METRONOMIC CYCLOPHOSPHAMIDE AND METHOTREXATE COMBINED WITH ZOLEDRONIC ACID AND SIROLIMUS IN PATIENTS WITH ADVANCED SOLID TUMOR WITH BONE METASTASIS AND ADVANCED PRETREATED OSTEOSARCOMA.
A PHASE IB STUDY FROM THE FRENCH SARCOMA GROUP

Protocol *MetZolimOS*

Statistical Analysis Plan (SAP) – Phase I trial

Version n°1.1 – November 9th, 2021

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VERSIONS AND REVISIONS

Version	Date	Modification(s)	Context
1.0	February 2nd, 2015	-	-
1.1	November 9th, 2021	Non-inclusion criteria n°13 added Analysis of endpoints requiring centralized review for expansion cohort	

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1. Introduction

1.1 Synopsis (Version N°12.0 April 28th, 2021)

Title of the study	**Metronomic cyclophosphamide and Methotrexate combined with Zoledronic acid and Sirolimus in patients with advanced solid tumor with bone metastasis and advanced pretreated osteosarcoma. A Phase Ib study from the French Sarcoma Group**
Abbreviation of the trial	**MetZolimOS**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Doctor Maud Toulmonde** **Department of Medical Oncology**
Number of investigational sites planned	Dose escalation part, 1 centre : - Institut Bergonié (sponsor) Expansion cohort, 3 centres: - Institut Bergonié (sponsor) - Centre Léon Bérard - Centre Oscar lambret
Number of patients	**Phase I:** 20 - 26 patients
Duration of the study	Planned enrollment period: 78 months Treatment duration: 6 months Follow-up: 1 year Study period: 8 years
Medical conditions	Dose escalation part: adults with advanced solid tumor with bone metastasis and young and adult patients with unresectable locally advanced or metastatic osteosarcoma Expansion cohort: young and adult patients with unresectable locally advanced or metastatic osteosarcoma
Objectives	**Primary objective** To determine the recommended phase II dose, the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the Dose Limiting Toxicities (DLT) of sirolimus when prescribed in combination with Metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) in patients with solid tumor with bone metastasis and advanced pretreated osteosarcoma. **Secondary objectives** • To describe the pharmacokinetics (PK) of sirolimus, CP, MT given together, • To better assess the safety profile of sirolimus when administered in association with CP, MT and ZA (NCI-CTC v4), • To document any antitumor activity observed with sirolimus combined with CP, MT and ZA, in OSS patients, in terms of o 6-month objective response rate (ORR) as per RECIST 1.1 o best objective response rate (ORR) as per RECIST 1.1 o 6-month Non-progression rate (NPR) as per RECIST 1.1 o 1-year Progression-free survival (PFS) as per RECIST 1.1 o Growth modulation index (GMI) o 1-year Overall Survival (OS) • To explore Pharmacodynamics (PD) and mechanisms of action of CP + MT + ZA + sirolimus as well as potential predictive biomarkers.
Study design	**STUDY DESIGN** This is a prospective open-labeled phase I trial based on a dose escalating study design assessing two dose levels of sirolimus when prescribed in combination with

metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) followed by an expansion cohort once the MTD is established.

DEFINITIONS

Dose limiting toxicity (DLT)

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

- Is considered to be at least possibly related to the study treatment
- Occurs during the first cycle of treatment
- Is unrelated to disease, disease progression, inter-current illness, or concomitant medications
- Meets one of the criteria below, graded as outlined or according to NCI CTCAEv4.3:
    - Grade 4 non-haematological toxicity (not laboratory)
    - Grade 3 non-haematological toxicity > 3 days (not laboratory) (except for asthenia, 1rst episode of nausea/vomiting without maximal symptomatic/prophylactic treatment)
    - Grade ≥ 3 non-hematologic laboratory value if medical intervention is required to treat the patient, or the abnormality leads to hospitalization, or the abnormality persists for > 1 week
    - Grade ≥ 3 hematologic toxicity > 3 days (except for lymphopenia)
    - Grade 4 lymphopenia
    - Confirmed febrile neutropenia
- In addition treatment temporary interruption or dose modification leading to dose intensity lower than 70% will be considered as a DLT.

Maximum tolerated dose (MTD)

The MTD is defined as the dose associated with 25% of DLT.

Recommended phase II dose (RP2D)

RP2D will be identified by the steering committee based on the safety data, the PK data and the PD data. Data from all cycles will be used to refine the dose level of each combination to be recommended for further investigations in phase II. If a clear dose-activity relationship comes up, the maximum tolerated dose that is the dose whose probability of toxicity is closest to 25% will be considered as the RP2D.

DOSE ESCALATION PART

- Patients will receive CP, MT and ZA at fixed standard doses.
    - CP: 50mg x 2 /d, orally, on a 1 week on/1 week off schedule
    - MT: 2.5mg x 2 /d, orally, d1 d4 every week
    - ZA: 4mg, intravenously, every 4 weeks
- Two doses of sirolimus will be investigated.

Level	*-1*	1	2
Sirolimus	*2mg*	4mg	6mg

- The starting dose of sirolimus is 4 mg [1].
- The maximum dose of sirolimus is 6 mg and will not be exceeded.
- Dose escalation scheme will follow a classic 3 + 3 design. The dose of sirolimus will be escalated in fixed increments according to the dose escalation scheme outlined below.The planned number of patients per dose level will be 3 to 6 for a total of 6 to 12 patients.

Dose level	Sirolimus	Minimum number of patients
-1	*2 mg*	--
1 (starting)	**4 mg**	3
2	**6 mg**	3

- A minimum of 3 patients will be entered on each dose level.
- The first patient will be followed for 28 days and subsequent enrolment in the cohort will be based on the toxicity assessment. All 3 patients within a dose level must be observed for 4 weeks before accrual to the next higher dose level may begin.
- Dose escalation will proceed within each cohort according to the following scheme (Table 4).

Number of Patients with DLT at one dose level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximum administered dose (MAD). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, dose escalation will be stopped, and this dose declared the MAD. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at Maximum Feasible Dose (MFD)	This will be the recommended phase II dose (RP2D). At least 6 patients must be entered at the RP2D.

- As described above the MTD is the dose in which 2/3 or 2/6 patients experience DLT. One dose level below that dose will be considered the recommended phase II dose (RP2D). If the MTD is seen at the starting dose level, then dose level "-1" will be the recommended dose.

- **Patient's replacement:** If a patient cannot complete the full DLT evaluation period and goes off-treatment for reasons other than toxicity, this patient can be replaced. Patients with DLT will never be replaced. All patients will also be fully described in the analysis. Only patients who completed the DLT assessment period or who develop DLT are included in the analysis for escalation.

EXPANSION COHORT

Patients with relapsed OSS will be treated following the same regimen with the RP2D defined in the dose escalation part of the trial (see above).

Inclusion criteria	1. Histology: - Advanced solid tumor with radiologically proven bone metastasis, all tumor types (dose escalation part) - Patients with osteogenic osteosarcoma (dose escalation part and expansion cohort) histologically confirmed by central review (Pr. Coindre team), except if the diagnosis was already confirmed by the RRePS Network, 2. Metastatic or unresectable locally advanced disease, not eligible for alternative local treatment (radiotherapy for instance), 3. Age >= 13 years for patients with osteosarcoma, otherwise age >= 18 years for all other solid tumours, 4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1, 5. Life expectancy > 3 months, 6. Measurable disease according to RECIST v1.1. At least one site of disease must be uni-dimensionally ≥ 10 mm, 7. Patients must have histologically confirmed diagnosis of locally advanced and/or metastatic solid tumors, which are not amenable to standard treatment, including for patients with osteosarcoma conventional agents such as anthracyclines, platinum salts, ifosfamide and/or methotrexate, 8. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy, 9. Adequate haematological, renal, metabolic and hepatic function: a. Haemoglobin ≥ 10 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); leucocytes ≥ 3 x 10^9/l, lymphocytes ≥ 0.8 x 10^9/l, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, and platelet count ≥ 120 x 10^9/l. b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) c. Total bilirubin ≤ 1.5 x ULN d. Calculated creatinine clearance (CrCl) > 40 ml/min/1.73 m² (according to MDRD formula) e. Creatine phosphokinase (CPK) ≤ 2.5 x ULN f. Albumin > 25 g/l g. Corrected calcium within normal laboratory ranges. 10. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 11. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4), 12. Patients with a social security in compliance with the French law, 13. Voluntarily signed and dated written informed consent prior to any study specific procedure, 14. Women of childbearing potential must have a negative serum pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier.
Non Inclusion criteria	1. Previous treatment with sirolimus, 2. Concomitant diseases/conditions: ▪ Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions ▪ Unstable cardiac disease, pulse oximetry saturation < 90% at rest ▪ Clinically significant immunodeficiency, such as HIV or active Hepatitis B or C ▪ History of auto-immune disease, transplantation 3. Central nervous system malignancy (CNS), 4. Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding, 5. Patients receiving any substances that are inhibitors or inducers of CYP450 3A4

