STATISTICAL ANALYSIS PLAN

A6181209

OVERVIEW: PROSPECTIVE ANALYSIS OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CANCER (mRCC)

Prospective, multi-centre, comparative, cross-sectional then longitudinal, observational case-control study with 36-month follow-up of patients and constitution of a biobank

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LIST OF ABBREVIATIONS

CRO	Contract Research Organisation
eCRF	electronic Case Report Form
AE	Adverse events
CI	Confidence Interval
mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Center
WHO	World Health Organisation
OR	Odds Ratio
SAP	Statistical Analysis Plan
CR	Complete Remission
RECIST	Response Evaluation Criteria In Solid Tumours
VEGF	Vascular Endothelial Growth Factor

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) presents the definitions used for the efficacy and safety endpoints as well as the analysis sets. It also describes the data derived and indicates the statistical methods used.

This SAP is based on amended version no. 5 of the protocol dated 21/11/2017.

The analyses comply with the guidelines of the ICH industry standards (E3 - Structure and Content of Clinical Study Reports and E9 - Statistical Principles for Clinical Trials).

2 DESCRIPTION OF THE STUDY

2.1 Rationale

Complete remission (CR) is a rare event in metastatic renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitors; however, findings from two retrospective cohorts report that it occurs in 1-2% of patients treated with Sunitinib.

CR when taking Sunitinib has been described in the different prognostic subgroups and has also been reported in cases of multiple metastases. A series of reports also suggest that significant objective responses are achievable in a sub-population of patients receiving targeted therapy, and that complete residual metastasectomy may be beneficial in well-selected patients having presented a partial response to anti-angiogenic therapy.

No standardised management has been established for the continuation or discontinuation of treatment in patients achieving a complete remission with Sunitinib.

In addition, therapies targeting Vascular Endothelial Growth Factor (VEGF) have been associated with the development of resistance after 6-15 months of treatment. Sequential use of these molecules has become standard practice. In fact, activity is observed with an agent with the same or some common targets as one of the previous treatments and for which disease progression had been observed. This raises questions about resistance mechanism(s) and the optimal therapeutic approach in this context. However, it appears that this resistance is potentially reversible. In a retrospective review of mRCC patients treated with Sunitinib after disease progression following previous therapy with Sunitinib and other treatments, the reintroduction of Sunitinib was effective and well tolerated in most cases.

In CR patients receiving targeted therapy alone or in combination and an additional metastasectomy, one case series showed that in almost 50% of cases discontinuation of Sunitinib was followed by recurrence but that reintroduction of targeted therapy was effective in most cases.

Improving the characterisation of patients achieving a CR with Sunitinib is therefore necessary to provide doctors with information about the appropriate approach in such cases and to encourage surgeons to operate on patients with a single or minimal residual metastases.
The analysis of CR patients should compare these rare cases to the more common situation of patients treated with Sunitinib but who do not have a complete response. Given the rarity of the event being studied, it is proposed that the design of the study should be a case-control study.

2.2 Objectives of the study

2.2.1 Primary objective

The primary objective is to describe the characteristics of mRCC patients achieving a CR with Sunitinib (Cases) and compare them to the characteristics of mRCC patients not achieving a CR with Sunitinib (Controls) to identify factors associated with the occurrence of CR.

2.2.2 Secondary objective(s)

The secondary objectives are to:

- Describe the therapeutic management (discontinuation or continuation of systemic treatment in CR patients);
- Search for and describe various biomarkers in a histological sample bank when initiating Sunitinib in CR patients (Cases) and non-CR patients taking Sunitinib (Controls);
- Search for and describe various biomarkers in a histology specimen bank for CR patients with Sunitinib (Cases) and at the time of recurrence, if any;
- Compare the identified biomarkers of CR patients (Cases) with those of non-CR patients taking Sunitinib during the 36 months of the study (Controls).

