COMBINATION OF MK3475 AND METRONOMIC CYCLOPHOSPHAMIDE IN PATIENTS WITH ADVANCED SARCOMAS : MULTICENTRE PHASE II TRIAL

PEMBROSARC

MULTICENTRE PHASE II TRIAL

Statistical Analysis Plan (SAP) – Final Analysis
Stratum 1: Advanced Leiomyosarcomas
Version 1.1 of 17/12/2015

Source documents:
Protocol: version 3.0 of 20/07/2015
Database (Main): annoted CRF stratum 1: Leimyosarcomas / version 2.0 of 21/09/2015

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SYNOPSIS

Title of the study	**Combination of MK3475 and Metronomic Cyclophosphamide in patients with Advanced Sarcomas : Multicentre Phase II trial**
Abbreviation of the trial	**PEMBROSARC**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Doctor Antoine ITALIANO** **Department of Medical Oncology**
Number of investigational sites planned	8 centers: - Institut Bergonié - Centre Léon Bérard - Institut Gustave Roussy - Centre Oscar Lambret - Institut Curie - Institut Paoli Calmette - Institut Claudius Regaud - Institut de Cancérologie de l'Ouest – Site René Gauducheau
Number of patients	**Phase II, for each stratum:** - Leiomyosarcoma : 33 patients - Undifferentiated sarcoma : 33 patients - Sarcomas others : 33 patients - Osteosarcoma : 33 patients - GIST : 31 patients
Duration of the study	Planned enrollment period : 12 months Treatment duration : 2-years maximum Follow-up : 12 months Study period : 3 years
Medical conditions	**Advanced /metastatic sarcomas: leiomyosarcoma, undifferentiated sarcoma, other sarcoma, GIST and osteosarcoma.**
Objectives	**Primary objective** Assessment of the efficacy of MK3475 and Metronomic Cyclophosphamide (CP) independently for 5 strata as per RECIST v1.1 criteria : • Advanced leiomyosarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced undifferentiated sarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced other sarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced osteosarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced GIST (in terms of 6-month non-progression) **Secondary objectives** For each stratum: • Assessment of the efficacy of MK3475 and Metronomic CP in terms of best overall response (as per RECIST v1.1 criteria), 1-year Progression-free survival (PFS, as per RECIST v1.1 criteria), 6-month immune-related response (Wolchok 2009; central radiological review data), and 1-year

	overall survival (OS). • Assessment of the safety profile of MK3475 + metronomic CP. • Treatment safety (AEs, SAEs and laboratory abnormalities) graded according to the NCI-CTCAE version 4.0. • Growth modulation index (GMI), defined for each patient as the ratio of the PFS on MK3475 + metronomic CP to the PFS on the previous line of therapy (Von Hoff 1998), in patients with documented progression at inclusion. • Translational research : pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points). • Prospective determination of the proportion of STS that express PDL1. • Identification of prognostic biomarkers of treatment response.
Study design	This is a phase II trial with five independent strata: • **Advanced leiomyosarcoma (stratum 1)** o Single-arm phase 2 trial o Treatment : MK3475 + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced undifferentiated sarcoma (stratum 2)** o Single-arm phase 2 trial o Treatment : MK3475 + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced other sarcoma (stratum 3)** o Single-arm phase 2 trial o Treatment : MK3475 + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced osteosarcoma (stratum 4)** o Single-arm phase 2 trial o Treatment : MK3475 + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced GIST (stratum 5)** o Single-arm phase 2 trial o Treatment : MK3475 + Metronomic CP at standard doses. o 2-stage optimal Simon's design (Simon, 1989)
Inclusion criteria	1. Histology : Leiomyosarcoma, or UPS (undifferentiated pleomorphic sarcoma), or other sarcoma, or GIST (gastro intestinal stromal tumor) or osteosarcoma, histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network, 2. Advanced non resectable / metastatic disease, 3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less than 6 months interval within the 12 months before inclusion. 4. For stratum 5, documented disease progression according to RECIST criteria after the first line imatinib and second line sunitinib, 5. Have provided tissue from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy of a tumor lesion, 6. For strata 1, 2 and 3: no more of four previous lines of systemic therapy for metastatic disease 7. Age ≥ 18 years,

	8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, 9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm, 10. Life expectancy > 3 months, 11. ≥ 1 previous line (s) of chemotherapy in the palliative setting, 12. No symptomatic central nervous system disease, 13. No chronic use of glucocorticoids, 14. Adequate hematological, renal, metabolic and hepatic function: a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l, b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis). c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN. d. Albumin ≥ 25g/l. e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels > 1.5 x ULN. f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants, i. Thyroid functions within normal laboratory ranges (T3, T4 and TSH). 15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 16. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy, 17. 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 Event (NCI-CTCAE, version 4.0), 18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for four months after discontinuation of treatment. Acceptable methods for contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year. 19. Voluntary signed and dated written informed consents prior to any specific study procedure, 20. Patients with a French social security in compliance with the Law relating to biomedical research (Article 1121-11 of French Public Health Code).
Non Inclusion criteria	1. Previous treatment with MK3475 or CP, 2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), 3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases, 4. Men or women of childbearing potential who are not using an effective method