<table>
<tr><td></td><td>(non-exhaustive list on Appendix 3),
6. Ongoing or recent (<6 weeks) dental problem, including any severe tooth or jaw infection (mandible and maxilla), dental trauma, dental or stomatological surgery (implants). Current dental cares are allowed.
7. History of maxillary osteonecrosis or delayed healing after dental surgery,
8. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
9. Previous enrolment in the present study,
10. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
11. Known hypersensitivity to any involved study drug or any of its formulation components,
12. Patients receiving live vaccines within 30 days prior to the first dose of study therapy and while participating in study (Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1, rabies, BCG, and typhoid vaccine. However, if seasonally indicated, it is advised to give seasonal flu vaccine as recommended, > 15 days before C1J1.).
13. Known urinary tract obstruction.</td></tr>
<tr><td>Route of administration</td><td>Cyclophosphamide will be administered per os bi-daily (50 mg x 2), and given on a week on/week off schedule.
Methotrexate will be administered per os bi-daily (2.5 mg x 2), and given on day 1 and 4 every week.
Zoledronic acid will be administered at home by intravenous infusion (4 mg) on Day 2 of each cycle, every 4 weeks.
Sirolimus will be administered per os once daily, continuously.</td></tr>
<tr><td>Treatment schedule</td><td>Dose escalation
<table>
<tr><th colspan="5">Regimen Description</th></tr>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th></tr>
<tr><td>CP</td><td>50mg x 2</td><td>per os</td><td>Daily, 1 week on /1 week off</td><td rowspan="4">4 weeks</td></tr>
<tr><td>MT</td><td>2.5mg x 2</td><td>Per os</td><td>On day 1 and 4, every week</td></tr>
<tr><td>ZA</td><td>4mg</td><td>IV</td><td>On day 2, every 4 weeks</td></tr>
<tr><td>Sirolimus</td><td>as appropriate for assigned dose level</td><td>Per os</td><td>Continuously</td></tr>
</table>
A treatment cycle consists of 4 weeks. Treatment may continue until disease progression or study discontinuation (withdrawal of consent, intercurrent illness, unacceptable adverse event or any other changes rendering further treatment unacceptable, etc. see section 5.2)

2 dose levels :
<table>
<tr><th>Level</th><th>-1</th><th>1</th><th>2</th></tr>
<tr><td>Sirolimus</td><td>2 mg</td><td>4 mg</td><td>6 mg</td></tr>
</table>
Expansion cohort: All patients will receive the same regimen with sirolimus at the recommended dose defined in the dose escalation cohort, in combination with CP, MT and ZA</td></tr>
<tr><td>Endpoints</td><td><u>DOSE ESCALATION PART</u>

<u>Primary endpoint</u>
• Toxicity as graded using the common toxicity criteria from the NCI v4.03.
• Incidence rate of DLT at each dose level on cycle 1</td></tr>
</table>

	Secondary endpoints • PK measurements expressed as AUC, half-life and concentration peak for CP, MT and sirolimus • Antitumor activity observed with sirolimus combined with CP, MT and ZA, in terms of o 6-month objective response rate , defined as the rate of complete or partial response at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1 o Best objective response rate, defined as the rate of complete or partial response confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1 o 6-month Non-progression rate (NPR) defined as the percentage of patients with CR, PR or stable disease (SD) according to RECIST v1.1 o 1-year Progression-free survival (PFS), PFS is defined as the time from study treatment initiation to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment). o Growth modulation index (GMI) GMI will be defined for each patient as the ratio of its PFS on sirolimus + CP/MTX/ZA treatment to its PFS on a previous line of therapy. This method accounts for inter-patient variability, the patient serving as his/her own control and implies by the natural history of the disease that the PFS tends to become shorter in successive lines of therapy. Von Hoff suggested that an anti-cancer agent should be considered effective if the GMI is greater than 1.3 [2] o 1-year Overall Survival (OS), OS isdefined as the time from first infusion to death (of any cause) **EXPANSION COHORT** **Primary endpoint** Antitumor activity observed with sirolimus combined with CP, MT and ZA, in OSS patients, in terms of 6-month non-progression rate, defined as the rate of complete or partial response and stable disease at 6 months using RECIST v1.1 **Secondary endpoints** • Same as for the dose escalation cohort.
Statistical considerations	**NUMBER OF SUBJECTS NEEDED** **Dose escalation part** • The dose escalation part is designed to detect the MTD of sirolimus given in combination with metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) • The dose escalation design to identify the maximum tolerated dose will be the traditional 3+3 design. Adaptive designs, such a continual reassessment method (CRM) using likelihood inference [3] do not appear relevant in this context given there are only two dose levels investigated and the toxicity profile of sirolimus. • Since there are two dose levels investigated, a maximum of 12 eligible patients assessable for DLT is expected. **Expansion cohort** • The expansion cohort is designed to enable to detect antitumor activity observed with sirolimus combined with CP, MT and ZA. • Sample size is calculated based on the first stage of a 2-stage Gehan design

	assuming a 20% efficacy rate, 5% false positive rate and 10% precision (Gehan 1961). • 14 eligible and assessable subjects are required. • If at least 1 objective response or stable disease (> 24 weeks) is observed in the 14 patients recruited in the expansion cohort, the study drug association will be considered worthy of further testing in this indication. **STATISTICAL ANALYSIS** • All analyses will be descriptive; no p-values will be calculated. • For continuous variables, summary statistics will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate. • Categorical endpoints will be summarized using number of patients, frequency, percentages. • For survival endpoints, median survival time will be reported.

1.2 Objectives

1.2.1 Primary objective

To determine the recommended phase II dose (RP2D), the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28), the safety profile, and the Dose Limiting Toxicities (DLT) of sirolimus when prescribed in combination with metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) in patients with solid tumor with bone metastasis and advanced pretreated osteosarcoma.

1.1.2 Secondary objectives

- To describe the pharmacokinetics (PK) of sirolimus, CP, MT given together,
- To better assess the safety profile of sirolimus when administered in association with CP, MT and ZA (NCI-CTC v4),
- To document any antitumor activity observed with sirolimus combined with CP, MT and ZA, in OSS patients, in terms of

Antitumor activity observed with sirolimus combined with CP, MT and ZA, in OSS patients, in terms of

- 6-month objective response rate (ORR) as per RECIST 1.1
- best objective response rate (ORR) as per RECIST v1.1
- 6-month Non-progression rate (NPR) as per RECIST 1.1
- 1-year Progression-free survival (PFS) as per RECIST 1.1
- Growth modulation index (GMI)
- 1-year Overall Survival (OS)
- To explore Pharmacodynamics (PD) and mechanisms of action of CP + MT + ZA + sirolimus as well as potential predictive biomarkers.

2. Study methods

2.1 Study design

This is a prospective open-labeled phase I trial based on a dose escalating study design assessing two dose levels of sirolimus when prescribed in combination with metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA) followed by an expansion cohort once the MTD is established.

2.2 Randomization (if applicable)

Not applicable.