2.3 Methodology of the study

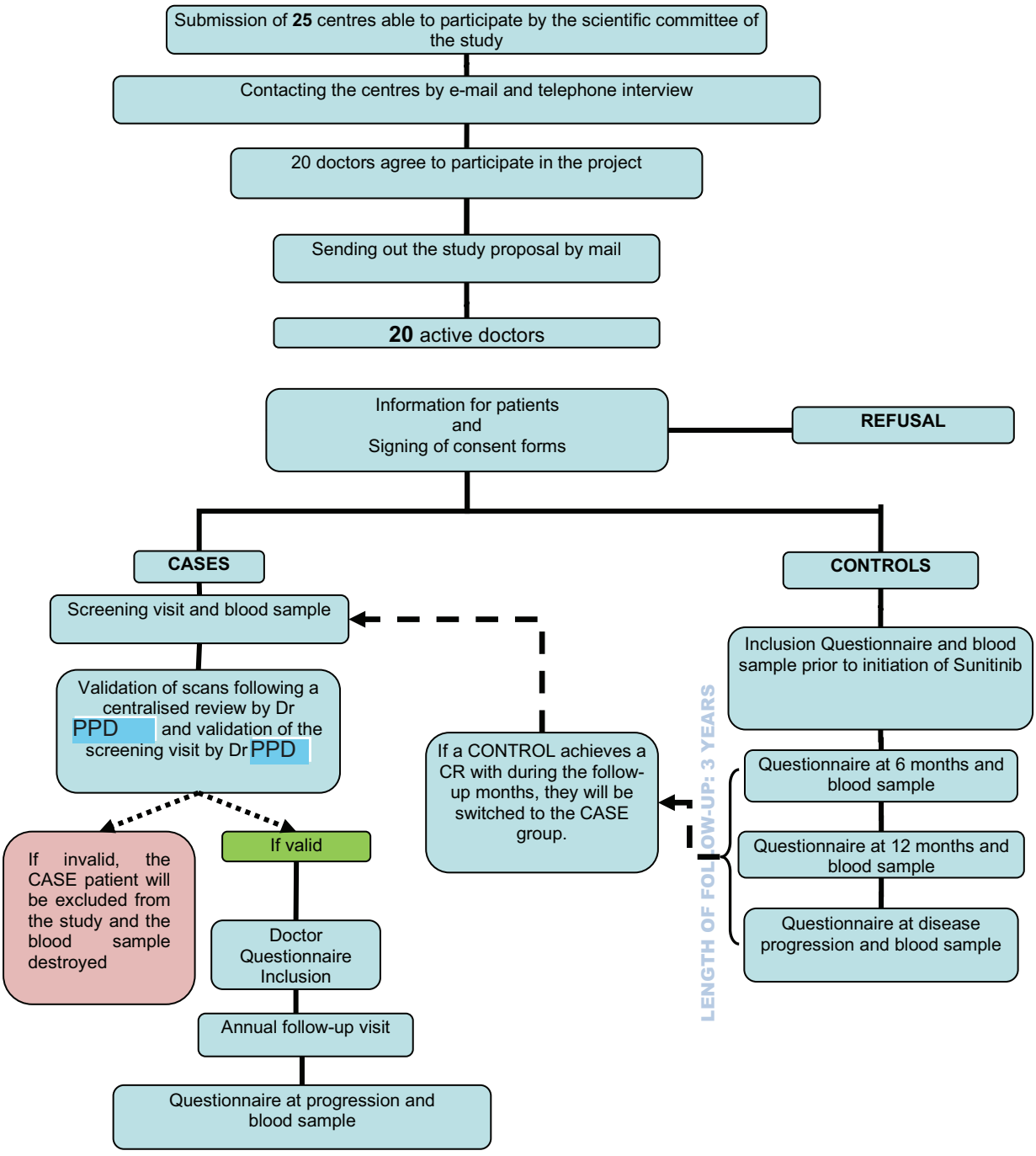
This is a prospective, multi-centre, comparative, cross-sectional then observational, case-control study including 40 mRCC patients with CR when taking Sunitinib (Cases) and 80 mRCC non-CR patients treated with Sunitinib as first-line therapy (Controls).

The active participation of 15-20 oncologists means that the conditions for statistical accuracy are sufficient to meet the objectives of the study.

Each doctor will include patients with metastatic renal cell carcinoma in CR with Sunitinib (Cases) in the study.

The teams of Dr PPD (PPD), Professor PPD (PPD), Dr PPD (PPD), Dr PPD (PPD) and Dr PPD (PPD) will include 80 patients with metastatic renal cell carcinoma without CR, at the initiation of Sunitinib, i.e. the control population. Given the rarity of the observed CR event (1.7%), it is believed that none of the patients in the control arm (N=80) will achieve a CR with Sunitinib. If any of the 80 controls achieve a CR with Sunitinib during the follow-up, they will be switched to the Case group.

These patients will be seen in consultation and should meet the inclusion and exclusion criteria.



Information will be collected via the documents listed below throughout the study.

Data relating to the doctor

- First name, Last name:
- Sex:
- Age:
- Postcode, Town;
- Type of practice;
- Sector of approval.

