oracle database architecture™, is designed for the overall management of clinical and epidemiological studies, meets the regulatory requirements related to this type of study. A data validation plan will be developed and will describe in detail the checks to be performed for each variable as well as the list of obvious corrections allowed.

A study-specific database will be created, tested and validated before entry begins.

The questionnaires will be completed in the form of an electronic questionnaire (decentralized entry possible). The data will then be checked by the management team using error messages from validation programs. Obvious errors will be corrected. Other errors, omissions or inconsistencies will be noted on correction request forms which will be sent to the investigator for resolution. As soon as the response is received, the corrections will be included in the database.

The database will be frozen after final quality control, then exported in the format suitable for statistical analysis according to an automated and validated procedure.

16.2 ARCHIVING

The sponsor must ensure the archiving of essential documents on the conduct of the study under conditions ensuring their security, for the minimum period provided for by the BPCs, i.e. 15 years after the end of the research

These documents are the protocol and annexes including any amendments, original information forms and consents signed, questionnaires, FIUs, monitoring documents, statistical analyses, the final report of the study

16.3 DATA PROPERTIES AND PUBLICATION RULES

The results of this study, owned by the promoter (Centre François Baclesse), will be published in the form of scientific articles. Publications concerning or resulting from this research will be communicated and submitted for rereading by the study coordinators to all investigators.

The authors will include the investigators who included the most patients, the biostatistician who carried out the data analysis, the project manager, as well as the participants who made a substantial contribution to the development of the study, the analysis and to the interpretation of the results and/or the writing of the manuscript. No publication will be made without the agreement without the agreement of the coordinator and the promoter. The organization that contributed to funding the study will be mentioned in the publication.

Publication rank will be defined based on the investment provided in developing and conducting the study.

This work will be the property of all authors and will be made available to them for the production of communications and transversal publications.

Publications relating to the results of possible additional studies will be subject to the prior agreement of the coordinating investigator and the methodologist; they will be subsequent to the publication of the main study, which must be cited as a reference.

17 FINANCING AND INSURANCE

17.1 STUDY BUDGET

Any additional costs referred to in the Public Health Code are the subject of an agreement negotiated between the CFB and the representative of the establishment, taking into account the financial means available to the CFB as part of its public promotion activity.

However, the CFB ensures the organization of the study and takes charge of providing the following equipment (protocol, observation notebook, investigator file) necessary for conducting the study. In the event that materials or treatments are provided by other partners, the conditions must be specified in the study agreement.

17.2 INSURANCE

The Promoter has taken out insurance for the entire duration of the study guaranteeing its own civil liability as well as that of any doctor involved in carrying out the study. It will also ensure full compensation for the harmful consequences of the research for the person who takes part in it and their beneficiaries, unless proven by them that the damage is not attributable to their fault or that of any participant, without that the act of a third party or the voluntary withdrawal of the person who had initially consented to take part in the research can be opposed. (cf. article L 1121-10).

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19 ANNEX 1:

List of genes involved in homologous recombination for NGS sequencing

BRCAness
ATM
ATR
BAP1
BARD1
BLM
BRCA1
BRCA2
BRCC3
BRIP1
CDK12
CHEK1
CHEK2
EMSY
ERCC1
FAM175A
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANCG
FANCI
FANCL
FANCM
H2AFX
MDC1
MERIT40
MRE11A
NBN
PALB2
PTEN (complete loss)
RAD17
RAD50
RAD51
RAD51B
RAD51C
RAD51D
RAD54L
RAP80
RBBP8
RNF168
RPA1
SLX4
TOPBP1
XRCC2
XRCC3