2.3 Sample size

Dose escalation part

- The dose escalation part is designed to detect the MTD for sirolimus given in combination with metronomic cyclophosphamide (CP), methotrexate (MT) and zoledronic acid (ZA)
- The dose escalation design to identify the maximum tolerated dose will be the tradiotional 3+3 design. Adaptive designs, such a continual reassessment method (CRM) using likelihood inference do not appear relevant in this context given there are only two dose levels investigated and the toxicity profile of sirolimus.
- Since there are two dose levels investigated, a maximum of 12 eligible patients assessable for DLT is expected.

Expansion cohort
- The expansion cohort is designed to enable to detect antitumor activity observed with sirolimus combined with CP, MT and ZA.
- Sample size is calculated based on the first stage of a 2-stage Gehan design assuming a 20% efficacy rate, 5% false positive rate and 10% precision (Gehan 1961).
- 14 eligible and assessable subjects are required.
- If at least one objective response or stable disease (> 24 weeks) is observed in the 14 patients recruited in the expansion cohort, the study drug association will be considered worthy of further testing in this indication.

2.4 Interim analysis (if applicable)

Not applicable.

2.5 Timing of analysis

Dose escalation part
- Analysis of DLT at each dose level
- Analysis of MTD at the end of dose escalation
- Final analysis will be conducted 12 months after the last participant is included.

Expansion cohort
- Primary endpoint analysis: Primary endpoint (non-progression rate at 6 months) will be assessed once inclusions are definitively stopped and 6 months after treatment onset for all patients evaluable for the primary endpoint included.
- Final analysis will be conducted 12 months after the last participant is included.

3. Trial population

3.1 Analysis populations

3.1.1 Definitions

Dose escalation part
Patients assessable for the dose escalation part, that is, for tolerance analysis are defined as follows:
- All the patients who have received at least one dose of one of the trial's products will be evaluable for toxicity and included in the tolerance analysis.
- To be evaluable in terms of DLT a patient must have received the complete C1 cycle (28 days: D1 to D28) or have exhibited a DLT during C1.
- Any patient non-evaluable for DLT will be replaced.

Expansion cohort
- Patients assessable for the expansion cohort, that is, for the efficacy analysis are defined as follows:
    - Received at least one complete or two incomplete treatment cycles,
    - And at least one disease measurement recorded not less than eight weeks after treatment onset.
- The following patients will also be included in the population evaluable for efficacy; they will be considered as failures for the primary endpoint (i.e. progressive disease at 6 months) and not be replaced in the primary efficacy analysis:
    - Any eligible patients who receive at least one treatment cycle and experience disease progression or die due to disease progression prior to response evaluation (will be considered as an "early progression").
    - Patients withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment.

- Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, or unrelated AEs without any tumor assessments after the start of study treatment.

- Safety population: all patients having received at least one treatment administration.

3.1.2 Protocol deviations

Major protocol deviations (specifically eligibility deviations) that occur during the study will be summarized for all patients included. A by-patient listing of all major and minor deviations will be provided.

A participant will be considered eligible if s/he did not have any major deviations from the patient eligibility criteria (see section 3.2). Any exclusion from the analysis will be assessed by the Steering Committee based on the review of the participant's screening and baseline data.

3.2 Eligibility criteria

3.2.1 Inclusion criteria

Table 1 : Inclusion criteria

Criteria	eFORM variable	Control
1. Histology: - Advanced solid tumor with radiologically proven bone metastasis, all tumor types (dose escalation part) - Patients with osteogenic osteosarcoma (dose escalation part and expansion cohort) histologically confirmed by central review (Pr. Coindre team), except if the diagnosis was already confirmed by the RRePS Network	**INCLUSION CRITERIA** **C1I** **PRE-TREATMENT VISIT(2/3)** **METAS** **RAD_SOL** **HIS_DIA** **DOS_ESC** **EXP_COH** **OOS_REW**	**OK If : C1I = 1 METAS=1 and RAD_SOL=1** **OK If : ((HIS_DIA=1 and DOS_ESC=2) or (HIS_DIA=2 and EXP_COH=1)) and OOS_REW=1**
2. Metastatic or unresectable locally advanced disease, not eligible for alternative local treatment (radiotherapy for instance)	**INCLUSION CRITERIA** **C2I** **PRE-TREATMENT VISIT(2/3)** **METAS** **UNRESEC** **EXC_RAD**	**OK If : C2I = 1** **(UNRESEC=1 or METAS=1) and EXC_RAD=1** **Investigator decision**
3. Age >= 13 years for patients with osteosarcoma, otherwise age >= 18 years for all other solid tumours,	**INCLUSION CRITERIA** **C3I** **PRE-TREATMENT VISIT(2/3)** **DOS_ESC** **EXP_COH**	**OK If : C3I = 1** **if (Date of consent - Birth date≥18) and DOS_ESC=1 or if (Date of consent - Birth date≥13) and DOS_ESC=2 or if (Date of consent - Birth date≥13) and EXP_COH=1**
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1	**INCLUSION CRITERIA** **C4I**	**OK If : C4I = 1**

	PRE-TREATMENT VISIT(1/3) **ECOG_PTR**	**ECOG_PTR = (0 or 1)**
5. Life expectancy > 3 months	**INCLUSION CRITERIA** **C5I**	**OK If : C5I = 1** **Investigator decision**
6. Measurable disease according to RECIST v1.1. At least one site of disease must be uni-dimensionally ≥ 10 mm	**INCLUSION CRITERIA** **C6I** **TUMOR ASSESSMENT (TUM_ASS)** **NUM_LM (number of measurable lesions)** **MEA1L_MEA5L**	**OK If : C6I = 1** **Depending on the value of NUM_LM (MEA1L or MEA2L or MEA3L or MEA4L or MEA5L) GE 10**
7. Patients must have histologically confirmed diagnosis of locally advanced and/or metastatic solid tumors, which are not amenable to standard treatment, including for patients with osteosarcoma Conventional agents such as anthracyclines, platinum salts, ifosfamide and/or methotrexate	**INCLUSION CRITERIA** **C7I**	**OK If : C7I=1** **Investigator decision**
8. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy	**INCLUSION CRITERIA** **C8I** **PRE-TREATMENT VISIT(2/3)** **CHE_REG** **CHE_LINE, NB_LINE** **DT_LCYC _ DT_8LCYC**	**Find the last treatment (DT_LTRT)** **If (CHE_REG filled in AND CHE_LINE=0)** **DT_LTRT = DT_LCYC** **Else if (CHE_REG filled in AND CHE_LINE=1)** **DT_LTRT =max(DT_LCYC, DT_2LCYC, DT_3LCYC, DT_4LCYC DT_5LCYC DT_6LCYC, DT_7LCYC, DT_8LCYC)** **Depending on NB_LINE** **OK If : C8I = 1 (Date of inclusion–DL_LTRT GE 3)**
9. Adequate haematological, renal, metabolic and hepatic function: a. Haemoglobin ≥ 10 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); leucocytes ≥ 3 x 10^9/l, lymphocytes ≥ 0.8 x 10^9/l, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, and platelet count ≥ 120 x 10^9/l. b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) · 2.5 x upper limit of normality (ULN)	**INCLUSION CRITERIA** **C9I** **PRE-TREATMENT VISIT(3/3)** **HEMO** **LEUC** **NEUT** **LYMP** **PLAT** **ALT** **AST** **BIL_TOT** **CCLE**	**OK If : C9I =1** **HEMO ≥10 and LEUC≥ 3 x 10^9 and NEUT ≥ 1.5 x 10^9 and LYMP and PLAT 120 x 10^9 and ALT ≤ 2.5 x upper limit of normality(ULN) and AST ≤ 2.5 x ULN and BIL_TOT**

c. Total bilirubin ▪ 1.5 x ULN d. Calculated creatinine clearance (CrCl) > 40 ml/min/1.73 m² (according to MDRD formula) e. Creatine phosphokinase (CPK) ▪ 2.5 x ULN f. Albumin > 25 g/l g. Corrected calcium within normal laboratory ranges.	**CPK** **ALBU**	**≤ 1.5 x ULN and CCLE > 40 and CPK ≤ 2.5 x ULN and ALBU > 25**
10. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma	**INCLUSION CRITERIA** **C10I**	**OK If : C10I=1** **Investigator decision**
11. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4)	**INCLUSION CRITERIA** **C11I**	**OK If : C11I=1** **Investigator decision**
12. Patients with a French social security in compliance with the French law relating to biomedical research (Article L.1121-11 of French Public Health Code).	**INCLUSION CRITERIA** **C12I**	**OK If : C12I=1** **Investigator decision**
13. Voluntarily signed and dated written informed consent prior to any study specific procedure	**INCLUSION CRITERIA** **C13I**	**OK If : C13I =1** **Date of signature of the informed consent**
14. Women of childbearing potential must have a negative serum pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier.	**INCLUSION CRITERIA** **C14I** **PRE-TREATMENT VISIT(1/3)** **RES_PREG**	**OK If : C14I=1** **RES_PREG=0** **Investigator decision**