Screening visit (for cases only)

- Date of screening visit;
- Date of signing the consent form;
- Inclusion and exclusion criteria;
- Demographic data: month and year of birth;
- Data on the diagnosis of the mRCC patient in CR: date of initial diagnosis of kidney cancer, date of diagnosis of metastatic renal cell carcinoma;
- Data on the condition of the patient in CR at initiation of Sunitinib: date of Sunitinib initiation, location of metastases, number of metastatic sites;
- CR data: date of achieving CR, method of achieving CR, radiological evaluation of CR using Response Evaluation Criteria In Solid Tumours (RECIST);
- Blood samples taken during the screening visit: sample (Yes/No) and date of sample. If samples are not available at the screening visit, a period of 6 weeks between screening and sampling will be allowed;
- Histology samples: sample (Yes/No), date of sample, type of sample, fixing method.

Data collected at inclusion

For Cases

- Data on the inclusion and demographic data: date of signing the consent form, date of consultation, birth year, age, sex, height, weight;
- Data on the diagnosis of the mRCC patient in CR: date of initial diagnosis of kidney cancer, date of diagnosis of metastatic renal cell carcinoma, nephrectomy, date and type of nephrectomy, World Health Organisation (WHO) pathological classification, TNM classification, tumour size, Furhman nuclear grade, necrosis, vascular embolism, sarcomatoid component;
- Data on the condition of the patient in CR at initiation of Sunitinib: date of initiation, location of metastases, number of metastatic sites; Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic classification;
- CR data: date of achieving CR, method of achieving CR, radiological evaluation of CR using Response Evaluation Criteria in Solid Tumours after the CR.

For Controls

- Data on the inclusion and demographic data: date of signing the consent form, date of consultation, month and year of birth, age, sex, height, weight, inclusion and exclusion criteria;
- Data on the diagnosis of the mRCC patient treated with Sunitinib: date of initial diagnosis of kidney cancer, date of diagnosis of metastatic renal cell carcinoma, date of initiation of Sunitinib, nephrectomy, date and type of nephrectomy, World Health Organisation (WHO) pathological classification, TNM classification, tumour size, Furhman nuclear grade, necrosis, vascular embolism, sarcomatoid component;
- Data on the condition of the mRCC patient before initiation of Sunitinib: blood sample (Yes/No), histology samples (Yes/No) and dates of samples, location of metastases, number of metastatic sites, MSKCC prognostic classification;

Data collected during follow-up visits

In this research, patients will be followed up for three years, according to the usual procedure for this disease (visits every 2 to 3 months in line with the expert opinion set out in the guide to long-term conditions of the French National Health Authority (HAS)).

For Cases

At the visit diagnosing disease progression:

- Date of visit;
- Duration of additional Sunitinib treatment (pseudo-adjuvant), starting at CR;
- Date of progression, type of progression (local or distant);
- Metastatic sites: location and number of metastatic sites;
- Blood sample and collection date;
- Treatment administered after progression (systemic/surgical).

At the annual follow-up visit:

- Date of visit;
- Status of the disease (change);
- Changes in treatment regimen (temporary or permanent discontinuation).

At the end-of-research visit (36 months after the inclusion visit):

- Visit (Yes/ No);
- Date of visit;
- Best response to treatment received post-progression;
- Duration of administration after progression with first-line Sunitinib;
- Last news: premature discontinuation of study, date of last news, persistent CR since inclusion visit, CR after treatment of post-CR progression, disease progression, number of subsequent lines after progression, post CR;
- Death (Yes/No), date of death.

For Controls

At the 6-month and 12-month follow-up visits of Sunitinib treatment:

- Date of visit;
- Clinical assessment using RECIST criteria (response to treatment, if progression: date of progression, progression at a known metastatic site or at a new site);
- Metastatic sites: location and number of metastatic sites;
- Blood sample and collection date.

If progression:

- Date of visit;
- Date of progression, type of progression (local or distant);
- Metastatic sites: location and number of metastatic sites;
- Blood sample and collection date

At the end-of-research visit (36 months after the inclusion visit):

- Visit (Yes/ No);
- Date of visit;
- Patient still treated with Sunitinib, if yes: response to treatment, if no: progression, new treatment, date of Sunitinib discontinuation;
- Number of subsequent treatment lines;
- Last news: study stopped prematurely, date of last news;
- Death (Yes/No), date of death.

Centralised review of Computerised Tomography Scan (CT Scan) - only for patients in CR

In this research, two of the scans of CR patients (Cases) will be reviewed centrally.