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<table>
<tr><td></td><td>of contraception as previously described; women who are pregnant or breast feeding,
5. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
6. Previous enrolment in the present study,
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
8. Known hypersensitivity to any involved study drug or of its formulation components,
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,
12. Has known active hepatitis B or hepatitis C,
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.</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.
MK3475 will be administered intraveinously, and given every 3 weeks on day 8.</td></tr>
<tr><td>Treatment schedule</td><td>
<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="2">3 weeks</td></tr>
<tr><td>MK3475</td><td>200 mg</td><td>IV</td><td>On day 8, every 3 weeks</td></tr>
</table>
A treatment cycle consists of 3 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).</td></tr>
<tr><td>Endpoints</td><td><u>Primary endpoint</u>
• The primary efficacy endpoint for advanced leiomyosarcoma (stratum 1), advanced undifferentiated sarcoma (stratum 2), advanced other sarcoma (stratum 3), advanced osteosarcoma (stratum 4) is a dual endpoint encompassing non-progression and objective response at 6</td></tr>
</table>

months (as per RECIST evaluation criteria v1.1).

- The primary efficacy endpoint for advanced **GIST** (stratum 5) is 6-month non-progression (as per RECIST evaluation criteria v1.1).
- Non-progression: complete response, partial response or stable disease more than 24 weeks as per RECIST evaluation criteria v1.1.
- Objective response: complete response or partial response as per RECIST evaluation criteria v1.1.
- Following RECIST v1.1 recommendations:
  - claimed responses will have to be confirmed at least 4 weeks later;
  - 6-month radiological data will be reviewed by an independent expert radiologist.
  - Primary efficacy analysis will be based on the central radiological review data.
  - Each patient will be assigned one of the following categories: Complete response, Partial response, Stable disease, Progression, Inevaluable for response.

Other endpoints

- Best overall response defined as per RECIST v1.1 criteria.
- 1-year progression-free survival (PFS): PFS is defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.
- 1-year overall survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
- Growth modulation index (GMI), defined for each patient as the ratio of the PFS on MK3475 + metronomic CP to the PFS on the previous line of therapy (Von Hoff, 1998), in patients with documented progression at inclusion.
- Immune-related response is defined following Wolchok et al. (Clinical Cancer Research 2009). Analysis will be based on data centrally reviewed by an expert radiologist.
- Toxicity will be graded using the common toxicity criteria from the NCI v4.0.
- Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points. Blood samples will be collected at predefined time points:
  - Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
  - Serum/plasma VEGF and TPS-1 levels (ELISA)
  - Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
  - Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS)
- Fresh pre-treatment (or archival material obtained from less than 12 weeks before inclusion) will be collected in consenting patients to assess pharmacodynamics biomarkers.
- Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers.

Statistical considerations	**NUMBER OF SUBJECTS NEEDED** **<u>Advanced leiomyosarcoma</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • MK3475 + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising • 30 eligible and assessable patients: MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients. • In order to account for not evaluable patients (+/- 10%), 33 patients with advanced leiomyosarcoma will be recruited. **<u>Advanced undifferentiated sarcoma</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • MK3475 + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising • 30 eligible and assessable patients: MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients. • In order to account for not evaluable patients (+/- 10%), 33 patients with advanced undifferentiated sarcoma will be recruited. **<u>Advanced other sarcoma</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • MK3475 + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising • 30 eligible and assessable patients: MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients. • In order to account for not evaluable patients (+/- 10%), 33 patients with advanced other sarcoma will be recruited. **<u>Advanced osteosarcoma</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • MK3475 + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising • 30 eligible and assessable patients: MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients. • In order to account for not evaluable patients (+/- 10%), 33 patients with advanced osteosarcoma will be recruited. **<u>Advanced GIST</u>** • Single-arm phase 2 trial • 2-stage Simon's design (Simon 1989). • MK3475 + metronomic CP will be considered promising if 6-month non-