3.2.2 Non-inclusion criteria

Table 2 : Non-inclusion criteria

Criteria	eFORM variable	Control
1. Previous treatment with sirolimus	**NON-INCLUSION CRITERIA** **C1NI**	**OK If : C1NI=0** **Investigator decision**
2. Concomitant diseases/conditions: ▪ Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions ▪ Unstable cardiac disease, pulse oximetry saturation < 90% at rest ▪ Clinically significant immunodeficiency,	**NON-INCLUSION CRITERIA** **C2NI**	**OK If : C2NI=0** **Investigator decision**

such as HIV or active Hepatitis B or C ▪ History of auto-immune disease, transplantation		
3. Central nervous system malignancy (CNS)	**NON-INCLUSION CRITERIA** **C3NI** **PRE-TREATMENT VISIT (2/3)** **SITE_ 1ME, SITE_ 2ME, SITE_ 3ME,…**	**OK If : C3NI = 0 and (SITE_ 1ME and SITE_ 2ME and SITE_ 3ME and …) ≠4**
4. Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding	**NON-INCLUSION CRITERIA** **C4NI**	**OK If : C4NI=0** **Investigator decision**
5. Patients receiving any substances that are inhibitors or inducers of CYP450 3A4 (non-exhaustive list on Appendix 3)	**NON-INCLUSION CRITERIA** **C5NI**	**OK If : C5NI=0** **Investigator decision**
6. Ongoing or recent (<6 weeks) dental problem, including any severe tooth or jaw infection (mandible and maxilla), dental trauma, dental or stomatological surgery (implants). Current dental cares are allowed.	**NON-INCLUSION CRITERIA** **C6NI**	**OK If : C6NI=0** **Investigator decision**
7. History of maxillary osteonecrosis or delayed healing after dental surgery	**NON-INCLUSION CRITERIA** **C7NI**	**OK If : C7NI=0** **Investigator decision**
8. Participation to a study involving a medical or therapeutic intervention in the last 30 days	**NON-INCLUSION CRITERIA** **C8NI**	**OK If : C8NI=0** **Investigator decision**
9. Previous enrolment in the present study	**NON-INCLUSION CRITERIA** **C9NI**	**OK If : C9NI=0** **Investigator decision**
10. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons	**NON-INCLUSION CRITERIA** **C10NI**	**OK If : C10NI=0** **Investigator decision**
11. Known hypersensitivity to any involved study drug or any of its formulation components	**NON-INCLUSION CRITERIA** **C11NI**	**OK If : C11NI=0** **Investigator decision**
12. Patients receiving live vaccines within 30 days prior to the first dose of study therapy and while participating in study (Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1, rabies, BCG, and typhoid vaccine. However, if seasonally indicated, it is advised to give seasonal flu vaccine as recommended, > 15 days before C1J1.).	**NON-INCLUSION CRITERIA** **C12NI**	**OK If : C12NI=0** **Investigator decision**
13. Known urinary tract obstruction.	**NON-INCLUSION CRITERIA** **C13NI**	**OK If : C13NI=0** **Investigator decision**

3.3 Indicator variable for trial populations (derived variables)

3.3.1 Dose escalation part

For each patient, assessment of the status "Evaluable for tolerance" will be checked based on the **TREATMENT (TRT) C1** eFORM. Whenever possible, controls will be implemented using variables from additional eFORMs.

Table 3 : Criteria for the dose escalation part

Criteria	eForm/Variable	Control
Population of tolerance	**TOL** (new variable) **TREATMENT (TRT) C1** **TOT_DOS** (total dose received during the cycle)	**TOL = 1** **If (TOT_DOS LE 0) then TOL=0**
DLT-evaluable	**ELI_DLT** (new variable) **C1D18, CYCLE 2 EXAMEN** **DOS_TOX** (any DLT) **TREATMENT (TRT) (cycle 1)** **DOS_TOX** (Presence of DLT) **TH_W1CYC** (therapy changes) **TH_W3CYC** (3=discontinuation) **TH_W1MET,TH_W2MET, TH_W3MET TH_W4MET** **TH_SIR**	**ELI_DLT =0** **If (DOS_TOX =1) then ELI_DLT=1** **IF (TH_W1CYC and TH_W3CYC and TH_W1MET and TH_W2MET and TH_W3MET and TH_W4MET and TH_SIR) NE 3 then ELI_DLT=1**

CREATION OF 2 NEW INDICATOR VARIABLES

New binary variable TOL
Label: « Evaluable for Tolerance»
TOL= 1 if the patient is evaluable for tolerance analysis
TOL =0 if the patient is not evaluable for tolerance analysis

New variable ELI_DLT
Label: « DLT-Evaluable »
ELI_DLT= 1 if the patient is evaluable in terms of DLT
ELI_DLT =0 if the patient is not evaluable in terms of DLT

3.3.2 Expansion cohort

3.3.2.1 Eligible population

CREATION OF A NEW INDICATOR VARIABLE

New binary variable ELI
Label: "Eligibility"
ELI = 1 if the patient is eligible
ELI =0 if the patient is not eligible

Table 4 : Criteria for the eligible status

Criteria	eFORM variable	Control
Eligible Population	**ELIGIBILTY FORM** **C1I C2I C3I C4I C5I C6I C7I C8I C9I C10I C11I C12I C13I C14I C15I** **C1NI C2NI C3NI C4NI C5NI C6NI C7NI C8NI C9NI C10NI C11NI C12NI C13NI C14NI C15NI C16NI C17NI C18NI C19NI C20NI C21NI C22NI C23NI C24NI C25NI**	**ELI=1** **If (C1I=0 OR C2I=0 OR C3I=0 OR C4I=0 OR C5I=0 OR C6I=0 OR C7I=0 OR C8I=0 OR C9I=0 OR C10I=0 OR C11I=0 OR C12I=0 OR C13I=0 OR C14I=0 OR C1NI=1 OR C2NI=1 OR C3NI=1 OR C4NI=1 OR C5NI=1 OR C6NI=1 OR C7NI=1 OR C8NI=1 OR C9NI=1 OR C10NI=1 OR C11NI=1 OR C12NI=1 OR C13NI=1) then ELI=0**

3.3.2.2 Population evaluable for efficacy

CREATION OF A NEW INDICATOR VARIABLE

New binary variable ELI_EFF
Label: "Efficacy Population"
ELI_EFF = 1 if the patient is assessable for efficacy
ELI_EFF = 0 otherwise

