NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Title	Prospective study of complete remissions observed with sunitinib in patients with metastatic renal cell carcinoma mRCC)
Protocol number	A6181209
Protocol version identifier	Final N°6 amended version
Date	25 February 2019
Principal objective of the study	Describe the characteristics of patients with mRCC and presenting CR with Sunitinib **(Cases)** and compare them with the characteristics of patients with mRCC and not presenting CR with Sunitinib (**Controls**) in order to identify factors associated with the occurrence of complete remission.
Country(-ies) of study	FRANCE
Author	Dr PPD , PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ANSM	*Agence Nationale de sécurité du médicament* (National sécurity medicine agency)
CCTIRS	*Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (French Advisory Committee for Data Processing in Health Research)
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French Data Protection Agency)
CNOM	*Conseil National de l'Ordre des Médecins (French National Board of Physicians)*
CR	*Complete Remission*
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	electronic Case Report Form
HAS	*Haute Autorité de Santé* (French Health Authority)
mRCC	metastatic Renal Cell Cancer
MSKCC	Memorial Sloan-Kettering Cancer Center
RCC	Renal Cell Cancer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
TKI	Tyrosine Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Titre	Nom	Prénom	Ville
Docteur	PPD	PPD	PPD
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ABSTRACT

Complete remission (CR) is a rare event during the treatment of metastatic renal cell carcinoma (mRCC) with tyrosine kinase inhibitors (TKIs), but results from two retrospective cohorts show that it occurs in 1 to 2% of patients treated with Sunitinib.

This CR with Sunitinib has been described in the different prognostic subgroups and it has also been reported in the case of multiple metastases. In addition, a series of reports suggests that significant objective responses can be obtained in a subpopulation of patients receiving targeted therapy and that a complete residual metastasectomy can be beneficial in carefully screened patients having presented a partial response to antiangiogenic treatment.

The continuation of treatment or its withdrawal in patients presenting CR with Sunitinib is not part of standardized treatment.

Moreover, treatments targeting vascular endothelial growth factor (VEGF) are associated with the onset of resistance after a treatment period of 6 to 15 months. The sequential use of these drugs has become standard practice. Indeed, activity can be observed with an agent having the same target as, or some targets in common with, one of the previous treatments and for which disease progression had been observed. This therefore raises questions regarding the mechanism(s) of this resistance and the optimal therapeutic approach in this context. This resistance appears to be a potentially reversible mechanism. In a retrospective review performed on patients with mRCC treated with Sunitinib, after disease progression occurring following previous treatment with Sunitinib and other treatments, the reintroduction of Sunitinib was effective and well-tolerated in the majority of cases.

In patients in CR with targeted treatment only or thanks to the combination of targeted treatment and an additional metastasectomy, one series indicates that, in almost half of cases, withdrawal of Sunitinib treatment was followed by a recurrence, but that reintroduction of this targeted therapy was effective in the majority of cases.

A better characterization of patients experiencing CR with Sunitinib is therefore required in order to provide information to physicians about the treatment approach to adopt in such cases and to encourage surgeons to operate on patients with single or minimal residual metastases.

The analysis of patients experiencing CR must compare these rare cases to the most common situation in patients treated with Sunitinib where no complete response is developed. Given the rarity of the event studied, the design proposed is that of a case-control study.

3.1. OBJECTIVES

Primary objective

To describe the characteristics of patients with mRCC and presenting CR with Sunitinib **(Cases)** and compare them with the characteristics of patients with mRCC and not presenting CR with Sunitinib (**Controls**) in order to identify factors associated with the occurrence of complete remission.

Secondary objectives:

- To describe the therapeutic treatment methods (discontinuation of treatment or continuation of systemic treatment in patients in CR)

- To investigate and describe various biomarkers in a blood bank of samples drawn during CR with Sunitinib in patients in CR (**Cases**) and at the time of recurrence, if it occurs
- To investigate and describe various biomarkers in a histological specimen collection bank prior to initiation of sunitinib in CR (Cases) and non-CR patients treated with sunitinib (controls).
- To compare biomarkers identified in patients in CR (**Cases**) to those in patients not in CR with Sunitinib (**Controls**).

3.2. METHODS

3.2.1. Physician population

This case-control observational study will be conducted by oncologists at around twenty metropolitan oncology centers in France.