- The scan at initiation of first-line Sunitinib;
- The scan showing CR.

This review will take place between the screening visit and the inclusion visit of the patient. Thus a patient can only be included after the scans have been reviewed to validate the CR.

2.4 Endpoints

The endpoints are:

- Characteristics of patients treated;
- Procedure for treating patients with mRCC in CR with Sunitinib (Case);
- Adverse events (AE).

The analysis of biological data and biomarkers will be the subject of a separate analysis plan.

2.5 Number of patients required

The primary objective of the study is to describe the characteristics of mRCC patients achieving a CR with Sunitinib (Cases) and to compare them to the characteristics of metastatic renal cell carcinoma patients not achieving a CR with Sunitinib to identify factors associated with the occurrence of complete remission.

A sample size of N = 40 cases and N = 80 controls will provide a power of 80% in the detection:

- For continuous variable with a normal distribution, of an effect size (Cohen's d) ≥0.55;
- For a dichotomous variable, of a frequency difference between cases and controls corresponding to the ORs presented in the table below:

Frequency in controls	10%	20%	30%	40%	50%	60%	70%	80%	90%
Odds Ratio	≥4.33	≥3.27	≤0.19 or ≥3.16	≤0.26 or ≥3.12	≤0.29 or ≥3.44	≤0.32 or ≥3.78	≤0.32 or ≥5.29	≤0.31	≤0.23

3 ANALYSIS SET

3.1 Population of active doctors

The population of doctors will include all oncologists who have included at least one patient.

3.2 Population of patients included

The patient population included will comprise patients who have signed their consent form and have completed the inclusion visit:

- The Case population will include patients with mRCC in CR (validated after the scan review) taking Sunitinib.
- The Control population will include non-CR patients with mRCC treated with first-line Sunitinib.

3.3 Population of followed-up patients

The population of followed-up patients will include all patients who have been including and who have attended at least one follow-up visit.

4 GENERAL CONSIDERATIONS FOR THE STATISTICAL ANALYSIS OF THE DATA

4.1 Statistical methods

The biostatistics department at AXIAL will perform the statistical analysis, with the exception of the analysis of biological data and biomarkers. Data will be analysed using SAS® software (version 9.4 or later - SAS Institute, North Carolina, USA).

Statistical tests will be carried out bilaterally at a 5% significance level (alpha).

Results will be presented in the form of tables per group (Cases/Controls) presenting:

- For quantitative parameters: number of patients (n), mean and standard deviation, minima and maxima, median and quartiles, and number of missing values.
- For qualitative parameters: number of patients, absolute and relative frequencies for each parameter modality, and number of missing values. Missing data will not be considered when calculating percentages.

Quantitative parameters will be compared between groups using the following methods: Beforehand, the distribution of the parameter will be checked graphically and by using Skewness and Kurtosis and Shapiro-Wilk statistics. If the distribution is considered normal, groups will be compared using a Student's t-test and the difference in means and the 95% Confidence Interval (CI) will be presented. If this is not the case, groups will be compared using a Wilcoxon rank sum test and Hodges-Lehmann estimator, with a presentation of the 95% CI.

For non-ordinal qualitative variables, groups will be compared using the Chi-2 test (or Fisher's exact test if the theoretical numbers <5) and the odds ratio will be presented when specified.

For ordinal qualitative variables, groups will be compared using the Cochran-Mantel-Haenszel test, ridit modified scores ('row mean score differ'). For ordinal qualitative count variables, groups will be compared using the Cochran-Mantel-Haenszel test, 'row mean score differ' table option.

4.2 Interim analysis

An interim analysis based on the descriptive analysis of the patients included patients and data collected will be produced during the study. This analysis will be performed as soon as 20 CR patients (Cases) are included and have been followed up for six months.

No statistical tests will be performed for this interim analysis.

5 DATA MANAGEMENT CONVENTIONS

5.1 Missing data

Missing data will not be replaced during the data management process and will not be replaced for the statistical analysis, with the exception of the specific cases described in the sections below.

5.2 Derivative data

The following variables will be calculated:

- Interval between visit X and inclusion (in months):
  (Date of follow-up visit X - Date of inclusion visit) / 365.25 x 12.

- Total length of follow-up (in months):
  (Maximum date between Date of last visit or Date of last news or Date of death - Date of inclusion visit) / 365.25 x 12.
  Note: In case of incomplete dates (date of last news or date of death):
  If the day is missing, it will be replaced by the first day of the month.
  If the month is missing, it will be replaced by the month of January.
  If the date completed is earlier than the last visit carried out, then the date will be replaced by the last visit carried out.