	progression rate is promising • 28 eligible and assessable patients: MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 13 patients are progression-free (out of the 28 evaluable patients). • Control arm: none • In order to account for not evaluable patients (+/- 10%), 31 patients with advanced GIST will be recruited. **STATISTICAL ANALYSIS** • Each stratum will be analysed independently. No statistical comparison will be performed between strata. • The primary efficacy endpoint will be analysed based on the eligible and assessable population and based on the central radiological review data. • Efficacy of MK3475 in association with metronomic CP will be assessed in terms of : o 6-month objective response (complete response and partial response) and 6-month non-progression (complete response, partial response or stable disease more than 24 weeks) for leiomyosarcoma, undifferentiated sarcoma, other sarcoma, osteosarcoma (dual endpoint) o 6-month non-progression for GIST (single endpoint) • Objective response and non-progression are defined as per RECIST v1.1 criteria. • Each patient will be assigned one of the following categories: Complete response, Partial response, Stable disease, Progression, Inevaluable for response. • The rates of objective response and non-progression at 6 months will be reported • The safety analysis will be performed on the safety population. • Interim Statistical Analyses o Early review of safety data: Safety data will be reviewed following the inclusion of the first 3 treated patient with at least 2-month follow-up data (independently of the stratum), then after 10 treated patients, and every trimester thereafter. o Additionally, for each stratum, an interim statistical analysis will be performed at the end of the 1st stage of recruitment. Results of these interim statistical analyses will be presented to the IDMC members.

1 PROTOCOL (SUMMARY)

1.1 OBJECTIVES

1.1.1 Primary objective

Assessment of the efficacy of MK3475 and Metronomic Cyclophosphamide (CP) independently for 5 strata (as per RECIST v1.1 criteria):

- Advanced leiomyosarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced undifferentiated sarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced other sarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced osteosarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced GIST (in terms of 6-month non-progression).

1.1.2 Secondary objectives

For each stratum:

- Assessment of the efficacy of MK3475 and Metronomic CP in terms of best overall response (as per RECIST v1.1 criteria), 1-year Progression-free survival (PFS, as per RECIST v1.1 criteria), and 1-year overall survival (OS).
- 6-month immune-related response (Wolchok et al. Clinical Cancer Research 2009) based on centrally reviewed radiological data.
- Assessment of the safety profile of MK3475 + metronomic CP using the common toxicity criteria from the NCI v4.0.
- Growth modulation index (GMI), defined for each patient as the ratio of the PFS on MK3475 + metronomic CP to the PFS on the previous line of therapy (Von Hoff 1998), in patients with documented progression at inclusion.
- Translational research: pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points).
- Prospective determination of the proportion of STS that express PDL1.
- Identification of prognostic biomarkers of treatment response.

1.2 STUDY DESIGN

This is a phase II trial with five independent strata:

- **Advanced leiomyosarcoma (stratum 1)**
  - Single-arm phase 2 trial
  - Treatment: MK3475 + Metronomic CP at standard doses.
  - 2-stage dual endpoint design
- **Advanced undifferentiated sarcoma (stratum 2)**
  - Same design/treatment as for leiomyosarcoma
- **Advanced other sarcoma (stratum 3)**
  - Same design/treatment as for leiomyosarcoma
- **Advanced osteosarcoma (stratum 4)**
  - Single-arm phase 2 trial
  - Treatment: MK3475 + Metronomic CP at standard doses.
  - 2-stage dual endpoint design

- **Advanced GIST (stratum 5)**
  - Single-arm phase 2 trial
  - Treatment: MK3475 + Metronomic CP at standard doses.
  - 2-stage optimal Simon's design

1.3 PATIENT SELECTION

1.3.1 Inclusion criteria

1. Histology: Leiomyosarcoma, or UPS (undifferentiated pleomorphic sarcoma), or other sarcoma, or GIST (gastro intestinal stromal tumor, or osteosarcoma, histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Advanced non resectable / metastatic disease,
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 6 months interval within the 12 months before inclusion,
4. For strata 5, documented disease progression according to RECIST criteria after the first line imatinib and second line sunitinib,
5. Have provided tissue from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy of a tumor lesion,
6. For strata 1, 2 and 3: no more of four previous lines of systemic therapy for metastatic disease,
7. Age ≥ 18 years,
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm,
10. Life expectancy > 3 months,
11. ≥ 1 previous line (s) of chemotherapy in the palliative setting,
12. No symptomatic central nervous system disease,
13. No chronic use of glucocorticoids,
14. Adequate hematological, renal, metabolic and hepatic function:

a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l,
b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis).
c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN.
d. Albumin ≥ 25g/l.
e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN.
f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy
as long as PT or PTT is within therapeutic range of intended use of anticoagulants
h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
i. Thyroid function within normal laboratory ranges (T3, T4 and TSH).

15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy,
17. 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 Event (NCI-CTCAE, version 4.0),

18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for four months after discontinuation of treatment. Acceptable methods for contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
19. Voluntary signed and dated written informed consents prior to any specific study procedure,
20. Patients with a French social security in compliance with the Law relating to biomedical research (Article 1121-11 of French Public Health Code).