3.2.2. Patient population

40 patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**) and 80 patients with metastatic renal cell carcinoma receiving first-line treatment with Sunitinib (**Controls**) will be included in this research and followed for a period of 36 months.

Inclusion and exclusion criteria for <u>Cases</u>

Inclusion criteria

- Adult patients (≥ 18 years)
- Patients with mRCC confirmed by histological analysis
- Treated with Sunitinib according to a regimen in the section of the Summary of Product Characteristics (SmPC)
- Presenting a complete remission in the preceding 5 years (according to RECIST v1.1) with Sunitinib only or combined with localized treatment (surgery, radiotherapy, cryoablation or radiofrequency ablation)
- Patients of childbearing age using a mandatory method of contraception
- Affiliated to a social security scheme
- Informed about the study methods and having given their consent

Exclusion criteria

- Complete remission occurring in the absence of treatment with Sunitinib

Inclusion and exclusion criteria for <u>Controls</u>

Inclusion criteria

- Adult patients (≥ 18 years)
- Life expectancy ≥ 3 months
- Patients with mRCC confirmed by histological analysis
- No previous treatment with Sunitinib
- Patients for whom the indication of Sutent® is retained in compliance with the text in the SmPC
- Platelets ≥ 100 x 10^9/l, hemoglobin > 9 g/dl, neutrophils >1.5 x 10^9/l
- Bilirubin < 2 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) ≥ 2.5 times upper limit of normal or ≤ 5 times upper limit of normal in the presence of hepatic metastases
- Patients of childbearing age using a mandatory method of contraception
- Affiliated to a social security scheme
- Informed about the study methods and having given their consent

Exclusion criteria

- Previous systemic treatment
- Patients who are pregnant or breastfeeding
- Any contraindications to Sunitinib in accordance with the text in the SmPC

3.2.3. General study design

Cross-sectional then longitudinal, comparative, multicenter, prospective, case-control study including 40 patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**) and 80 patients with metastatic renal cell carcinoma with no CR receiving Sunitinib as first-line treatment (**Controls**).

Blood samples will be drawn from patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**) during screening visit and in the case of disease progression.

Blood samples will be drawn from patients with metastatic renal cell carcinoma in the absence of CR with Sunitinib (**Controls**) before start of Sunitinib, at 6 months, at 12 months and during disease progression.

Note that a patient in the Control group may move to the Case group if s/he presents a CR during follow-up with Sunitinib.

Duration of inclusions: 4 years

Follow-up of patients: 3 years

3.3. STATISTICAL METHODS

The primary objective of the study is to describe the characteristics of patients with mRCC and presenting CR with Sunitinib (**Cases**) and compare them with the characteristics of patients with metastatic renal cell carcinoma without CR with Sunitinib in order to identify factors associated with the occurrence of complete remission.

A sample size of N = 40 (**Cases**) and N = 80 (**Controls**) will give a statistical power of 80% in revealing:

• For a continuous variable with a normal distribution, an effect size (Cohen's d) ≥ 0.55;

• For a dichotomous variable, a difference in frequency between cases and controls corresponding to the ORs presented in the table below:

Frequency in the control	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

4. AMENDMENTS AND UPDATES

Amendment Number	Date	Modified section of the protcol	Modifications summarized	Reason
Amendment N°1	13-Feb-2012	Study qualification	Study qualification modification	Following the receipt of the CPP's letter of December 14, 2011 and at their request the protocol was requalified in observational study instead of current care study
Amendment N°2	30-Apr-2014	CT-Scan sending process	Wish to receive the last scan done before the full answer	In order to be able to determine the complete response, Dr. PPD wanted to receive the last scan before RC in order to be able to make a comparison
Amendment N°3	05-Mar-2015	Inclusion Criteria	Extension of the CR period and extension of the number of "CAS" patients	In order to improve the inclusions in the project, the members of the scientific committee in consultation with the medical team decided to extend the period of CR from 2 to 5 years and to lift the capping of 2 patients per center
Amendment N°4 et 4.1	09-Apr-2016	Biological sample and « TEMOINS » patient site inclusion	Constitution of a biological sample bank. Addition of centers recruiting patients "CONTROLS"	In addition to the blood samples, the members of the scientific committee wished to set up a histological sample bank from the slides and / or blocks already taken as part of the patient follow-up. In order to relaunch inclusions, it was also decided to allow other centers to include patients "CONTROLS"
Amendment N°5	21-Nov-2017	Planning and methodologist statistics	Update of the study schedule Added table to justify sample size for study	In order to reach the required number of patients, the inclusion period is extended until December 31, 2018. Following the rereading of the protocol by our statistician, the latter makes it possible to justify the number of patients included in the study for "CASE" and "CONTROLS"
Amendment N°6	25-Fev-2018	GDPR application and update protocol	Article on Data Management and Retention as well as "CAS" and "CONTROLS" Consents Update following the audit	Following the implementation of the patient data management regulation, the corresponding parts of the protocol as well as the consents have been updated to comply with this new law. Following the audit, update of the data collected at the screening page