- Age (in years):
  Year of inclusion – Year of birth.

- Time of diagnosis of metastatic renal cell carcinoma (in years):
  (Date of inclusion visit - Date of diagnosis of metastatic renal cell carcinoma) / 365.25.
  Note: In case of incomplete dates (date of diagnosis of metastatic renal cell carcinoma):
  If the day is missing, it will be replaced by the first day of the month.
  If the month is missing, only the year will be used.

- Time from diagnosis of metastatic renal cell carcinoma to nephrectomy (in months):
  (Date of nephrectomy - Date of diagnosis of metastatic renal cell carcinoma) / 365.25 x 12
  Note: In case of incomplete dates (date of nephrectomy or date of diagnosis of metastatic renal cell carcinoma):
  If the day is missing, it will be replaced by the first day of the month.

- Time between diagnosis of metastatic renal cell carcinoma and initiation of Sunitinib (in months):
  (Date of Sunitinib initiation - Date of diagnosis of metastatic renal cell carcinoma) / 365.25 x 12
  Note: In case of incomplete dates (Sunitinib initiation date or date of diagnosis of metastatic renal cell carcinoma):
  If the day is missing, it will be replaced by the first day of the month.

For Cases:

- Time between diagnosis of metastatic renal cell carcinoma and local treatment (in months):
  (Date of local treatment - Date of diagnosis of metastatic renal cell carcinoma) / 365.25 x 12
  Note: In case of incomplete dates (date of local treatment or date of diagnosis of metastatic renal cell carcinoma):
  If the day is missing, it will be replaced by the first day of the month.

- Time between Sunitinib initiation and CR (in years):
  (Date of CR - Date of Sunitinib initiation) / 365.25.
  Note: In case of incomplete dates (date of CR or date of Sunitinib initiation):
  If the day is missing, it will be replaced by the first day of the month.
  If the month is missing, only the year will be used.

- Time between CR and progression (in months):
  (Date of progression - Date of CR) / 365.25 x 12
  Note: In case of incomplete dates (date of CR or date of progression):
  If the day is missing, it will be replaced by the first day of the month.

- Progression-free survival (in months):
  It is defined as the time between CR and progression or death.
  (Date of the event - Date of CR) / 365.25 x 12
  Note: Patients who have not progressed and who have not died will be censored at the date of last visit.

Event	**Censor decision**	**Date of the event or censor**
Progression	Non-censored	Date of progression
All-cause death without progression	Non-censored	Date of death
Lost to follow-up	Censored	Date of last visit
End of study without progression or death	Censored	Date of last news

For Controls:

- Time between initiation of treatment and progression (in months):
  (Date of progression - Date of treatment initiation) / 365.25 x 12
  Note: In case of incomplete dates (date of treatment initiation or date of progression):
  If the day is missing, it will be replaced by the first day of the month.

- Progression-free survival (in months):
  It is defined as the time between treatment initiation and progression or death.
  (Date of the event - Date of treatment initiation) / 365.25 x 12
  Note: Patients who have not progressed and who have not died will be censored at the date of last visit.

Event	**Censor decision**	**Date of the event or censor**
Progression	Non-censored	Date of progression
All-cause death without progression	Non-censored	Date of death
Lost to follow-up	Censored	Date of last visit
End of study without progression or death	Censored	Date of last news

- Duration of treatment with Sunitinib (in months):
  (Date of treatment discontinuation - Date of treatment initiation + 1) / 365.25 x 12
  Note: In case of incomplete dates (initiation date or discontinuation date):
  If the day is missing, it will be replaced by the first day of the month.

6 STATISTICAL ANALYSIS

6.1 Layout

The number of active doctors (oncologists) will be described.

The number of patients included and the number of patients followed up will be described by group (Cases/Controls).

The number of patients per visit, the time interval (in months) between inclusion and the follow-up visit for each visit (continuous) and the total duration of follow-up (in months) will be described per group (Cases/Controls).

6.2 Description of doctors

Study population: Population of active doctors

The characteristics of active doctors will be described overall:

- Age (years);
- Sex (male/ female);
- Type of practice (Hospital/Surgery/Independent);
- Sector of approval (Sector 1 / Sector 2 - Registered doctor charging private fees / Sector 3 - Not approved).

The characteristics of the sample of oncologists (age, sex, type of practice) will, if possible, be compared with those of the national database to ensure that the sample is representative.