1.3.2 Non-inclusion criteria

1. Previous treatment with MK3475 or CP,
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),
3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases,
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. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
6. Previous enrolment in the present study,
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
8. Known hypersensitivity to any involved study drug or of its formulation components,
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,
12. Has known active hepatitis B or hepatitis C,
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

1.4 STUDY ENDPOINTS

1.4.1 Primary endpoint

- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months.
    - Non-progression is defined as complete response, partial response or stable disease more than 24 weeks as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2 of the protocol).
    - Objective response is defined as complete response or partial response as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2 of the protocol)
    - The rates of objective response and non-progression at 6 months will be reported.

- All eligible and assessable patients (section 10.2 of the protocol) will be included in the denominator for the calculation of the response rate or non-progression rate.
- The rate of non-progression will be calculated as the number of patients remaining alive and progression-free at 6 months from the start of the treatment divided by the number of patients eligible and assessable (section 10.2 of the protocol).
- The rate of objective response will be calculated as the number of patients alive with complete or partial response at 6 months divided by the number of patients eligible and assessable (section 10.2 of the protocol).
- The 95% two-sided confidence limits will be provided for the calculated rates (binomial law).
- Trial conclusions will be based on these rates for all eligible and assessable patients (section 10.2 of the protocol).

- Tumor measurements will be repeated every 6 weeks. Documentation (radiologic) will be provided for patients removed from study for progressive disease.
- Following RECIST v1.1 recommendations:
  - Claimed responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
  - 6-month radiological data will be reviewed by an independent expert radiologist.
  - Primary efficacy analysis will be based on the central radiological review data.

1.4.2 Secondary endpoints

- Efficacy of the association MK3475 + metronomic CP in terms of:
  - Best overall response is defined as the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation as per RECIST v1.1 criteria (appendix 2 of the protocol) :
    - The rate of best overall response will be reported.
    - All eligible and assessable patients (section 10.2 of the protocol) will be included in the denominator for the calculation of the rate.
    - The rate of best overall response will be calculated as the number of patients alive with the best response (recorded from the start of the treatment) divided by the number of patients eligible and assessable (section 10.2 of the protocol).
    - The 95% two-sided confidence limits will be provided for the calculated rate (binomial law).

    Following RECIST v1.1 recommendations:
    - The best overall response is determined once all the data for the patient is known.
    - Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (>= 4 weeks later).
  - 1-year progression-free survival (PFS): PFS is defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.
  - 1-year overall survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
  - Immune-related response is defined following Wolchok et al. (Clinical Cancer Research 2009, Appendix 6 of the protocol). Analysis of Immune-related response will be based on central radiological review data.
  - Growth modulation index (GMI), defined for each patient as the ratio of the PFS on MK3475 + metronomic CP to the PFS on the previous line of therapy (61), in patients with documented progression at inclusion.

- Assessment of the safety profile of the association MK3475 + metronomic CP. Toxicity will be graded using the common toxicity criteria from the NCI v4.0.
- Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points. Blood samples will be collected at predefined time points:
    - Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
    - Serum/plasma VEGF and TPS-1 levels (ELISA)
    - Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
    - Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS).
    - Additional details are provided in section 17 of the protocol.
- Fresh pre-treatment (or archival material obtained from less than 12 weeks before inclusion) will be collected in consenting patients to assess pharmacodynamics biomarkers. Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers. Additional details are provided in section 17 of the protocol.
- Prospective determination of the proportion of STS that express PDL1 will be assessed as detailed in section 17 of the protocol.

1.5 HYPOTHESES AND NUMBER OF SUBJECTS NEEDED

We rely on a single-arm phase 2 trial based on 2-stage dual endpoint design.

MK3475 + metronomic CP will be considered promising if either tumour response rate or 6-month non-progression rate is promising.

Hypotheses under MK3475 + metronomic CP are the following:

- Hypotheses for non-progression at 6 months:
    - 40% non-progression rate (null hypothesis),
    - 60% non-progression rate (alternative hypothesis),
- Hypotheses for objective response at 6 months:
    - 5% objective response rate (null hypothesis),
    - 20% objective response rate (alternative hypothesis),
- Maximal type I error of 5% rate and 80% minimum power.

Assuming 30 eligible and assessable patients:

- Stage 1 (15 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 3 or non-progression is observed for 7 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- Stage 2 (15 additional eligible and assessable patients): MK3475 + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses, or at least 20 non-progression at six months are observed among the 30 evaluable patients.

Inclusions will be suspended after the recruitment of the first 15 patients while data are being analysed for the first stage of inclusion.

In order to account for not evaluable patients (+/- 10%), 33 patients with advanced leiomyosarcoma will be recruited.

1.6 DEFINITION OF STUDY POPULATIONS

- Eligible population: All patients included without major violation of eligibility criteria.
- Population eligible and assessable for the primary endpoint : eligible patients who received at least one administration of MK3475 and one administration of Metronomic CP
- Safety population: All patients with at least one treatment (any) administration.

Replacement of patients: patients who do not comply with the definition of the population "eligible and assessable for the primary endpoint" will be replaced.