5. MILESTONES

Milestone	Planned date
Start of data collection	Juillet 2014
End of data collection	Décembre 2021
Rapport intermédiaire	Janvier 2019
Final study report	Novembre 2022

6. RATIONALE AND BACKGROUND

Context

The incidence of renal carcinoma in France was estimated at 10,125 cases in 2009 [1]. It represents around 3% of malignant tumors in adults. In 85% of cases, it is a renal cell carcinoma (RCC). The incidence of renal carcinoma has been increasing over the last 30 years; probably related to a greater number of incidental diagnoses. It is twice as frequent in men. The average age at diagnosis is around 65 years. The number of estimated deaths in 2009 was about 3,830. This number is decreasing, partly associated with earlier discovery of these cancers. In fact, worldwide, the relative survival at 5 years is 63% [2]. For a localized stage (58% of diagnoses), this increases to 90%. Peak mortality occurs between 75 and 85 years[3].

It is estimated that 10 to 40% of patients diagnosed with renal carcinoma already have a metastatic form of the disease. Despite initial curative treatment, 10 to 30% will develop metastases, with an average time of 36 months to appearance of metastases. These metastatic forms have a poor prognosis (survival rate at 2 years of 10% - 20% [4]) because of the increased resistance to conventional chemotherapies and to radiotherapy. For many years, the treatment of metastatic renal cell carcinoma has been based on nephrectomy and adjuvant immunotherapy (interleukin 2, interferon alpha); often toxic and of limited efficacy in terms of survival [5].

Since 2009, the treatment of metastatic renal cell carcinoma remains partially surgical, particularly for excision of the primary tumor, but equally for individual metastatic localizations. Outside of these indications, the standard treatment is based on antiangiogenic drugs. For patients belonging to the good or moderate prognosis group, the choice of first-line treatment, according to ASCO and CCAFU (Oncology Committee of the French Urology Association), is Sunitinib, the combination Bevacizumab/interferon α or Pazopanib. These targeted therapies have revolutionized the treatment of patients with metastases, achieving a significant therapeutic response and an improvement in patients' survival rates. However, numerous questions remain as to the methods of using these antiangiogenic treatments [5].

Study rationale

Complete remission (CR) is a rare event during the treatment of mRCC with tyrosine kinase inhibitors (TKIs), but results from two retrospective cohort studies show that it occurs in 1 to 3% of patients treated with Sunitinib. (Motzer 2008 [6]: 1%; Motzer 2009 [7]: 3%; Heng 2007 [8]: 2.7%; Albiges ASCO 2010 [9]: 1.7%).

CR with Sunitinib has been described in the different prognostic subgroups as defined by the modified classification of Motzer 2002 [10] [Memorial Sloan-Kettering Cancer Center (MSKCC) classification] and has also been reported in cases with multiple metastases [9]. In addition, a series of reports suggests that significant objective responses can be obtained in a subpopulation of patients receiving targeted therapy and that a complete residual metastasectomy can be beneficial in carefully screened patients having presented a partial response to antiangiogenic treatment [8, 9, 12].

The continuation of treatment or its withdrawal in patients presenting CR with Sunitinib is not currently considered to be standard treatment.

Moreover, treatments targeting VEGF are associated with the onset of resistance after a treatment period of 6 to 15 months. The sequential use of these drugs has become standard practice. Indeed, activity can be observed with an agent having the same target as the previous treatment having led to a disease progression. This therefore raises questions regarding the mechanism(s) of this resistance and the optimal therapeutic approach in this context [13]. This resistance appears to be a potentially reversible mechanism. A retrospective review was done on patients with mRCC treated with Sunitinib after disease progression occurring after prior treatment with Sunitinib and other treatments. The reintroduction of Sunitinib was effective and well-tolerated [14].