6.3 Description of patients at inclusion

6.3.1 Demographical characteristics

Study population: Population of patients included

The demographic characteristics of the patients will be described by group and compared:

- Age (years);
- Sex (male/ female);
- Height (cm);
- Weight (kg).

6.3.2 Other characteristics

Study population: Population of patients included

The demographic characteristics of the patients will be described by group and compared:

- Time of diagnosis of metastatic renal cell carcinoma;
- Nephrectomy (Yes/ No)*;

  If Nephrectomy:
  - Extended or partial;
  - With or without adrenalectomy;
  - With or without curettage;
  - Open or laparoscopic approach;
  - Time between diagnosis of metastatic renal cell carcinoma to nephrectomy (in months);

- Pathological classification (Clear cell carcinoma / Papillary carcinoma / Chromophobe carcinoma / Bellini duct carcinoma / Medullary carcinoma / Sarcomatoid carcinoma / Other);
  A list of other classifications will be presented.
- TNM classification (T / N / M and TNM);
- Tumour size (mm);
- Furhamn nuclear grade (I / II / III / IV);
- Necrosis (Yes/ No)*;
- Pulmonary embolism (Yes/No)*;
- Sarcomatoid component (Yes/No)*.

** For these qualitative variables, the odds ratio (Case versus Control) will be presented.*

The demographic characteristics of the patients, at initiation of Sunitinib, will be described by group and compared:

- Time between diagnosis of metastatic renal cell carcinoma and initiation of Sunitinib (in months);
- Location of metastases:
  - Lung (Yes/ No);
  - Bones (Yes/No);
  - Liver (Yes/ No);
  - Adrenal glands (Yes/No);
  - Pancreas (Yes/No);
  - Brain (Yes/No);
  - Lymph nodes (Yes/No);
    If Lymph nodes:
    - Supra-diaphragmatic (Yes/No);
    - Sub-diaphragmatic (Yes/No);
  - Recurrence at nephrectomy site (Yes/No) ;
  - Other (Yes/ No);
    A list of the other locations will be presented.
- Number of metastatic sites;
- MSKCC prognostic classification (Good prognosis/Intermediate prognosis/Poor prognosis).

The characteristics of the patients in CR will be described for the Cases:

- Time between Sunitinib initiation and CR (years);
- Method of achieving the CR (Medical treatment alone/Combined with local treatment);
  If combined:
  - Surgery (Yes/No);
  - Radiotherapy (Yes/ No);
  - Radiofrequency (Yes/ No);
  - Cryoablation (Yes/ No);
  - Metastasectomy (Yes/ No);
  - Other (Yes/ No);

  A list will be presented of local treatments including dates of treatment, time between the diagnosis of metastatic renal cell carcinoma and local treatment and sites exposed.

- Radiological assessment of the CR:
  - Disappearance of all known target lesions (Yes/No);
  - Disappearance of all non-target lesions (Yes/No);
  - No new lesions (Yes/No);
  - All target and non-target lymph nodes <10 mm (Yes/No);
- Therapeutic strategy after CR (Continuation of Sunitinib treatment/Discontinuation of Sunitinib treatment).

6.4 Description of follow-up visits for mRCC patients in CR (Cases)

Study population: Population of followed-up patients - Cases

Patient follow-up data will be described for the cases at 12 and 24 months:

- Disease progression (Complete response / Partial response / Progression / Stabilisation / Not assessed);
- Sunitinib treatment ongoing (Yes/No);
  If yes:
  - Current dose (mg/d);
  - Current regimen (4/2 / 2/1 / Continuous / Other);
    A list of the other regimens will be presented.
- Temporary discontinuation of Sunitinib (Yes/No);
  If yes:
  - Number of temporary discontinuations per patient
  - The temporary discontinuations will then be described (the statistical unit considered will then be the temporary discontinuation and not the patient):
    - Reason for temporary discontinuation (Progression / Intolerance / Complete response / Local treatment / Other);
      A list of the other reasons will be presented.
    - Treatment resumed (Yes/No);
    - Duration of temporary discontinuation (days);
- Permanent discontinuation (Yes/No);
  If yes:
  - Reason for permanent discontinuation (Progression / Intolerance / Decision of patient or doctor / Other);
    A list of the other reasons will be presented.
  - Duration of treatment with Sunitinib since CR (months);

Patient follow-up data will be described for the cases at the time of the progression:

- Time between CR and progression (months);
- Duration of additional Sunitinib treatment (pseudo-adjuvant), starting at CR (months)
- Type of progression (Local Progression/Distant Progression);
  If distant progression:
  - at which level (at a known metastatic site/new metastatic site);
- Location of metastases:
  - Lung (Yes/ No);
  - Bones (Yes/No);
  - Liver (Yes/ No);
  - Adrenal glands (Yes/No);
  - Pancreas (Yes/No);
  - Brain (Yes/No);

  - Lymph nodes (Yes/No);
    If Lymph nodes:
    - Supra-diaphragmatic (Yes/No);
    - Sub-diaphragmatic (Yes/No);
  - Recurrence at nephrectomy site (Yes/No) ;
  - Other (Yes/ No);
    A list of the other locations will be presented.
- Number of metastatic sites;
- Systemic treatment after progression (Yes/No)
- Description of systemic treatments after progression by type of treatment (Bevacizumab with interferon / Bevacizumab without interferon / Sunitinib restart / Sorafenib / Temsirolimus/ Everolimus / Other)

  A list of the other systemic treatments will be presented.

  A list of systemic treatments including daily dose will be presented.

Patient follow-up data will be described for the cases at the end-of-study visit:

- Best objective response observed after progression (Complete / Partial / Progressive / Stabilised);
- Duration of treatment received after progression with first-line Sunitinib (months);
- Early termination of the study (Yes/No);
- Response achieved (persistent CR since inclusion visit / CR after treatment of recurrence / Disease progression);
- Number of subsequent treatment lines from progression, post CR;
- Death (Yes/ No).

Progression-free survival at the end of the study will be analysed using the Kaplan Meier method, with a presentation of the survival curve. The progression-free survival rate will be estimated with a 95% confidence interval.

6.5 Description of follow-up visits for mRCC patients treated with first-line Sunitinib, non CR (Controls)

Study population: Population of followed-up patients - Controls

Patient follow-up data will be described for the controls at 6 and 12 months of treatment:

- Sunitinib dose (50 mg / 37.5 mg / 25 mg);
- Current regimen (4/2 / 2/1 / Continuous);
- Clinical assessment (Complete Response / Partial Response / Stable Disease / Progression);
  If Partial Response:
  - Percentage of tumour reduction (%)
- Location of metastases:
  - Lung (Yes/ No);
  - Bones (Yes/No);
  - Liver (Yes/ No);
  - Adrenal glands (Yes/No);
  - Pancreas (Yes/No);
  - Brain (Yes/No);
  - Lymph nodes (Yes / No); If Lymph nodes:
    - Supra-diaphragmatic (Yes/No);

        - Sub-diaphragmatic (Yes/No);
    - Recurrence at nephrectomy site (Yes/No) ;
    - Other (Yes/ No);
      A list of the other locations will be presented.
- Number of metastatic sites;

Patient follow-up data will be described for the controls at the time of the progression:

- Time between initiation of treatment and progression (in months);
- Type of progression (Local Progression/Distant Progression);
  If distant progression, at which level (at a known metastatic site/new metastatic site);
- Location of metastases:
    - Lung (Yes/ No);
    - Bones (Yes/No);
    - Liver (Yes/ No);
    - Adrenal glands (Yes/No);
    - Pancreas (Yes/No);
    - Brain (Yes/No);
    - Lymph nodes (Yes / No); If Lymph nodes:
        - Supra-diaphragmatic (Yes/No);
        - Sub-diaphragmatic (Yes/No);
    - Recurrence at nephrectomy site (Yes/No) ;
    - Other (Yes/ No);
      A list of the other locations will be presented.
- Number of metastatic sites;

Patient follow-up data will be described for the controls at the end-of-study visit:

- Patients still receiving Sunitinib (Yes/No);
  If yes:
    - Response (Complete Response / Partial Response / Stable Disease / Progression);
  If No:
    - Progression (Yes/ No);
    - Duration of Sunitinib treatment (months);
    - New treatments (Yes/No);
      A list of new treatments will be presented.
- Number of subsequent treatment lines.
- Early termination of the study (Yes/No);
- Death (Yes/ No).

Progression-free survival at the end of the study will be analysed using the Kaplan Meier method, with a presentation of the survival curve. The progression-free survival rate will be estimated with a 95% confidence interval.

6.6 Description of adverse events

Study population: Population of followed-up patients

The number of AEs, the number and percentage of patients with at least one AE will be described by group for the following event categories:

- All AEs by system organ class,
- All AEs likely to be related to the study drug ('Yes' or Missing response method) by system organ class,
- All serious AEs by system organ class,
- All serious AEs likely to be related to the study drug ('Yes' or Missing response method) by organ class,

The AEs will be described according to severity, action taken regarding the study treatment, and progression.