1.6.1 Statistical analysis

1.6.1.1 Endpoint analysis

- Patients entered into the study will be described according to the following characteristics:
    - Compliance with eligibility criteria,
    - Sociodemographic characteristics,
    - Clinical and laboratory characteristics,
    - Treatment characteristics.

- Primary efficacy endpoint analysis
    - The primary efficacy endpoint will be analysed based on the eligible and assessable population.
        - Efficacy of MK3475 in association with metronomic CP will be assessed in terms of :
            - 6-month objective response (complete response and partial response) and 6-month non-progression (complete response and partial response, stable disease more than 24 weeks) for leiomyosarcoma, undifferentiated sarcoma, other sarcoma, osteosarcoma (dual endpoint)
            - 6-month non-progression for GIST (single endpoint)
        - Objective response and non-progression are defined based on radiological and clinical data as defined as per RECIST v1.1 criteria.
        - Primary efficacy analysis will be based on the central radiological review data.
        - Each patient will be assigned one of the following categories:
            - Complete response
            - Partial response
            - Stable disease
            - Progression
            - Inevaluable for response.
        - The rates of objective response and non-progression at 6 months will be reported.
        - All eligible and assessable patients will be included in the denominator for the calculation of the response rate.
        - The 95% two-sided confidence limits will be provided for the calculated response rate (binomial law).
        - Trial conclusions will be based on the response rates for all eligible and assessable patients.

- As regards to the other efficacy endpoints, the analyses will be carried out in the eligible and assessable population.
- The safety analysis will be performed on the safety population.
- Quantitative variables will be described using means and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).
- Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.
- Prognostic role of biomarkers will be assessed using logistic or survival models depending on the nature of the outcome variable (time-to-event or binary endpoint). Multivariate models will be constructed following a backward selection approach based on candidates variables selected following univariate analyses.

1.6.1.2Interim Analysis

- Safety data will be reviewed following the inclusion of the first 10 treated patients (independently of the stratum), and once 2-month follow-up data are available.
- For each stratum, an interim statistical analysis will be performed at the end of the 1st stage of recruitment. Results of these interim statistical analyses will be presented to the IDMC members.
- An interim statistical analysis will be carried out once inclusions for the first stage of the dual endpoint design (15 eligible and assessable patients) will be completed in the experimental arm (MK3475 + metronomic CP).
- Inclusions will continue if either objective response is observed in at least 3 patients or non-progression is observed for 7 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

2 STUDY POPULATIONS

Three study populations are distinguished:
- Eligible population: All patients included without major violation of eligibility criteria.
- Population eligible and assessable for the primary endpoint : eligible patients who received at least one administration of MK3475 and one administration of Metronomic CP
- Safety population: All patients with at least one treatment (any) administration.

Replacement of patients: patients who do not comply with the definition of the population "eligible and assessable for the primary endpoint" will be replaced.

2.1 ELIGIBLE POPULATION

2.1.1 Definition

All patients included without major violation of eligibility criteria.

2.1.2 Assessment

- The eligible status will be assessed using the data gathered in the e-CRF (cf. table 1).
- If a protocol violation is observed, the steering comity (COPIL) will meet to decide whether the violation must be considered as major or minor.
- For each eligibility criteria, the number and proportion of patients satisfying the criteria, along with the number of minor and major violations, will be reported.
- In order to be eligible, patients must satisfy EVERY criterion detailed in table 1 and 2.

Table 1: Inclusion criteria

INCLUSION criteria	eFORM variable	Tests / new variables
1. Histology: Leiomyosarcoma	**Inclusion – Eligibility form** Inclusion criteria 1: C1I **Inclusion – Assessment of inclusion** Histology: HISTO **Inclusion – Pre-Visit Treatment (2)** Histology confirmed by central review or RRePS Network: HIS_REV	HISTO = 1 C1I = 1 HIS_REV = 1
2. Advanced non resectable / metastatic disease	**Inclusion – Eligibility form** Inclusion criteria 2: C2I **Inclusion – Pre-Visit Treatment (2)** Metastasis: METAS Unresectable locally advanced disease: UNRESEC	C2I = 1 METAS = 1 OR UNRESEC = 1
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 6 months interval within the 12 months before inclusion	**Inclusion – Eligibility form** Inclusion criteria 3: C3I **Inclusion – Pre-Visit Treatment (2)** Progressive disease confirmed by central review: PD_REV Date of the first imaging: DT_1IMA Type of first imaging: TYP_1IMA Date of the second imaging confirming progressive disease: DT_2IMA Type of second imaging: TYP_2IMA **Inclusion – Assessment of inclusion** Date of inclusion: DT_INC	C3I = 1 PD_REV = 1 AND (DT_2IMA-DT_1IMA < 182.625) AND (DT_INC-DT_1MA < 365.25) AND TYP_1IMA in (1 2) AND TYP_2IMA in (1 2)
4. For strata 5, documented disease progression according to RECIST criteria after the first line imatinib and second line sunitinib		
5. Have provided tissue from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy of a tumor lesion	**Inclusion – Eligibility form** Inclusion criteria 5: C5I	C5I = 1
6. For strata 1, 2 and 3: no more of four previous lines of systemic therapy for metastatic disease	**Inclusion – Eligibility form** Inclusion criteria 6: C6I	C6I = 1