Recently, in 36 patients (including 22 on Sunitinib) in CR with targeted therapy only or absence of signs of the disease after an additional metastasectomy, Johannsen et al. [15] demonstrated that withdrawal of treatment was followed by a recurrence, but that the reintroduction of this targeted therapy was effective.

A better characterization of patients experiencing CR with Sunitinib is therefore required in order to provide information to physicians about the treatment approach to adopt in such cases and to encourage surgeons to operate on patients with single or minimal residual metastases.

Because complete remission is a rare event, one can stipulate that this situation should be a model for studying the pathology of mRCC in response to Sunitinib. It should also permit the sensitivity and resistance to Sunitinib to be explored.

Research is also required to identify markers that can facilitate the screening of patients who would be at low risk of recurrence after complete remission and could potentially benefit from a discontinuation of treatment.

To this end, it is essential to explore the characteristics of the patient at the time of the complete remission compared to those observed at the time of the recurrence, if this occurs, in order to attempt to answer the following questions:

- Is it possible to identify a differential blood marker at the time of the CR compared to the recurrence phase?
- Does one have to distinguish between a CR obtained with medical treatment only and one obtained with the combination of "medical treatment + localized treatment" when, during the retrospective analysis of a series of cases, the 2 cohorts presented the same time to recurrence?
- Can we identify serum or histologic biomarkers that are potentially predictive of a recurrence or CR?
- Is there a correlation between biomarkers identified in patients in CR with Sunitinib compared to patients not in CR with Sunitinib?
- Does the identification of biomarkers help physicians make the decision to stop or continue treatment after obtaining a complete response under sunitinib?

Several biomarkers belonging to different categories, are undergoing investigation because they could reflect the emergence of a resistance or sensitivity to the medicinal product:

- Adhesion molecules (cadherin-6, E-cadherin, MUC1/EMA, ICAM-1, VCAM-1, ELAM- 1, KSA)
- Inducers of immunosuppression (HLA class 1, IL-6, IL-8, IP-10, MIG, MIP1b, B7-H1, B7-H4, CD44)
- Growth factor receptors (VEGFR-3, TGFbR-II, FGFR)
- Hypoxia-inducible factors (CAIX, CAXII, CXCR-4, HIF-1a, VEGF, IGF-I)
- Proliferation markers (Ki-67, PCNA, Ag-NORs)
- Cell cycle regulatory proteins (p53, Bcl-2, PTEN, cyclin A, Akt, p27)
- Analysis of single nucleotide polymorphisms (SNPs) of VEGF and of VEGFRs
- Others (VHL, mTOR, ribosomal protein S6, survivin, IMP3, caveolin-1, PCR, vimentin, fascin, serum amyloid A, NGAL, IGF-1).

Some of these biomarkers can be detected in the serum (SDF1a, IL-6, IL-8, bFGF, sICAM1, LDH, VEGF, PlGF, soluble VEGF receptors, collagen IV, CPCs, SNPs of VEGF) [16] and will be explored in the context of CR, especially IL-8, which has been the most documented [17].

Other potential biomarkers expressed on the surface of tumor cells or immune cells can be investigated by immunohistochemistry such as:

- The expression of BAP1, SETD2, PBRM1, as well as PD1 or PDL1
- Potential biomarkers of inflammation and lymphocyte infiltrate

A classification according to the tumor expression profile will be performed (B. Beuselinck et al, CCR, 2015).

In addition, we will be able to carry out the sequencing of the most frequently mutated genes (PBRM1, BAP1, VHL)

Because, at present, circulating tumor cells can only be studied in fresh blood, and because this marker has not yet been validated as regards mRCC, this investigation will not be possible with our cohort. However, circulating free DNA is currently being investigated as a substitute for circulating tumor cells in various tumor models (prostate, colon and breast) and we regard it as a good candidate for study in our population at the time of CR compared to recurrence, if it occurs.