AEs reported during the study will be coded using the MedDRA dictionary, version 20.0.

ANNEX 1. ANALYSIS TABLES - MODELS

Study: A6181209 - OVERVIEW
Group: XXXXX

Table X - Patient layout

	Cases	Controls	Total
Active doctors			xx
All patients	xx	xx	xx
Patients included	xx	xx	xx
Patients followed-up	xx	xx	xx

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW
Group: XXXXX

Table X - Layout of visits

	Cases (N=XX)	Controls (N=XX)
Number of patients at each visit		
Screening visit	xx (xx.x%)	
Inclusion visit	xx (xx.x%)	xx (xx.x%)
Visit at 6 months		xx (xx.x%)
Visit at 12 months	xx (xx.x%)	xx (xx.x%)
Visit at 24 months	xx (xx.x%)	
Visit with diagnosis of progression	xx (xx.x%)	xx (xx.x%)
End-of-study visit	xx (xx.x%)	xx (xx.x%)
Time between inclusion and 12-month visit		
n	x	x
Mean (standard deviation)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min. ; Max.	xx; xx	xx; xx
Missing data	x	x
…		
Total length of follow-up (months)		
n	x	x
Mean (standard deviation)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min. ; Max.	xx; xx	xx; xx
Missing data	x	x

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW Page X / N
Group: XXXXX

Table X - Description / Analysis of qualitative and quantitative variables

	Cases (N=XX)	Controls (N=XX)	p
Quantitative variable			x.xxx (T)
n	xx	xx	
Mean (standard deviation)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min. ; Max.	xx; xx	xx; xx	
Missing data	xx	xx	
Qualitative variable			x.xxx (C)
n	xx	xx	
Category 1	xx (xx.x%)	xx (xx.x%)	
…	…	…	
Modality n	xx (xx.x%)	xx (xx.x%)	
Missing data	xx	xx	
(T) Student's t test / (W) Wilcoxon test *(C) Chi-2 test / (F) Fisher test* …			

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW
Group: XXXXX

Table X - Qualitative and Quantitative Variables - Case Versus Control Comparison

	Total (N=XX)
Normal quantitative variable - Difference in means [95% CI]	xx.x [xx.x ;xx.x]
Non-normal Quantitative variable - Hodges Lehmann estimator [95% CI]	xx.x [xx.x ;xx.x]
Qualitative variable - Odds Ratio [95% CI]	xx.x [xx.x ;xx.x]

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW
Group: XXXXX

Table X - Progression-free survival analysis (months) - Kaplan-Meier

	Total (N=XX)
Progression-free survival (months)	
Number of subjects	99
Event	99 (99.9)
Censored*	99 (99.9)
Min	99.9
Max	99.9
Q3 [95% CI]	99.9 [99.9;99.9]
Median [95% CI]	99.9 [99.9;99.9]
Q1 [95% CI]	99.9 [99.9;99.9]
Mean progression-free survival [95% CI]	99.9 [99.9;99.9]

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW Page X / N
Group: XXXXX

Table X – Description of adverse events (AE) by System Organ Class (SOC) and Preferred term (PT)

	Cases (N=XX)		Controls (N=XX)	
	Nb of events	Nb (%) of patients	Nb of events	Nb (%) of patients
At least one adverse event	xx	x (xx.x%)	xx	x (xx.x%)
Body system 1	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)	xx	xx (xx.x%)
…				
Preferred term n	xx	xx (xx.x%)	xx	xx (xx.x%)
Body system 2	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)	xx	xx (xx.x%)
…				
Preferred term n	xx	xx (xx.x%)	xx	xx (xx.x%)
….				
Body system n	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)	xx	xx (xx.x%)
…				
Preferred term n	xx	xx (xx.x%)	xx	xx (xx.x%)

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm*nom_du_programme*.sas
Date and time when programme was executed: DDMMMYYYY HH:MM

Study: A6181209 - OVERVIEW
Group: XXXXX

Table X - Description of adverse events

	Cases (N=XX)	Controls (N=XX)
Qualitative variable		
n	xx	xx
Category 1	xx (xx.x%)	xx (xx.x%)
…	…	…
Modality n	xx (xx.x%)	xx (xx.x%)
Missing data	xx	xx
Note: the unit of analysis is the adverse event		

Name of the SAS programme: P:\XXXXX\XXXX\Analyse\Pgm\nom_du_programme.sas
Date and time when programme was executed: DDMMMYYYY HH:MM