SYNOPSIS – PROTOCOL REGOBONE

A) CLINICAL TRIAL IDENTIFICATION

SPONSOR - PROTOCOL CODE NUMBER: UC-0150/1309
EUDRACT N°: 2013-003910-42
VERSION & DATE: VERSION 8.0 – 27/06/2019

TRIAL TITLE: - A Randomized Phase II, placebo-controlled , multicenter study evaluating efficacy and safety of regorafenib in patients with metastatic bone sarcomas

ABBREVIATED TITLE: REGOBONE

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PLANNED NUMBER OF INVESTIGATIONAL SITES: APPROXIMATELY 20 SITES	**NUMBER OF PATIENTS:** 159

B) SPONSOR IDENTIFICATION

NAME OF THE INSTITUTION: UNICANCER

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C) TRIAL GENERAL INFORMATION

INDICATION:

Metastatic bone sarcomas: conventional high grade osteosarcoma, Ewing sarcoma of bone, chondrosarcomas and chordomas and either bone or soft tissue metastatic CIC-rearranged sarcomas

METHODOLOGY:
Randomized, placebo-controlled, multicentric, phase II study
-This is a **double-blind placebo-controlled trial,** with 5 cohorts:
Cohort A: Osteosarcoma
Cohort B: Ewing sarcoma
Cohort C: Chondrosarcoma
Cohort D : Chordoma
Cohort E : CIC-rearranged sarcoma

Cohorts A, B and C will involve a total of **36 evaluable patients each (24** Regorafenib **+ 12** placebo), cohort D will involve a total of **24 evaluable patients** (**16** Regorafenib **+ 8** placebo) and cohort E will involve a total of **27 evaluable patients (18** Regorafenib + **9** placebo).
159 patients who meet the eligibility criteria will be randomly assigned in a 2: 1 ratio to the following treatment groups :

The Arm A:
Regorafenib (160 mg/d or 120 mg/d) once daily for the 3 weeks on / 1 week off plus Best Supportive Care (BSC) until progression (according to RECIST 1.1), intolerance or withdrawal of consent .
Patients receiving regorafenib who experience disease progression and for whom in the investigator opinion, treatment with regorafenib is still providing clinical benefit, may continue the treatment following consultation with the study coordinator and the sponsor.

The Arm B:
Placebo plus BCS until progression (according to RECIST V1.1) intolerance or withdrawal of consent. Patients who have received placebo will receive open-label regorafenib after objective tumour progression has been documented.
Patients will be stratified at randomization according to histology.

PRIMARY OBJECTIVE:

The principal objective of the trial is to investigate the antitumour activity of regorafenib according to RECIST 1.1 criteria based on central radiological review.

SECONDARY OBJECTIVES:

To evaluate:

1. The progression free survival (PFS) according to RECIST 1.1 criteria
2. Objective response rate [defined as complete response (CR) or partial response (PR) according to RECIST V 1.1 for all cohorts, and CHOI criteria for chordomas] .
3. Overall survival (defined as the time from the date of randomization to the date of death due to any cause).
4. Duration of response.
5. Disease control rate at 6 months is defined as the proportion of patients who have a best response rating of CR, PR or stable disease [SD] according to RECIST guidelines 1.1. SD should be at least 8 weeks.
6. Progression-free rates at 3 and 6 months (PFR-3 and PFR-6), time to progression.
7. Treatment safety will be assessed using the NCI CTC-AE version 4.0 .
8. Growth Modulation Index (GMI).
9. Identification and characterization of biomarkers
10. Time to progression (measured from date of randomization until the date of first observation of progression)
11. Pain assessment for chordomas
12. Progression Free Survival according to CHOI criteria for chordomas

C) TRIAL GENERAL INFORMATION (…)

INCLUSION CRITERIA:

1. Patients must have a histologically confirmed diagnosis of bone sarcoma (osteosarcoma, Ewing sarcoma of bone, chondrosarcoma or chordoma [adults patients only for chordomas]) or CIC-rearranged sarcoma (either bone or soft tissue) with available Formalin Fixed Paraffin Embedded (FFPE) blocks obtained for centralized review;
   For CIC-rearranged sarcoma, diagnosis must be confirmed by molecular analysis.
2. Patients with confirmed disease progression at study entry. The “baseline” radiological evaluation should demonstrate disease progression by RECIST V 1.1 for all cohorts (and CHOI criteria especially for chordoma) when compared to a prior disease assessment done

within a prior period of 3 month for osteosarcomas, Ewing sarcomas and CIC-rearranged sarcomas and within 6 months period for chondrosarcomas and chordomas prior to screening Note: radiographic progression of disease will be based on at least 2 sets of scans (either MRI or CT) in the 3-month (for osteosarcomas, Ewing sarcomas and CIC-rearranged sarcomas) or 6-month period (for chondrosarcomas and chordomas) prior to or during screening in which radiographic progression of disease, as defined by RECIST for all cohorts (and CHOI criteria especially for chordoma), is demonstrated. No central review of scans (either MRIs or CTs) will be required for study eligibility; these scans must be sent for central review within 10 days after randomization;

3. Metastatic disease (and/or locally advanced disease for chondrosarcomas, CIC rearranged sarcomas, and chordomas) not amenable to surgical resection or radiation with curative intent;
4. Patients must have measurable disease (outside any previous irradiated field) defined as at least one unidimensionally lesion that can be accurately measured as ≥ 10 mm with CT scan according to RECIST V1.1 for all cohorts, and CHOI criteria especially for chordoma. Locally advanced chordomas, with no distant metastatis, can be included, only if MRI is done as the reference imaging exam in order to measure the disease according to RECIST 1.1 criteria.

5. Prior treatment :
   at least one, but no more than two prior (combination) chemotherapy regimen for metastatic disease (or locally advanced disease if applicable) for osteosarcoma, chondrosarcoma and Ewing sarcoma; at least one but no more than three prior chemotherapy regimen for metastatic disease or locally advanced for CIC-rearranged sarcoma; neo-adjuvant /maintenance therapy are not counted towards this requirement. Chordoma not pretreated or with 1 or 2 prior (combination) chemotherapy regimen or with one or two prior molecularly targeted therapy, but no more than 2 prior lines of treatment (whateever the indication) can be included;. At least 4 weeks since last chemotherapy (6 weeks in case of nitrosoureas and mitomycin C), immunotherapy or any other pharmacological treatment and/or radiotherapy;
6. Age ≥ 10 years for osteosarcomas, Ewing sarcomas, chondrosarcomas and CIC-rearranged sarcomas (for chordomas, patients must be ≥ 18 years);
7. Body Surface Area ≥ 1.30 m^2
8. Life expectancy of greater than 3 months;
9. ECOG performance status < 2 (Karnofsky ≥ 60%) for adults patients;
10. Karnofsky scale ≥ 60 % for children aged > 12 years old / Lansky scale ≥ 60 % for children aged ≤ 12 years old
11. Patients must have adequate bone marrow, renal, and hepatic function, as evidenced by the following within 7 days of study treatment initiation : normal organ function as defined below :
    - **a.** Absolute neutrophil count ≥ 1.5 Giga/L
    - **b.** Platelets ≥ 100 Giga/L
    - **c.** Hemoglobin≥ 9 g/dL
    - **d.** Serum creatinin ≤ 1.5 x ULN
    - **e.** Glomerular filtration rate (GFR) ≥30 ml/min/1.73m2 according to the modified Diet in Renal Disease (MDRD) abbreviated formula
    - **f.** AST and ALT ≤2.5 x ULN (≤5.0 × ULN for patients with liver involvement of their cancer
    - **g.** Bilirubin ≤1.5 X ULN
    - **h.** Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in patient with liver involvement of their cancer). If Alkaline phosphatase > 2.5 ULN, hepatic isoenzymes 5-nucleotidase or GGT tests must be performed; hepatic isoenzymes 5-nucleotidase must be within the normal range and/or GGT < 1.5 x ULN
    - **i.** lipase ≤1.5 x ULN.
    - **j.** Spot urine must not show ≥ 1 “+”protein in urine or the patient will require a repeat urine analysis. If repeat urinalysis shows 1 “+” protein or more, a 24-hour urine collection will be required and must show total protein excretion <1000 mg/24 hours
12. INR/PTT ≤1.5 x ULN;
    Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation

parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care;
13. Recovery to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug/procedure related toxicity (except alopecia, anemia, and hypothyroidism);
14. Women of childbearing potential and male patients must agree to use adequate contraception for the duration of study participation and up to 3 months following completion of therapy;
15. Women of childbearing potential must have a negative serum β-HCG pregnancy test within 7 days prior randomization and/or urine pregnancy test within 48 hours before the first administration of the study treatment;
16. Signed informed consent form by adult patients and/orpatients parents/legal representatives (if age < 18 years) and age appropriate assent form by the patients' parents/legal representatives obtained before any study specific procedure is conducted
17. Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures;
18. Patients or parents/legal representativesaffiliated to the Social Security System.

NON-INCLUSION CRITERIA:

1. Prior treatment with any VEGFR inhibitor (thus, any prior exposure to sunitinib, sorafenib, pazopanib, bevacizumab, or other VEGFR inhibitor would render the patient ineligible for this study);
2. Soft tissue sarcomas (including Ewing soft tissue sarcomas) except for CIC-rearranged sarcoma patients;
3. Other cancer (different histology) within 5 years prior to randomization;
4. Major surgical procedure, open biopsy, significant trauma, within the last 28 days before randomization;
5. Cardiovascular dysfunction:
   - Left ventricular ejection fraction (LVEF) < 50%
   - Congestive heart failure (New York Heart Association [NYAH]) ≥ 2
   - Myocardial infarction <6 months before study
   - Cardiac arrhythmias requiring therapy (beta blockers or digoxin are permitted)
   - Uncontrolled hypertension (systolic blood pressure (SBP) > 150mmHg or diastolic blood pressure (DBP) > 90mmHg despite optimal treatment or for children/adolescents SBP and/or DBP > 95th percentile + 5 mmHg)
   - Unstable (angina symptoms at rest) or new-onset angina (begun within the last 3 months)
6. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the last 6 months before randomization;
7. Severe hepatic impairment (Child-Pugh C);
8. Ongoing infection > Grade 2 according to NCI-CTCAE v4.0;
9. Known history of human immunodeficiency virus (HIV) infection;
10. Active hepatitis B or C or chronic hepatitis B or C requiring treatment with antiviral therapy ;
11. Difficulties with swallowing study tablets;
12. Prior anticancer therapy, including radiotherapy, endocrine therapy, immunotherapy, chemotherapy (CT) within the last 4 weeks (6 weeks for nitrosoureas and mitomycin C), or other investigational agents ; Concomitant antalgic palliative radiotherapy allowed;
13. Concurrent enrolment in another clinical trial in which investigational therapies are administered;
14. Known hypersensitivity to the active substance or to any of the excipients;
15. Pregnant women, women who are likely to become pregnant or are breast-feeding;
16. For adult patients, individual deprived of liberty or placed under the authority of a tutor;

17. Patients with any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial;
18. Patients with history of non compliance to medical regimens or unwilling or unable to comply with the protocol.
19. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent
20. Non-healing wound, non-healing ulcer, or non-healing bone fracture
21. Patients with evidence or history of any bleeding diathesis, irrespective of severity
22. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study medication
23. Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks of study entry.

EVALUATION

PRIMARY CRITERIA:

The primary efficacy endpoint is the non-progression rate at 8 weeks for osteosarcoma, Ewing sarcoma and CIC-rearranged sarcoma patients, at 12 weeks for chondrosarcoma patients and at 6 months for chordoma patients.

The non-progression rate will be defined as the proportion of patients without disease progression at the defined timepoint after confirmation by central radiological review (using RECIST 1.1).