Therefore, the aims of this multicenter prospective study on patients with metastatic renal cell carcinoma in CR with Sunitinib with or without associated localized treatment and control patients with metastatic renal cell carcinoma treated with Sunitinib are:

a) To analyze the characteristics of patients with mRCC in CR with Sunitinib
b) To assess the possibility of patients in CR to discontinue Sunitinib
c) To collect a prospective bank of blood samples in order to study blood biomarkers in the context of the CR and during recurrence
d) to collect a bank of histological specimens to study biomarkers before the initiation of sunitinib;
e) To assess the correlation between biomarkers analyzed in patients in CR and patients not in CR with Sunitinib

7. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are as follows:

Primary objective

- To describe the characteristics of patients with mRCC and presenting CR with Sunitinib (**Cases**) and compare them with the characteristics of patients with metastatic renal cell carcinoma without CR with Sunitinib in order to identify factors associated with the occurrence of complete remission.

Secondary objectives

- To describe the methods of therapeutic treatment (discontinuation of treatment or continuation of systemic treatment in patients with CR).
- To investigate and describe various biomarkers in a blood bank of samples drawn during CR with Sunitinib in patients in CR (**Cases**) and at the time of recurrence, if it occurs
- To investigate and describe various biomarkers in a bank of histological samples collected during the CR with Sunitinib and at the time of the recurrence, if it occurs (FGF, IL-8, VEGF, VEGF SNPs etc.).
- To compare the biomarkers identified in patients with CR (**Cases**) to those of without CR with Sunitinib during the 36 months of the study (**Controls**).