Table 5 : Criteria for the efficacy population

Criteria	eForm/Variable	Control
Population evaluable for EFFICACY	**ELI_EFF** (new variable)	**ELI_EFF = 1** **AND**
• Received one complete or two incomplete treatment cycles	**CYCLE 1 EXAMEN, C1D18, C2, TREATMENT**	Date of start cycle Total dose given during cycle Therapy changes during cycle **AND**
• one disease measurement recorded not less than eight weeks after treatment onset	**TUMOR ASSESSMENT C3 (TUM_CYC)** **DIS_EVA (1= week 8)**	**DIS_EVA =1 and** Information on tumor assessment completed at cycle 3 and date of tumor assessment at cycle 3
		OR If
❖ Received at least one treatment cycle and experience disease progression or die due to disease progression prior	**CYCLE 1 EXAMEN, C1D18, TREATMENT** **DOS_MOD** (dose modification) **DOS_REA** (reason , 1= progression) **END OF STUDY (END_STU)** **EOS_REA** (3 =death)	**ELI =1** Date of start cycle Total dose given during cycle Therapy changes during cycle **(DOS_MOD=1 and DOS_REA=1)**

to response evaluation after the start of study treatment.	**DT_DEATH** **CA_DEATH** (1 =progression) **TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement)	**OR (EOS_REA = 3 and DT_MEAC** is blank **and** **CA_DEATH=1)** **OR If**
❖ withdrawn due to drug-related toxicity without any tumor assessments after the start of study treatment	**TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement) **(EXAMEN) C1D18, C2, C2D15, C3, C4, C5, C6, ADDITIONAL VISIT** **TRT_CON** (1=definitively stop) **DOS_MOD** **DOS_REA** (0=toxicity)	**DT_MEAC** is blank **AND** **TRT_CON=1 AND DOS_MOD=1 AND DOS_REA=0** **OR If**
❖ withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, or unrelated AEs without any tumor assessments after the start of study treatment	**TUMOR ASSESSMENT (TUM_CYC)** **DT_MEAC** (Date of measurement) **END OF TREATMENT (EOTF)** **DT_STRT,DT_ETRT** (start and end of treatment) **EOT_REA** (11= changes in patient's condition) **ADVERSE EVENT FORM (AEV4)** **DT_AE, DTENDAE** (start and end date) **TRTMODIF** **IMP_SIR, IMP_MET, IMP_ZOL, IMP_CYC** (drugs related or not)	**DT_MEAC** is blank **EOT_REA=11** **DT_AE and DTENDAE** filled in **TRTMODIF**=definitively stop **IMP_SIR and IMP_MET and IMP_ZOL and IMP_CYC** = Unrelated

3.3.2.3 Population evaluable for safety

CREATION OF A NEW INDICATOR VARIABLE

New binary variable SAFE
Label: "Safety Population"
ELI_EFF = 1 if the patient is assessable for safety
ELI_EFF = 0 otherwise

Table 2 : Criteria for the safety population

Criteria	eFORM variable	Control
All patients having received at least one treatment administration	**CYCLE 1 TREATMENT** DS_W1CYC… DS_W4CYC DS_W1MET… DS_W4MET DS_ZOL TOT_ DOS	**Ok if :** DS_W1CYC ge 0 or DS_W1MET ge 0 or DS_ZOL ge 0 or TOT_ DOS ge 0

3.4 Recruitment

The following data will be presented:

- Number of included participants
- Number of participants included in the analyses and reasons of exclusion if needed
- Protocol deviations
- Inclusions curve (evolution of participants frequency between first and last inclusion)
- Flow chart according to CONSORT recommendations will be presented.

4. Statistical principle

4.1 Descriptive methods

4.1.1 Calculation rules (Duration, dates and delays)

- Calculation rules in the statistical analyses
  - Duration between two dates in months: (Date 2 – Date 1 + 1) / 30.4375.
  - Duration between two dates in years will be calculated as number of years between the two dates.
  - Duration between two dates in days will be calculated as the number of days between the two dates: (Date 2 – Date 1 + 1) / 365.25.
  - Difference between two measurements will be calculated according to the following formula: Delta = (measurement at time 1 – measurement at time 2).

- Dates and delays
  - Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry and summaries presented using the median and range.
  - Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

4.1.2 Continuous variables

  - Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale CTCAE v4.03 from the NCI will be used).
  - Other continuous variables (for example age) are presented using using mean and standard deviations if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles). If appropriate, continuous data may also be presented in categories (for example age may also be grouped in decades).

4.1.3 Categorical variables

  - Variables will be described with counts and proportions.
  - Frequency tables will be tabulated for all categorical variables by the levels of the variables as they appear on the CRF (counts and proportions).
  - Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the participant's fulfilling the condition for the specification (participant id, institution, treatment group, value of the item and text field contents).

4.2 Confidence interval and P values

- No p-values will be calculated for primary and secondary endpoints : one arm
- The 95% two-sided confidence limits (binomial law) will be provided for the calculated rates (progression-free rate, objective response rate and best overall response rate).
- Exploratory analyses upon request: a 2-sided alpha of 0.05 will be used.

4.3 Analysis methods

4.3.1 Sensitivity analysis

No sensitivity analysis is planned.

4.3.2 Subgroup analyses

No subgroup analysis is planned.

4.3.3 Exploratory analysis

No exploratory analysis is planned.

4.4 Handling of missing data

- For each variable, the number of missing data will be described. The reason for the missing data will be documented as far as possible to allow for its interpretation.
- For dates:
  - In case of missing day: it will be replaced by 15 which correspond to the middle of the month.
  - In case of missing day and month: it will be replaced by the 15th of June (6) which corresponds to the middle of the year. These imputations will allow calculation of the time to occurrence of the events.
- Missing efficacy or safety data will not be imputed unless otherwise specified.

5. Statistical Analysis

5.1 Baseline patients characteristics

- Characteristics of the patients will be described for each of the following populations:
  - Population assessable for efficacy (patients evaluable for the primary endpoint)
  - Safety population

- The participants will be described at baseline and during follow-up according to the following variables:
  - Compliance with eligibility criteria,
  - Epidemiological characteristics,
  - Clinical and laboratory characteristics,
  - Treatment characteristics.
  - Adverse events
  - Deviations
  - Deaths

5.2 Extent of exposure and treatment compliance

Data from patients in the safety population will be used to summarize the extent of exposure, compliance, and dose modification of study drug.

Summary statistics will be presented by treatment group as actual treatment received for all patients in the safety population as follows:
- Number of issued cycles and full cycles (completed)
- Cumulative dose received over the study

Dose modifications will be summarized as follows:
- Patients with at least 1 dose modification will be summarized
- A listing by patient of the reason for the dose modifications will be provided.

Treatment discontinuation will be described as follows:
- Number of patients who discontinue treatment
- Summary table of reasons for discontinuation
- A listing of the other reason of discontinuation will be provided by patient.

End of study will be described as follows:
- Number of patients who discontinue the study and reasons

- Number of deaths and reasons of death.

5.3 Endpoint analysis

5.3.1 Primary endpoint

5.3.1.1 Dose escalation part

5.3.1.1.1 Definition

- Toxicity graded using the common toxicity criteria from the NCI v4.03.
- Incidence rate of DLT at each dose level on cycle 1

5.3.1.1.2 Analysis

- Toxicities observed at each dose level will be recorded in terms of number of events, event type, frequency, severity, dates of beginning and end, reversibility and evolution. Data will be gathered in tables summarizing toxicities and side effects for each dose level and cycle.

5.3.1.1.3 Calculation or transformation used to derive the outcome

eFORM variables	Control TOL=1 and
CYCLE_ EXAMEN **/TOXI** (any toxicity observed)	TOXI =1
TREATMENT **DT_S1SIR, DT_E1SIR** (start and end date) **DS_SIR** (dose sirolimus) **DT_S1CYC- DT_E3CYC, DS_W1CYC- DS_W3CYC (CP)** **DT_1D1ME-DT_4D4ME, DS_W1MET-DS_W4MET** (METHOTREXATE) **DT_ZOL, DS_ZOL** (ZA)	completed
ADVERSE EVENT FORM**/ AEVENT** (adverse event)	Filled in
ADVERSE EVENT FORM**/ AESAE** (is a serious adverse event)	Filled in
ADVERSE EVENT FORM**/ DT_SAE , DT_AE** (date of beginning)	Filled in
ADVERSE EVENT FORM**/ DTENDAE** (date of the end or death)	Filled in
ADVERSE EVENT FORM**/ INIT_INT, MAX_INT** (intensity)	Filled in

- Incidence rate of DLT at each dose level on cycle 1 will be also measured.

eFORM variables	Control ELI_DLT=1 and
TREATMENT **DT_S1SIR, DT_E1SIR** (start and end date) **DS_SIR** (dose sirolimus) C1D18, C2 **DOS_TOX** (any DLT observed) DOSE-LIMITING TOXICITY FORM **DT_TOX** (date of the event) **ANO_DLT** (another DLT) **DS_C1SIR** (dose of sirolimus)	**DT_S1SIR and DT_E1SIR and DS_SIR** filed in **DOS_TOX** filled in **ANO_DLT** filled in

5.3.1.2 Expansion cohort

5.3.1.2.1 Definition

Antitumor activity observed with sirolimus combined with CP, MT and ZA, in OSS patients, in terms of 6-month non-progression rate, defined as the rate of complete or partial response or stable disease at 6 months using RECIST v1.1.