INCLUSION criteria	eFORM variable	Tests / new variables
7. Age ≥ 18 years	**Inclusion – Eligibility form** Inclusion criteria 7: C7I **Inclusion – Assessment of inclusion** Date of inclusion: DT_INC Date of birth: DT_BIRTH	C7I = 1 DT_INC-DT_BIRTH > 6574.5
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1	**Inclusion – Eligibility form** Inclusion criteria 8: C8I **Inclusion – Pre-Visit Treatment (1)** ECOG performance status: ECOG_PTR	C8I = 1 ECOG_PTR in (0 1)
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm	**Inclusion – Eligibility form** Inclusion criteria 9: C9I **Inclusion – Tumour assessment** Number of measurable lesions according to Recist Criteria V1.1: NUM_LM	C9I = 1 NUM_LM > 0
10. Life expectancy > 3 months	**Inclusion – Eligibility form** Inclusion criteria 10: C10I	C10I = 1
11. ≥ 1 previous line (s) of chemotherapy in the palliative setting	**Inclusion – Eligibility form** Inclusion criteria 11: C11I	C11I = 1
12. No symptomatic central nervous system disease	**Inclusion – Eligibility form** Inclusion criteria 12: C12I	C12I = 1
13. No chronic use of glucocorticoids	**Inclusion – Eligibility form** Inclusion criteria 13: C13I	C13I = 1

INCLUSION criteria	eFORM variable	Tests / new variables
14. Adequate hematological, renal, metabolic and hepatic function: a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l, b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis). c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN. d. Albumin ≥ 25g/l. e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN. f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants, i. Thyroid function within normal laboratory ranges (T3, T4 and TSH).	**Inclusion – Eligibility form** Inclusion criteria 14: C14I **Inclusion – Pre-Visit Treatment (3)** Hemoglobin: HEMO Absolute neutrophil count: NEUT Platelet count: PLAT Albumin: ALBU	C14I = 1 HEMO >= 9 AND NEUT>= 1.5 AND PLAT >= 100 AND ALBU >= 25
15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma	**Inclusion – Eligibility form** Inclusion criteria 15: C15I	C15I = 1

INCLUSION criteria	eFORM variable	Tests / new variables
16. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy	**Inclusion – Eligibility form** Inclusion criteria 16: C16I **Inclusion – Assessment of inclusion** Date of inclusion: DT_INC **Inclusion – Pre-Visit Treatment (3)** Date of last surgery: DT_SURG Date of last sequence of radiotherapy: DT_LSEQ Date of last neoadjuvant chemotherapy: DT_LCYN Date of last adjuvant chemotherapy: DT_LCYA Date of lines of chemotherapies: DT_1LIM, DT_2LIM, DT_3LIM, DT_4LIM	C16I = 1 DT_INC-(max(DT_SURG, DT_LSEQ, DT_LCYN, DT_LCYA, DT_1LIM, DT_2LIM, DT_3LIM, DT_4LIM)) > 21
17. 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 Event (NCI-CTCAE, version 4.0)	**Inclusion – Eligibility form** Inclusion criteria 17: C17I	C17I = 1
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for four months after discontinuation of treatment. Acceptable methods for contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year	**Inclusion – Eligibility form** Inclusion criteria 18: C18I **Inclusion – Assessment of inclusion** Sex: SEX Menopausal status: MEN_STA **Inclusion – Pre-Visit Treatment (1)** Pregnancy test: TES_PREG Results of the pregnancy test: RES_PREG Double contraceptive method: CONT_PTR	C18I = 1 SEX = 1 OR (SEX = 2 and MEN_STA in (1 2)) (SEX = 2 AND MEN_STA not in (1 2)) and TES_PREG = 1 and RES_PREG = 0 (SEX = 1 OR (SEX = 2 and MEN_STA not in (1 2))) and CONT_PTR = 1)

INCLUSION criteria	eFORM variable	Tests / new variables
19. Voluntary signed and dated written informed consents prior to any specific study procedure	**Inclusion – Eligibility form** Inclusion criteria 19: C19I **Inclusion – Assessment of inclusion** Date of consent: DT_CONS Date of inclusion: DT_INC	C19I = 1 DT_INC-DT_CONS >= 0
20. Patients with a French social security in compliance with the Law relating to biomedical research (Article 1121-11 of French Public Health Code)	**Inclusion – Eligibility form** Inclusion criteria 20: C20I	C20I = 1