8. RESEARCH METHODS

8.1. Study design

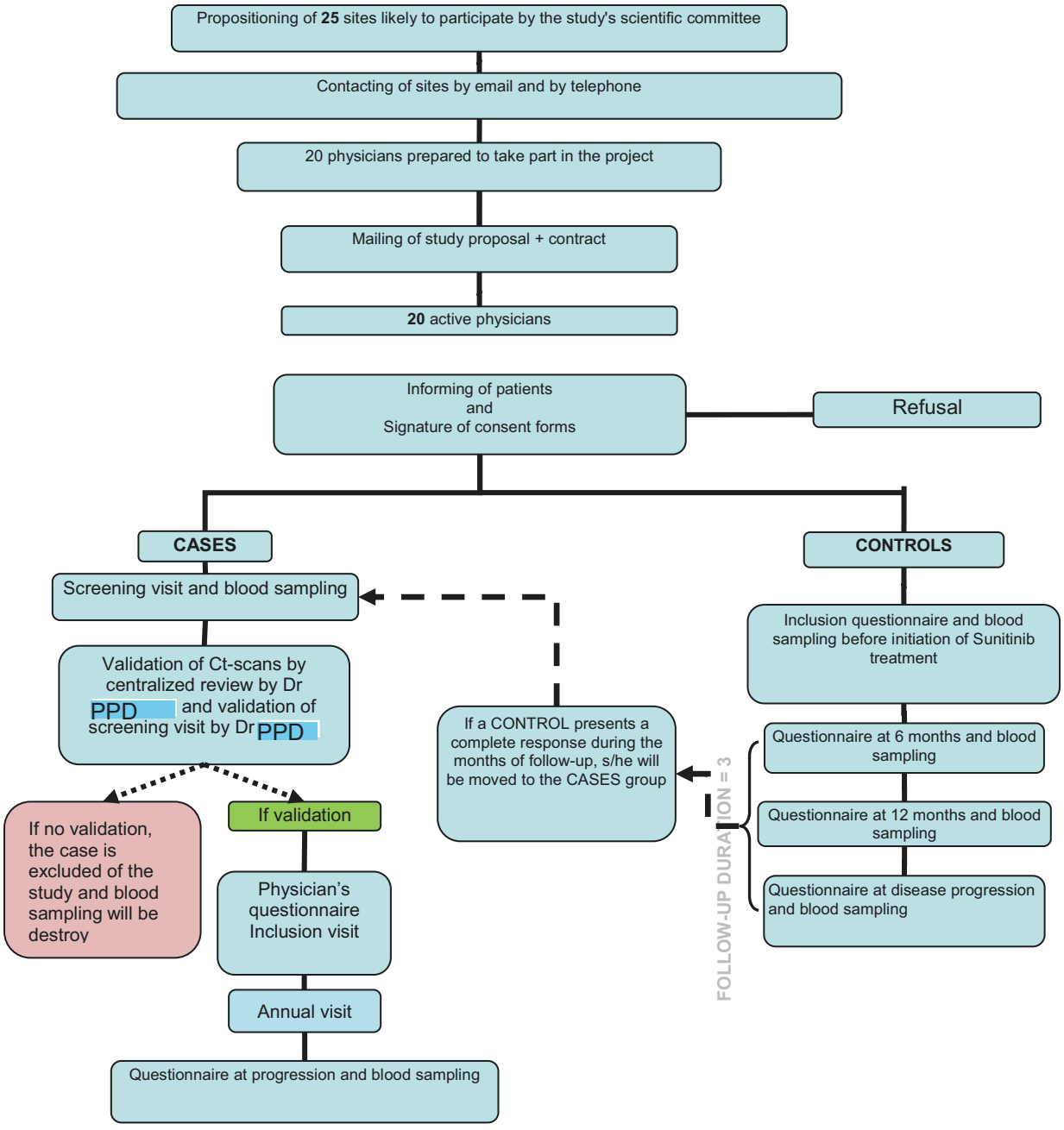
8.1.1. Type of study

It is a cross-sectional then longitudinal, comparative, multicenter, prospective, case-control observational study with collection of blood samples.

In addition to the patient's usual medical treatment, as described in the HAS's long-term diseases guide, validated by a multidisciplinary working group [19], the specific monitoring methods provided for in this research comprise of:

- Blood sampling of 2 times 5 ml into 2 EDTA tubes done at screening visit during CR and during disease progression, if it occurs, in the 40 patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**).
- Blood sampling of 2 times 5 ml into 2 EDTA tubes done before starting Sunitinib, at 6 months, at 12 months and during disease progression, in 80 patients with metastatic renal cell carcinoma without CR with Sunitinib throughout the 36 months of the study (**Controls**).

Therefore, these monitoring methods only involve negligible risks and constraints.



8.1.2. Study schedule

The provisional schedule for the study is as follows:

- Submission of the protocol to the CCTIRS and the EC: November 2011
- Submission of the protocol to the French National Board of Physicians (CNOM): November 2011
- Submission of the protocol to the CNIL: February 2012
- Informing of the ANSM: November 2011
- Submission of the protocol to the Ministry of Research: November 2011
- Recruitment of participating physicians: September 2013 – June 2018

- Recruitment of patients: July 2014 – Until inclusion of all the patient in the study or later in December 2018
- End of follow-up: July 2014 – December 2021
- Database freeze and initial analysis: February 2022
- Final report: November 2022

8.1.3. Obtaining of patient's informed consent

An informed consent form, accompanied by a patient information leaflet in which the purpose of the blood samples collected will be clearly stated, will be signed by each patient before any data collection.

In addition, it will be mentioned that the histological samples taken at the diagnosis of the patients will be collected in order to constitute a bank of samples

A second informed consent form specific to the genetic analyses will be signed by each patient prior to all sampling.

8.1.4. Data collected in the individual case report form for each patient included (Appendix 3)

A) Data relating to the physician

- Surname, first name
- Gender
- Age
- Zip code, Town
- Public or private practice
- Type of contract

B) Screening form (only for cases)

- Visit screening date
- Consentment sign date
- Inclusion and non inclusion criteria
- Demographic data: month and year of birth (MM/AAAA)
- Data relating to the initial treatment of the patient: date of diagnosis of the initial renal cancer, date of diagnosis of renal cell carcinoma
- Data relating to the status of the patient in complete remission: Sunitinib start date, number and localization of metastatic sites at initiation of Sunitinib
- Blood samples during the screening visit: yes / no sampling and date of collection. If the samples are not available during the screening visit, a period of 6 weeks between screening and sampling will be allowed.
- Histological samples: date of sampling, type of sample, method of fixation.

C) Data collected at inclusion
For the cases

- Demographic data: age, gender, height, weight
- Data on the diagnosis of patients with metastatic renal cancer in complete remission: date of initial diagnosis of kidney cancer, date of diagnosis of metastatic renal cell carcinoma, nephrectomy (Yes / No), date of nephrectomy, type of nephrectomy; fixation method, OMS pathological classification, TNM classification 2009, Furhman nuclear grade, presence of necrosis, tumor size, presence or absence of a sarcomatoid embolus component
- Data relating to the state of the patient in CR at initiation of Sunitinib: initiation date, location of metastases, number of metastatic sites, prognostic classification MSKCC
- Data on complete remission: date of complete remission; obtained by medical treatment alone or combined with local treatment, radiological assessment of complete remission, Therapeutic strategy after complete remission: continuation or discontinuation of treatment