Centralized radiological review will be performed to confirm disease status at 6 months in comparison with baseline, Week#8 and Week#16. For patients included in the reference center, CT scan will be initially read by a radiologist who differs from the expert.
Review process will be centralized at Institut Bergonié and will be performed by a radiologist expert in soft tissue sarcomas.

5.3.1.2.2 Analysis

Primary endpoint will be analyzed on the population assessable for efficacy.
The 6-month non-progression rate will be described using frequency, percentage and 95% confidence interval (binomial law).

5.3.1.2.3 Calculation or transformation used to derive the outcome

CREATION OF A NEW INDICATOR VARIABLE

New binary variable NP_6M
Label: "Progression-free status at 6 months"
NP_6M = 1 if the patient is progression-free at 6 months
NP_6M = 0 otherwise

Criterion	eFORM variable	Control
Non-progression at 6 months defined as the proportion of patients with complete response, partial response or stable disease as per RECIST v1.1 criteria.	**TUMOR ASSESSMENT – RCR (TUMOR)** **DT_MEACR** Date of measurement **MEA1RTLC- MEA5RTLC** Measures of lesions **SUM_RTLC** Largest diameters **EVA1LNMR-EVA5LNMR** Non-measurable lesions evaluation **RES_TLR, RES_NTLR** Response target and non-target lesions **OV_RESPR** Overall response CR=1, PR=2, SD=3, PD=4, NE=5	**DT_MEASC** filled in **MEA1RTLC- MEA5RTLC** (filled in if needed) **SUM_RTLC** filled in and check RECIST 1.1 criteria **RES_RTL, RES_RNTL** (filled in) **NP_6M=1 if patients with OV_RESPR in (1 2 3) at 6 months for at least 24 weeks, with CR (OV_RESPR=1) or PR (OV_RESPR=2) confirmed at the next tumor assessment**

5.3.2 Secondary endpoints

5.3.2.1 Dose escalation part

5.3.2.1.1 Definition

- PK measurements expressed as AUC, half-life and concentration peak for CP, MT and sirolimus
- Antitumor activity observed with sirolimus combined with CP, MT and ZA, in terms of
  - 6-month objective response rate , defined as the rate of complete or partial response at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1
  - Best objective response rate, defined as the rate of complete or partial response confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1
  - 6-month Non-progression rate (NPR), NPR is defined as the percentage of patients with CR, PR or stable disease (SD) at 6 months according to RECIST 1.1
  - 1-year Progression-free survival (PFS), PFS is defined as the time from study treatment initiation to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment).
  - Growth modulation index (GMI) GMI will be defined for each patient as the ratio of its PFS on sirolimus + CP/MTX/ZA treatment to its PFS on a previous line of therapy. This method accounts for inter-patient variability, the patient serving as his/her own control and implies by the natural history of the disease that the PFS tends to become shorter in successive lines of therapy. Von Hoff suggested that an anti-cancer agent should be considered effective if the GMI is greater than 1.3 [2]
  - 1-year Overall Survival (OS), OS is defined as the time from first infusion to death (of any cause)

5.3.2.1.2 Analysis

- Efficacy analysis: efficacy endpints will be reported in terms of counts and proporitons for each dose leves.
- Data analyses will be provided by dose groups and for all study patients, combined wherever appropriate.
- For continuous variables, summary statistics will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
- Categorical endpoints will be summarized using number of patients, frequency, percentages.
- For survival endpoints, median survival time will be reported.

5.3.2.1.3 Calculation or transformation used to derive the outcome

Criteria	eFORM variable	Control
PK measurements expressed as AUC, half-life and concentration peak for CP, MT and sirolimus	**PHARMA C1D1, C1D18, C2D1, C2D15, C3D1** **DT_SIRO, DT_CYCL, DT_METH** (date) **TM_SIRO,TM_CYCL,TM_METH** (time) **DS_SIROL, DS_CYCL, DS_METH** (dose)	

6-month objective response rate , defined as the rate of complete or partial response at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1	**TUMOR (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2 **PHARMA (Cycle 1 day 1)** **DT_SIRO** (first infusion of sirolimus), **TM_SIRO** (time) ,**DS_SIROL** (dose) New variables : **NB_ORR** (nb of objective response case at 6months)	**DT_SIRO and TM_SIRO and DS_SIROL** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in and check recist1.1 criteria **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) **NB_ORR**=sum for each patient **((DT_MEAC-DT_SIRO≥6) and OV_RESP=(1 or 2))** Checking 4 weeks after **Result=NB_ORR/sum(TOL)**
Best objective response rate, defined as the rate of complete or partial response confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1	**TUMOR (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2, SD=3, PD=4,NE=5 New variables : **NB_BORR** (nb of objective response case)	**Status at each TUMOR ASSESSMENT** **Date of end of treatment (DT_ETRT)** Checking 4 weeks after
6-month Non-progression rate (NPR) defined as the percentage of patients with CR, PR or stable disease (SD) according to RECIST v1.1	**TUMOR (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **ME1L_ME5L** (measures of lesions) **SUM_TL** (largest diameters) **EVA1LNM_EVA5LNM** (non-measurable lesions eval) **RES_TL, RES_NTL** (target and non-target lesions) **OV_RESP** (overall response) CR=1, PR=2, SD=3 **PHARMA (Cycle 1 day 1)** **DT_SIRO** (first infusion of sirolimus), **TM_SIRO** (time) ,**DS_SIROL** (dose) New variables : **NB_NPR** (nb of non-progression case at 6 months)	**DT_SIRO and TM_SIRO and DS_SIROL** filled in **ME1L_ME5L** (filled in if needed) **SUM_TL** filled in and check recist1.1 criteria **EVA1LNM_EVA5LNM** (filled in if needed) **RES_TL, RES_NTL** (filled in) **NB_NPR**=sum for each patient ((**DT_MEAC-DT_SIRO≥6**) and **OV_RESP**=(1 or 2 or 3)) Result=**NB_NPR/ sum(TOL)*100**
1-year Progression-free survival (PFS), PFS is defined as the time from study treatment initiation to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment).	**TUMOR (TUMOR ASSESSMENT)** **DT_MEAC** (date of measurement) **OV_RESP** (overall response) CR=1, PR=2, SD=3,PD=4 **END OF TREATMENT FORM** **DT_STRT** (Date of start of treatment) **EOT_STA** (Status) **EOT_REA** (Reason end) **DT_PROG** (Date of progression if occurred) Type of progression (if progression occurred)	Check if everything is filled in **If (DT_PROG is blank) then Do;** **If (PRO_LAS=0) then {** **PFS= DT_EOS-DT_STRT ;** **If (EOS_REA ='death') then** **IND_PFS=1** **Else IND_PFS=0** **}** **Else {**