Table 2: Non-inclusion criteria

INCLUSION criteria	eFORM variable	Tests / new variables
1. Previous treatment with MK3475 or CP	**Inclusion – Eligibility form** Non-inclusion criteria 1: C1NI	C1NI = 0
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)	**Inclusion – Eligibility form** Non-inclusion criteria 2: C2NI	C2NI = 0
3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases	**Inclusion – Eligibility form** Non-inclusion criteria 3: C3NI	C3NI = 0
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	**Inclusion – Eligibility form** Non-inclusion criteria 4: C4NI **Inclusion – Assessment of inclusion** Sex: SEX Menopausal status: MEN_STA **Inclusion – Pre-Visit Treatment (1)** Double contraceptive method: CONT_PTR	C4NI = 0 (SEX = 1 OR (SEX = 2 and MEN_STA not in (1 2))) and CONT_PTR = 1)
5. Participation to a study involving a medical or therapeutic intervention in the last 30 days	**Inclusion – Eligibility form** Non-inclusion criteria 5: C5NI	C5NI = 0
6. Previous enrolment in the present study	**Inclusion – Eligibility form** Non-inclusion criteria 6: C6NI	C6NI = 0
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons	**Inclusion – Eligibility form** Non-inclusion criteria 7: C7NI	C7NI = 0
8. Known hypersensitivity to any involved study drug or of its formulation components	**Inclusion – Eligibility form** Non-inclusion criteria 8: C8NI	C8NI = 0

INCLUSION criteria	eFORM variable	Tests / new variables
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study	**Inclusion – Eligibility form** Non-inclusion criteria 9: C9NI	C9NI = 0
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment	**Inclusion – Eligibility form** Non-inclusion criteria 10: C10NI	C10NI = 0
11. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted	**Inclusion – Eligibility form** Non-inclusion criteria 11: C11NI	C11NI = 0
12. Has known active hepatitis B or hepatitis C	**Inclusion – Eligibility form** Non-inclusion criteria 12: C12NI	C12NI = 0
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies)	**Inclusion – Eligibility form** Non-inclusion criteria 13: C13NI	C13NI = 0
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment	**Inclusion – Eligibility form** Non-inclusion criteria 14: C14NI	C14NI = 0

2.2 POPULATION ELIGIBLE AND ASSESSABLE FOR THE PRIMARY ENDPOINT

2.2.1 Definition

Patients satisfying the following criteria:

1. Eligible
2. Received at least one administration of MK3475 and one administration of Metronomic CP

2.2.2 Assessment

- The number and proportion of patients included in the population eligible and assessable for the primary endpoint, along with the causes of exclusion, will be reported.
- In order to be eligible and assessable for the primary endpoint, patients must satisfy all eligible criterions detailed in table 1 and 2 and the assessable criterion (table 3).

Table 3: Criteria for the assessable status

ASSESSABLE criteria	eFORM / variable	Tests / new variables
Received at least one administration of MK3475 and one administration of Metronomic CP	**Cycle 1 – Treatment** Total daily dose: DS_1T Total dose administered: TDS_TRT	DS_1T > 0 and TDS_TRT > 0

2.3 SAFETY POPULATION

2.3.1 Definition

All patients with at least one treatment (any) administration.

2.3.2 Assessment

- The number and proportion of patients included in the safety population will be reported.
- In order to be included in the safety population, patients must have received at least one treatment administration (table 4).

Table 4: Safety population

SAFETY criteria	eFORM / variable	Tests / new variables
Received at least one treatment (any) administration.	**Cycle 1 – Treatment** Total daily dose: DS_1T Total dose administered: TDS_TRT	DS_1T > 0 or TDS_TRT > 0

3 STATISTICAL ANALYSIS

- Statistical analyses will be performed using SAS v9.3 software.
- Quantitative variables will be described using means and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).

3.1 DESCRIPTIVE ANALYSIS

- Patients entered into the study will be described according to the following characteristics:
  - Compliance with eligibility criteria,
  - Sociodemographic characteristics,
  - Clinical and laboratory characteristics,
  - Treatment characteristics.

3.2 STATISTICAL ANALYSIS OF THE PRIMARY ENDPOINT

3.2.1 Definition

- The primary efficacy endpoint will be analysed based on the eligible and assessable population.
- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months:
  - Non-progression is defined as complete response, partial response or stable disease more than 24 weeks as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2 of the protocol).
  - Objective response is defined as complete response or partial response as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2 of the protocol)
- Objective response and non-progression are defined based on radiological and clinical data as defined as per RECIST v1.1 criteria.
- Following RECIST v1.1 recommendations:
  - claimed responses will have to be confirmed at least 4 weeks later;
  - 6-month radiological data will be reviewed by an independent expert radiologist.
  - Primary efficacy analysis will be based on the central radiological review data.
  - Each patient will be assigned one of the following categories: Complete response, Partial response, Stable disease, Progression, Inevaluable for response.
- All eligible and assessable patients will be included in the denominator for the calculation of the response and non-progression rates.