For the controls

- Data relating to the inclusion and demographic data : consultation date ; demographic data : year of birth, age, sex, size, weight
- Data relating to the renal metastatic cancer initial treatment for a patient in complete remission : date of initial diagnosis of renal cancer, date of diagnosis of metastatic renal cancer, date of intitiation of Sutent, nephretomy (Yes/No), date and nephrectomy type, histology, OMS anatomopathologic classification, TNM 2009 classification, Furhman nuclear grad, necrosis presence, vascular embolism, blood sample date before initiation od Sutent
- Data relating to a patient state with a mRRC before initiation of sunitinib: blood and histological sample (Yes/No) and sample date. If the sample are not available during the screening visit, un six week time limit between screening and inclusion visit is authorized metastasis localisation, number of metastasis, MSKCC prognostic classification

D) Data collected during follow-up visits

In this research, patient follow-up will be carried out over a period of 3 years, in accordance with the normal treatment procedures for this disease (visits every 2 to 3 months as per the expert opinion reported in the long-term diseases guide of the HAS).

For the cases

During the visit to diagnose possible disease progression, the following data will be recorded in the case report form:

- Date of the visit,
- Date of progression, progression type, for a known metastatic site ou a new metastatic site
- Localization and number of metastatic sites
- Blood sample date
- treatment administered during progression

During the annual visit, following data will be recorded in the case report form:

- disease evolution
- treatment modification (temporary stop, definitive stop),
- No sample to be made

During the end of research visit (36 months after the inclusion visit), the following data will be recorded in the case report form :

- 36 months visit : Yes/No ; Date of the visit, treatment best answer post progression, duration of administration, local treatment associated
- Last news : premature stop of the study ; date of latest news ; persistant remission complete since visit of inclusion ; complete remission after treatment of progression post RC ; progression of cancer ; number of subsequent line of treatment after Sutent
- Deaths (YES / NO), date of death

For the controls

During the follow-up visits at 6 and at 12 months, the following data will be recorded in the case report form :

- Data relating to a patient state with a mRRC at 6 and 12 months of treatment with Sutent : date of the visit, clinic evaluation with RECIST criteria, : response to the treatment, stability of the disease or progression, date of the progression, type of progression ; metastatic sites ; localization and number of metastatic sites ; blood sample and date of sample.

During the visit of progression: the following data will be recorded in the case report form :

- Data relating to a patient with a mRRC with a progression : date of the visit, date of progression, to a known metastatic site, new metastatic site, metastatic sites : localization and number of metastatic sites ; blood sample and sample date.

During the end of research visit (36 months after the inclusion visit), the following data will be recorded in the case report form :

- 36 months visit : Yes/No ; Date of the visit, treatment best answer after progression, duration of administration receives after progression with Sutent
- Last news : premature stop of the study ; date of latest news ; persistant remission complete since visit of inclusion ; complete remission after treatment of progression post RC ; progression of cancer ; number of subsequent line of treatment after Sutent
- Deaths (YES / NO), date of death

E) Centralized review of CT scans (only for patients in CR)

In this research, the CT scan data from patients in CR (CASES) will undergo a centralized of two of their scanner

- The scanner at baseline (at the initiation of sutent at first line)
- The scanner where the complete remission is present

This review will take place during the patient's screening visit. The latter will not be included until after the review of the CT scan, which will validate the complete response.

For this purpose, they should be burnt onto two CD-ROM :

- 1 CD-ROM for the scanner at baseline (at the initiation of Sutent in first line)
- 1 CD-ROM for the scanner where the complete remission is present

The CD-ROM will be send just after the screening visit to the IGR with the screening visit printed with e-CRF, 2 CD-ROM by patient and the envelopes will be provided by Pfizer.

Contact and address for the sending of the CD-ROM :
Dr PPD
PPD
Telephone :PPD

F) Establishment of a bank of blood samples (see Appendix 11)

For patients with metastatic renal cell carcinoma in CR with Sunitinib (Cases)

- One blood sample of 2 times 5 ml will be collected during screening visit
- One blood sample of 2 times 5 ml will be collected in the event of disease progression

If the sample are not available during the screening visit, a six week time limit is authorized between screening and sample.

For patients with metastatic renal cell carcinoma without CR at the start of Sunitinib and during the 36 months of the study (Controls)

- One blood sample of 2 times 5 ml will be collected before starting Sunitinib, at 6 months, at 12 months and during disease progression.