	FOLLOW UP FORM **DT_FUP** (date of visit) **STA_FUP** (Vital status) **PRO_LAS, DT_FPRO** (date of progression)	**PFS=DT_FPRO – DT_STRT;** **IND_PFS=1}** **End;** **Else {** **PFS= DT_PROG – DT_STRT;** **IND_PFS=1}**
Growth modulation index (GMI) GMI will be defined for each patient as the ratio of its PFS on sirolimus + CP/MTX/ZA treatment to its PFS on a previous line of therapy. This method accounts for inter-patient variability, the patient serving as his/her own control and implies by the natural history of the disease that the PFS tends to become shorter in successive lines of therapy. Von Hoff suggested that an anti-cancer agent should be considered effective if the GMI is greater than 1.3 [2]	**PRE-TREATMENT VISIT(2/3)** Date of 1st cycle of last line of therapy **DT_1CYC** or **DT_xCYC** Date of progression **DT_1PRO or DT_xPRO** **END OF TREATMENT FORM** **DT_STRT** (Date of start of treatment) **EOT_STA** (Status) **EOT_REA** (Reason end) **DT_PROG** (Date of progression) Type of progression (if progression occurred)	**GMI= (DT_xPRO-DT_xCYC) / (DT_PROG-DT_STRT)**
1-year Overall Survival (OS), OS is defined as the time from first infusion to death (of any cause)	**END OF TREATMENT (EOTF)** **DT_STRT** (Date of start of treatment) **EOT_STA** (Status) **EOT_REA** (Reason end) **FOLLOW UP FORM** **DT_FUP** (date of visit) **STA_FUP** (Vital status) **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **EOS_REA** (reason) **DT_DEATH** (date of death)	Check if everything is filled in **If (STA_FUP NE 'dead') then do;** **if (EOS_REA='death') then {** **OS= DT_DEATH-DT_STRT;** **IND_OS=1;** **}** **Else {OS= DT_EOS-DT_STRT;** **IND_OS=0;** **}** **end;** **Else { OS= DT_LNEW-DT_STRT;** **IND_OS=1; }**

5.3.2.2 Expansion cohort

5.3.2.2.1 Definition

- Antitumor activity observed with sirolimus combined with CP, MT and ZA, in terms of
  - 6-month objective response rate , defined as the rate of complete or partial response at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1
  - Best objective response rate, defined as the rate of complete or partial response confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1
  - 1-year Progression-free survival (PFS), PFS is defined as the time from study treatment initiation to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment).
  - Growth modulation index (GMI) GMI will be defined for each patient as the ratio of its PFS on sirolimus + CP/MTX/ZA treatment to its PFS on a previous line of therapy. This method accounts for inter-patient variability, the patient serving as his/her own control and implies by the natural history of the disease that the PFS tends to become shorter in successive lines of therapy. Von Hoff suggested that an anti-cancer agent should be considered effective if the GMI is greater than 1.3 [2]
  - 1-year Overall Survival (OS), OS is defined as the time from first infusion to death (of any cause)

- Toxicity graded using the common toxicity criteria from the NCI v4.03.
- PK measurements expressed as AUC, half-life and concentration peak for CP, MT and sirolimus.

5.3.2.2.2 Analysis

- Efficacy analysis:
  - Will be analyzed on the population assessable for efficacy,
  - Efficacy endpoints will be reported in terms of counts and proportions.
  - For continuous variables, summary statistics will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate.
  - Categorical endpoints will be summarized using number of patients, frequency, percentages.
  - For survival endpoints, median survival time will be reported.
- Safety analysis :
  - Will be based on the population assessable for safety,
  - Toxicities will be recorded in terms of event type, severity, dates of beginning and end, reversibility and evolution. Data will be gathered in tables summarizing toxicities and side effects for each dose level and cycle.

5.3.2.2.3 Calculation or transformation used to derive the outcome

New variable OS
Label : « Overall Survival »

New variable IND_OS:
Label : « censure OS »
OS =1 if the patient died
OS=0 otherwise

New variable PFS
Label : «Progression-free-survival»

New variable IND_PFS:
Label : « censure PFS»
PFS=1 if le patient died or experienced progression (recist)
PFS=0 otherwise

Criteria	eFORM variable	Control
PK measurements expressed as AUC, half-life and concentration peak for CP, MT and sirolimus	**PHARMA C1D1, C1D18, C2D1, C2D15, C3D1** **DT_SIRO, DT_CYCL, DT_METH** (date) **TM_SIRO,TM_CYCL,TM_METH** (time) **DS_SIROL, DS_CYCL, DS_METH** (dose)	completed
6-month objective response rate , defined as the rate of complete or partial response at 6 months confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of	**TUMOR ASSESSMENT – RCR (TUMOR)** **DT_MEACR** Date of measurement **MEA1RTLC- MEA5RTLC** Measures of lesions	**DT_SIRO and TM_SIRO and DS_SIROL** filled in **MEA1RTLC_ MEA5RTLC** (filled in if needed) **SUM_ RTLC** filled in and check

tumor assessments using RECIST v1.1	**SUM_RTLC** Largest diameters **EVA1LNMR-EVA5LNMR** Non-measurable lesions evaluation **RES_TLR, RES_NTLR** Response target and non-target lesions **OV_RESPR** Overall response CR=1, PR=2 **PHARMA (Cycle 1 day 1)** **DT_SIRO** (first infusion of sirolimus), **TM_SIRO** (time) ,**DS_SIROL** (dose) New variables : **NB_ORR** (nb of objective response case at 6months)	recist1.1 criteria **EVA1LNMR _ EVA5LNMR** (filled in if needed) **RES_ TLR, RES_ NTLR** (filled in) **NB_ORR**=sum for each patient **((DT_MEAC-DT_SIRO≥6) and OV_ RESPR =(1 or 2))** Checking 4 weeks after **Result=NB_ORR/sum(ELI_EFF)**
Best objective response rate, defined as the rate of complete or partial response confirmed ≥ 4 weeks after initial documentation, as determined by investigator review of tumor assessments using RECIST v1.1	**TUMOR ASSESSMENT – RCR (TUMOR)** **DT_MEACR** Date of measurement **MEA1RTLC- MEA5RTLC** Measures of lesions **SUM_RTLC** Largest diameters **EVA1LNMR-EVA5LNMR** Non-measurable lesions evaluation **RES_TLR, RES_NTLR** Response target and non-target lesions **OV_RESPR** Overall response CR=1, PR=2, SD=3, PD=4,NE=5 New variables : **NB_BORR** (nb of objective response case)	**Status at each TUMOR ASSESSMENT** **Date of end of treatment (DT_ETRT)** Checking 4 weeks after
1-year Progression-free survival (PFS), PFS is defined as the time from study treatment initiation to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment).	**TUMOR ASSESSMENT – RCR (TUMOR)** **DT_MEACR** (Date of measurement) **OV_ RESPR** (overall response) CR=1, PR=2, SD=3,PD=4 **END OF TREATMENT FORM** **DT_STRT** (Date of start of treatment) **EOT_STA** (Status) **EOT_REA** (Reason end) **DT_PROG** (Date of progression if occurred) **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **FOLLOW UP FORM** **DT_FUP** (date of visit) **STA_FUP** (Vital status) **PRO_LAS, DT_FPRO** (date of progression)	Check if everything is filled in and **If (DT_PROG is blank) then Do;** **If (PRO_LAS=0) then {** **PFS= DT_EOS-DT_STRT ;** **If (EOS_REA ='death') then IND_PFS=1** **Else IND_PFS=0** **}** **Else {** **PFS=DT_FPRO – DT_STRT;** **IND_PFS=1}** **End;** **Else {** **PFS= DT_PROG – DT_STRT;** **IND_PFS=1}**
Growth modulation index (GMI) GMI will be defined for each patient as the ratio of its PFS on sirolimus + CP/MTX/ZA treatment to its PFS on a previous line of therapy. This method accounts for inter-patient variability, the patient serving as his/her own control and implies by the natural history of the	**PRE-TREATMENT VISIT(2/3)** Date of 1st cycle of last line of therapy **DT_1CYC** or **DT_xCYC** Date of progression **DT_1PRO or DT_xPRO** **END OF TREATMENT FORM** **DT_STRT** (Date of start of treatment)	**GMI= (DT_xPRO-DT_xCYC) / (DT_PROG-DT_STRT)**

disease that the PFS tends to become shorter in successive lines of therapy. Von Hoff suggested that an anti-cancer agent should be considered effective if the GMI is greater than 1.3 [2]	**EOT_STA** (Status) **EOT_REA** (Reason end) **DT_PROG** (Date of progression) Type of progression (if progression occurred)	
1-year Overall Survival (OS), OS is defined as the time from first infusion to death (of any cause)	**END OF TREATMENT (EOTF)** **DT_STRT** (Date of start of treatment) **EOT_STA** (Status) **EOT_REA** (Reason end) **FOLLOW UP FORM** **DT_LNEW** (date of last new) **STA_FUP** (Vital status) **END OF STUDY (END_STU)** **DT_EOS** (date of end of study) **EOS_REA** (reason) **DT_DEATH** (date of death)	**If (STA_FUP NE 'dead') then do;** **if (EOS_REA='death') then {** **OS= DT_DEATH-DT_STRT;** **IND_OS=1;** **}** **Else {OS= DT_EOS-DT_STRT;** **IND_OS=0;** **}** **end;** **Else { OS= DT_LNEW-DT_STRT;** **IND_OS=1; }**

5.4 Safety

The safety analysis will be performed on the safety population. Drug toxicities and adverse events (AEs) will be described according to the NCI-CTCAE V4.03. Each of the following will be described:

- Counts and proportions of drug toxicities and AEs described by SOC, event term and grade.
- Counts and proportions of patients with at least one drug toxicities, AEs described by SOC, event term and grade.
- Listing of Serious Adverse Events (SAE).