3.2.2 Assessment

- The rates of objective response and non-progression at 6 months will be reported.
- The 95% two-sided confidence limits will be provided for the calculated response and non-progression rates (binomial law).

3.3 STATISTICAL ANALYSIS OF THE SECONDARY ENDPOINTS

3.3.1 Definitions

- Efficacy of the association MK3475 + metronomic CP in terms of:
    - Best overall response is defined as the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation as per RECIST v1.1 criteria (appendix 2 of the protocol) :
        - The rate of best overall response will be reported.
        - All eligible and assessable patients (section 10.2 of the protocol) will be included in the denominator for the calculation of the rate.
        - The rate of best overall response will be calculated as the number of patients alive with the best response (recorded from the start of the treatment) divided by the number of patients eligible and assessable (section 10.2 of the protocol).
        - The 95% two-sided confidence limits will be provided for the calculated rate (binomial law).

      Following RECIST v1.1 recommendations:
        - The best overall response is determined once all the data for the patient is known.
        - Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (>= 4 weeks later).
    - 1-year progression-free survival (PFS): PFS is defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.
    - 1-year overall survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
    - Immune-related response is defined following Wolchok et al. (Clinical Cancer Research 2009, Appendix 6 of the protocol). Analysis of Immune-related response will be based on central radiological review data.
    - Growth modulation index (GMI), defined for each patient as the ratio of the PFS on MK3475 + metronomic CP to the PFS on the previous line of therapy (61), in patients with documented progression at inclusion.
- Assessment of the safety profile of the association MK3475 + metronomic CP. Toxicity will be graded using the common toxicity criteria from the NCI v4.0.
- Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points. Blood samples will be collected at predefined time points:
    - Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
    - Serum/plasma VEGF and TPS-1 levels (ELISA)
    - Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
    - Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS).
    - Additional details are provided in section 17 of the protocol.
- Fresh pre-treatment (or archival material obtained from less than 12 weeks before inclusion) will be collected in consenting patients to assess pharmacodynamics biomarkers. Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers. Additional details are provided in section 17 of the protocol.
- Prospective determination of the proportion of STS that express PDL1 will be assessed as detailed in section 17 of the protocol.

3.3.2 Assessment

- As regards to the other efficacy endpoints, the analyses will be carried out in the eligible and assessable population.
- The safety analysis will be performed on the safety population.
- Quantitative variables will be described using means and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).
- Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.
- Prognostic role of biomarkers will be assessed using logistic or survival models depending on the nature of the outcome variable (time-to-event or binary endpoint). Multivariate models will be constructed following a backward selection approach based on candidates variables selected following univariate analyses.

3.4 SAFETY ANALYSIS

3.4.1 Definition

The safety analysis will be performed on the **safety population**.
The safety profile of MK3475 + metronomic CP will be assessed using the common toxicity criteria from the NCI v4.0.

3.4.2 Assessment

Adverse Events (AE) and Serious Adverse Events (SAE) will be described in terms of:

- System organ class (SOC)
- Type of adverse event
- Maximal intensity grade
- Imputability to Cyclophosphamide and MK3475
- Outcome of the event
- Delay from treatment initiation

Table 5: Safety assessment

Endpoint	Database - eFORM Variables
Safety	**Main - Adverse event form** Adverse event: AEVENT Considered a SAE: AESAE Date of event: DT_AE Maximum intensity: MAX_INT Imputability to Cyclophosphamide: IMP_CYC Imputability to MK3475: IMP_MK Outcome: AE_OUTC System organ class: SOC Adverse event: BLOO, CARDIACA, CONGENIT, EARS, ENDOCRIN, EYES, GASTRO, GENERA, HEPATOB, IMMUNE, INFECTI, INJURY, INVESTI, METABOLI, MUSCULOS, NEOPLASM, NERVOUS, PREGN, PSY, RENALU, REPROD, RESP, SKIN, SOCIAL, SURGICAL, VASCULAR **PV – Serious adverse event form** Serious adverse event: DIAG_SYM Date of event: DT_SAE Grade minimum: TOX_SAE Grade maximum: GRAD_AE Type of SAE: TYPE_SAE Outcome: OUT_SAE Investigator's opinion about imputability: REL_INV, IMPx_INV, NREL_INV Sponsor's opinion about imputability: REL_SPO, IMPx_SPO, NREL_SPO System organ class: SOC Adverse event: BLOOD, CARDIACA, CONGENIT, EARS, ENDOCRIN, EYES, GASTRO, GENERA, HEPATOB, IMMUNE, INFECTI, INJURY, INVESTI, METABOLI, MUSCULOS, NEOPLASM, NERVOUS, PREGN, PSY, RENALU, REPROD, RESP, SKIN, SOCIAL, SURGICAL, VASCULAR