SECONDARY CRITERIA:

1. Progression-Free Survival [defined using RECIST 1.1] will be measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression).
2. Objective response rate [defined as complete response (CR) or partial response (PR) according to RECIST 2009, version 1.1, for all cohorts, and CHOI criteria for chordoma] ;
3. Disease control rate at 6 months (defined as the proportion of patients who a best response rating of CR, PR or stable disease [SD]), SD should be at least 8 weeks ;
4. Overall survival (defined as the time from the date of randomization until the date of death due to any cause); if the patients is alive at the date of data base cut off then he will be censored at the data base cut off date;
5. Duration of response (defined as the time from date of first documented objective response of CR or PR, whichever is noted earlier, to first disease progression or death before progression ;
6. Progression-free rate at 3 and 6 months (PFR-3 and PFR-6), defined as the proportion of patients without progression at 3 and 6 months post randomization;
7. Time to progression (measured from date of randomization until the date of first observation of progression);
8. Growth Modulation Index (GMI) defined as ratio of time to PD under regorafenib to TTP under previous treatment. The GMI will be explored in patients receiving regorafenib after randomization;
9. Identification and characterization of biomarkers
10. Toxicity according to NCI-CTC V4.0
11. Pain assessment for chordomas
11. Progression Free Survival according to CHOI criteria for chordomas

All efficacy assessments using CHOI criteria (only for chordomas) will be performed by central radiological reviewers.

D) DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

DRUGS:

Drug Name (IDN)	Commercial Name	Pharmaceutical Form	Route of Administration	Posology
Regorafenib		40 mg tablets	Per os	≥ 18 years old:160 mg daily for 3 weeks / 1 week off < 18 years old: 120 or 160 mg daily for 3 weeks / 1 week off according to BSA

THERAPEUTIC SCHEME:

- This is a French multicentre randomized phase II study, and patients will be recruited in around ***20*** **French** centers.
- Unicancer in France will serve as regulatory sponsor and will perform the monitoring, data management and analyses

- This is a **double-blind placebo-controlled trial,** with 5 cohorts:

Cohort A: Osteosarcomas
Cohort B: Ewing sarcomas
Cohort C: Chondrosarcomas
Cohort D: Chordomas
Cohort E: CIC-rearranged sarcoma

159 patients who meet the eligibility criteria will be randomly assigned in a 2 : 1 ratio to the following treatment groups :

The Arm A:

For adult patients (≥ 18 years old), regorafenib (without exceeding 160 mg/d) once daily for the 3 weeks on / 1 week off plus Best Supportive Care (BSC) until progression (according to RECIST 1.1), intolerance or withdrawal of consent. If the treatment provides clinical benefit to the patient despite radiological progression, he may continue regorafenib following consultation with the coordinator and sponsor.

For children Age ≥ 10 years to < 18 years old and BSA ≥ 1.30 m^2, regorafenib (82 mg/m^2) once daily for the 3 weeks on/1 week off (without exceeding 160mg/day) plus Best Supportive care (BSC) until progression (according to RECIST 1.1), intolerance or withdrawal of consent. If the treatment provides clinical benefit to the patient despite radiological progression, they may continue regorafenib following consultation with the study coordinator and sponsor.

The Arm B:

Placebo plus BSC until progression (according to RECIST 1.1) or unacceptable toxicity. Patients who have received placebo will receive open-label regorafenib after objective tumour progression has been documented.
Patients will be stratified at randomization according to histology.

TREATMENT DURATION: until progression confirmed by central review and investigator decision or unacceptable toxicity

E) STATISTICAL ANALYSIS

SAMPLE SIZE:

The number of patients to include has been calculated for the experimental arm only using a A' Hern's [A'Hern 2001] single-stage procedure for phase II trials (Similar to a Fleming phase II design [Fleming, 1982] but assuming a exact Binomial distribution). Then, the half number of patients has been added to form the placebo arm depending on the randomization ratio 2:1.
Using hypotheses similar to those described above, the number of patients has been calculated as follows:
π is the true probability of success (non progressive patients at **8 weeks** under regorafenib treatment for osteosarcoma and Ewing sarcoma ; at **12 weeks** for chondrosarcoma):

- π_0 = 0.40 non progressive patients at 8 weeks (0.5 non progressive patients at 12 weeks for chondrosarcoma): the largest non progression proportion which, if true, would clearly imply that the Regorafenib does not warrant further investigation.
- π_1 = 0.67 non progressive patients at 8 weeks (0.75 non progressive patients at 12 weeks for chondrosarcoma): the smallest non progression proportion that would imply that Regorafenib warrants further investigation.