5.5 Statistical software

The main statistical analyses will be performed using SAS V9.4. Other statistical software to produce grahics, for example, could be used.

5.6 References

Data management plan v1.0, March 26th, 2015

6. Appendix

6.1 LIST OF DATALISTINGS

6.1.1 INCLUSION FORM

- Datalisting 1.1. Inclusion and non-inclusion criteria.

6.1.2 PATIENT CHARACTERISTICS AT BASELINE

- Datalisting 2.1. Medical history at baseline: pathology code, date of beginning, date of end, ongoing.

6.1.3 TUMOR CHARACTERISTICS AT BASELINE

- Datalisting 3.1. Prior surgery: date of surgery, Margin
- Datalisting 3.2. Prior radiotherapy: date of 1st sequence, Date of last sequence, Total dose, Sequence, Exclusive radiotherapy
- Datalisting 3.3. Prior chemotherapy: Initial regimen, drug information (Anthracyclines, Ifosfamide, and/or Platinum salts, Methotrexate), (neo)adjuvant setting, Date of 1st cycle, Date of last cycle, best response RECIST, date of progression, other line of chemotherapy.

6.1.4 TUMOR ASSESSMENT AT BASELINE

- Datalisting 4.1. Measurable lesions: Other localization of measurable lesions
- Datalisting 4.2. Non-measurable lesions: Other localization of non-measurable lesions

6.1.5 DRUG DELIVERY

- Datalisting 5.1. CYCLOPHOSPHAMIDE: Week 1 Start date, Week 1 stop date, week 1 dose, Week 1 therapy change, Week 1 reason, Week 3 Start date, Week 3 stop date, week 3 dose, Week 3 therapy change, Week 3 reason.
- Datalisting 5.2. METHOTREXATE: Week 1 Day 1, week 1 Day, week 1 dose, week 1 therapy change, week 1 reason, same info for weeks 2, 3, 4.
- Datalisting 5.3. ZA: Date of injection, dose, therapy change, reason for change.
- Datalisting 5.4. SIROLIMUS: Start date, stop datedose, therapy change, reason.

6.1.6 DOSE-LIMITING TOXICITY AT EACH CYCLE

- Datalisting 6.1. DLT (1): dose-limiting toxicity (Y/N), toxicity since last visit (Y/N).
- Datalisting 6.2. DLT (2): Date C1D1, Dose Sirolimus, Date last intake, Date Event, NH tox gr4, NH tox gr3, haemato tox gr3, lymphopenia gr4, febrile neutropenia, trt interruption or dose modif.

6.1.7 TUMOR ASSESSMENT DURING TREATMENT

- Datalisting 7.1. . Global response: Week, change from baseline, change from NADIR, overall response

6.1.8 END OF TREATMENT

- Datalisting 8.1. End of treatment: Date of start, date of end, status (complete response,…), reason for the end of the treatment, date of progression, type of progression

6.1.9 FOLLOW-UP

- Datalisting 9.1. Vital status: Status, Date last news/date of death, tumor status, Death cause
- Datalisting 9.2. Progression: Tumor evaluation required, Clinical and radiological tumor assessment performed, progression since last follow-up, date of Progression
- Datalisting 9.3. Other: new anti-tumor therapy, toxicity observed

6.1.10 ADVERSE EVENT

- Datalisting 10.0. Event, date of event, serious adverse event, sae start date, initial intensity, maximum intensity, treatment modification, date of the end or death, treatment introduced, concomitant treatment (dose, route, start date, end date)

6.1.11 CONCOMITANT MEDICATION

- Datalisting 11.0. Treatment, Indication, Daily dose, Route, Start date, ongoing, End date

6.1.12 END OF STUDY

- Datalisting 12.0. End date, Main reason, consent withdrawn, patient is lost to follow-up, death and cause

6.2 LIST OF TABLES

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- Table 1.1. Description of center
- Table 1.2. Number of patients registered, treated, eligible, evaluable for safety, evaluable for efficacy by dose level

6.2.2 PATIENT CHARACTERISTICS AT BASELINE

- Table 2.1. Demographic characteristics at baseline : age, sex
- Table 2.2. General medical conditions at baseline : weight, height, Heart rate, O2, performance status
- Table 2.3. Medical and surgical history (Y/N) at baseline
- Table 2.4. Medical and surgical history (pathology) at baseline
- Table 2.5. Ongoing concomitant treatments at baseline
- Table 2.6. Descriptive statistics for hematological parameters at baseline
- Table 2.7. Descriptive statistics for biochemical parameters at baseline
- Table 2.8. Descriptive statistics for urine analysis parameters at baseline
- Table 2.9. Descriptive statistics for serology parameters at baseline
- Table 2.10. Descriptive statistics for other parameters at baseline

6.2.3 TUMOR CHARACTERISTICS AT BASELINE

- Table 3.1. Description of disease diagnosis
- Table 3.2. Description of histological diagnosis
- Table 3.3. Description of Anatomic location
- Table 3.4. Description of Grade
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- Table 3.7. Description of sites of Metastasis
- Table 3.8. Description of prior surgery
- Table 3.9. Description of prior radiotherapy
- Table 3.10. Description of prior chemotherapy

6.2.4 TUMOR ASSESSMENT AT BASELINE

- Table 4.1. Description of measurable lesions
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6.2.5 DRUG DELIVERY

- Table 5.1. Dose levels: Number of patients

- Table 5.2. For each treatment (CYCLOPHOSPHAMIDE, METHOTREXATE, ZOLEDRONIC ACID, SIROLIMUS): Frequency of delivered cycle by dose level
    - Table 5.2.1. Delivery of CYCLOPHOSPHAMIDE : frequency of delivered cycles
    - Table 5.2.2. Delivery of CYCLOPHOSPHAMIDE : number of patients
- Table 5.3. Cumulative dose of CYCLOPHOSPHAMIDE by dose level per patient
- Table 5.4. Cumulative dose of METHOTREXATE by dose level per patient
- Table 5.5. Cumulative dose of ZOLEDRONIC ACID by dose level per patient
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6.2.6 TREATMENT MODIFICATION

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- Table 6.2. Dose adaptations: frequency of adapted patients by dose level.
- Table 6.3. Reasons of delayed administration by dose level : description of reason and others.
- Table 6.4. Reduced and delayed cycles by dose level: frequency of cycles by dose level.

6.2.7 END OF TREATMENT

- Table 8.1. Status at end of treatment
- Table 8.2. Reasons for end of treatment

6.2.8 DOSE-LIMITING TOXICITIES

- Table 8.1. Dose-limiting toxicities by dose level
- Table 8.2. Grade 4 non-hematological toxicity (not laboratory) by dose level
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- Table 8.4. Grade ≥ 3 non-hematologic laboratory value [if medical intervention is required to treat the patient, or the abnormality leads to hospitalization, or the abnormality persists for > 1 week] by dose level
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6.2.9 EFFICACY: Response, Progression and Survival

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- Table 9.2. Frequency distribution of 6-month objective response by dose level on population evaluable for efficacy (expansion cohort) and population evaluable for tolerance (dose escalation)
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- Table 9.4. Descriptive statistics for GMI by dose level on population evaluable for efficacy (expansion cohort) and population evaluable for tolerance (dose escalation)
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6.2.10 LIST OF FIGURES