Assuming a type I error alpha of 0.05 and 80% power, the number of patients required in the experimental arm is 23 patients to reject the null hypothesis H_0: $\pi \leq \pi_0$ versus the alternative hypothesis H_1: $\pi \geq \pi 1$ in a one-sided situation. At the end of the study, Regorafenib will be considered as interesting for further investigation if at least 14 patients are non progressive after 8 weeks of treatment in the experimental arm (for osteosarcoma and Ewing sarcomas) and if at least 16 patients are non progressive after 12 weeks of treatment in the experimental arm for chondrosarcomas.
No formal comparison between the experimental arm and the control arm will be performed.
The placebo arm will only be used to strengthen the results obtained in the experimental arm (randomization avoids patient selection biases). Hence, more patients will be included in the experimental arm, using a 2:1 randomization ratio. Therefore each cohort will involve a total of **36 evaluable patients (24 + 12).**

Using a similar design as for the other cohorts, the sample size **for chordomas** cohort has been calculated as follows:
π is the true probability of success (non progressive patient at **6 months** under regorafenib treatment):

- π_0 = 0.40 non progressive patients at 6 months : the largest non progression proportion which, if true, would clearly imply that the Regorafenib does not warrant further investigation. This hypothesis is based on Stacchiotti S *et al* 2012 work showing 6 month PFS rate = 50% ; IC95% (28.8 – 71.1)
- π_1 = 0.75 non progressive patients at 6 months : the smallest non progression proportion that would imply that Regorafenib warrants further investigation. This hypothesis is supported by Bompas E et al. Ann Oncol 2015 showing 6 month PFS rate = 85.3% ; IC95% (60.7 – 95.1)

Assuming a type I error alpha of 0.05 and 80% power, the number of patients required in the experimental arm is 16 patients to reject the null hypothesis H_0: $\pi \leq \pi_0$ versus the alternative hypothesis H_1: $\pi \geq \pi 1$ in a one-sided situation.
At the end of the study, Regorafenib will be considered as interesting for further investigation if at least 10 patients are non progressive after 6 months of treatment in the experimental arm.
As for other cohorts, No formal comparison between the experimental arm and the control arm will be performed. The placebo arm will only be used to strengthen the results obtained in the experimental arm (randomization avoids patient selection biases). Hence, more patients will be included in the experimental arm, using a 2:1 randomization ratio.
Therefore chordoma cohort will involve a total of **24 evaluable patients (16+8).**

Using a similar design as for the other cohorts and using the results of Regobone osteosarcoma cohort (Duffaud et al. Lancet oncol 2019) showing that median PFS on placebo was 4 weeks for osteosarcoma patients, the sample size **for CIC-rearranged** cohort has been calculated as follows:
π is the true probability of success (non progressive patient at **8 weeks** under regorafenib treatment for CIC -rearranged sarcomas):

- π_0 = 0.25 non progressive patients at 8 weeks (like median PFS of 4 weeks): the largest non progression proportion which, if true, would clearly imply that the Regorafenib does not warrant further investigation.
- π_1 = 0.55 non progressive patients at 8 weeks (like median PFS of 9 weeks): the smallest non progression proportion that would imply that Regorafenib warrants further investigation.

Assuming a type I error alpha of 0.05 and 80% power, the number of patients required in the experimental arm is 18 patients to reject the null hypothesis H_0: $\pi \leq \pi_0$ versus the alternative hypothesis H_1: $\pi \geq \pi 1$ in a one-sided situation.

At the end of the study, Regorafenib will be considered as interesting for further investigation if at least 8 patients are non progressive after 8 weeks of treatment in the experimental arm.

No formal comparison between the experimental arm and the control arm will be performed. The placebo arm will only be used to strengthen the results obtained in the experimental arm (randomization avoids patient selection biases).
Hence, more patients will be included in the experimental arm, using a 2:1 randomization ratio. Therefore, **CIC-rearranged** cohort will involve a total of **27 evaluable patients (18+9).**

F) TRIAL DURATION

INCLUSION PERIOD: Approximately 96 months (8 years)

TREATMENT PERIOD: until progression confirmed by central review or unacceptable toxicity: 6 Months (estimate)

Follow-up period: 18 months

OVERALL TRIAL DURATION: Approximately 10 years