All samples will be centrifuged and frozen to produce 2 aliquots (minimum) of plasma and 2 pellets of whole blood. These tubes will be labeled, stored at -80 °C and transported frozen for centralized storage at the IGR's biobank, which is the responsibility of Prof PPD and Dr PPD

The biomarkers studied in these blood samples will be as follows: FGF, IL-8, PIF and analysis of single nucleotide polymorphisms (SNPs) of VEGF This list is not exhaustive. Other biomarkers may be examined, following agreement from the Scientific Committee, depending on how basic knowledge advances.

G) Establishment of a bank of histological samples (see Appendix 12)

In view of the progress made in the context of histological analyzes, these one would make it possible to detect certain markers predictive of a complete response.

Participating physicians and pathologists are encouraged to submit histologic sample, if available, as a block or failing 4µm white slides. The histological sample will be from the primary tumor.
These will be used for genomic and immune histochemical analyzes. These analyzes will aim to identify predictive biomarkers of complete response.

If the samples were not taken or were not planned, they should not have been made in the specific context of this observational study.

Tissue fixation should be performed in 10% buffered formalin at neutral pH (pH 7.2-7.6 aqueous)

The histological specimens should have been technically fabricated as follows: The tissue should have been immediately immersed in 10% buffered formalin, fixed for 24-48 hours at room temperature and finally fixed with paraffin, according to the laboratory routine. It is necessary that the paraffin be melted at 60 ° C for 30. The resulting slides should contain 4 µm paraffinic samples.

All samples will be labeled, stored at room temperature in the package provided as part of the study and centralized at the IGR Biobank under the responsibility of Prof. PPD and Dr. PPD .

8.2. Setting

8.2.1. Population of physicians/health care professionals

The active participation of 15 - 20 oncologists ensures conditions of sufficient statistical accuracy to meet the objectives of the study.

Each physician will include patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**).

The teams of Dr PPD (IGR), of Prof. PPD (PPD) including doctors PPD and PPD , of Dr PPD (PPD), of Dr PPD (PPD , PPD), of Dr PPD (PPD) and Dr PPD (PPD) will include 80 patients with metastatic renal cell carcinoma without CR at the start of Sunitinib administration. This is the control population. Given the rarity of the CR event observed (1.7%), it is expected that none of the patients in the control group (n = 80) will present CR with Sunitinib. **If any of the 80 controls present CR with Sunitinib during follow-up, s/he will be moved to the Cases group.**

These patients are seen in consultation and meet the inclusion and exclusion criteria.

The study's scientific committee has identified 25 sites that are likely to participate in this project. These sites have all been contacted (by email and by telephone) as part of a feasibility study (Appendix 14). At the end of this process, twenty sites have agreed to participate in the study.

If the evaluation of the number of patients that can be included by those 20 sites remains below 40 **Cases** and 80 **Controls**, the pool of participating physicians may be increased.

A description of the population of physicians will be made retrospectively on the basis of the identification data for the participating physicians (gender, age, location etc.).

In order to ensure the external validity of the study, it will then be verified that the population of participating physicians is representative of the total population of oncologists in France.

8.2.2. Patient population

The study plans to include a total of 40 patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**) and 80 patients with metastatic renal cell carcinoma with no CR receiving Sunitinib throughout the 36 months of the study (**Controls**).

The calculation of this study population size is justified on page 5.0 "Statistical Methods".

. Inclusion and exclusion criteria for Cases:

8.2.3. Inclusion criteria

- Adult patients (≥ 18 years)
- Patients with mRCC confirmed by histological analysis
- Treated with Sunitinib according to a regimen in the text of the SmPC
- Presenting a complete remission in the preceding 5 years (according to RECIST v1.1) with Sunitinib only or combined with localized treatment (surgery, radiotherapy, cryoablation or radiofrequency ablation)
- Patients of childbearing age using a mandatory method of contraception
- Affiliated to a social security scheme
- Informed about the study methods and having given their consent

Exclusion criteria

- Complete remission occurring in the absence of treatment with Sunitinib

8.2.4. Inclusion and exclusion criteria for Controls

Inclusion criteria

- Adult patients (≥ 18 years)
- Life expectancy ≥ 3 months
- Patients with mRCC confirmed by histological analysis
- No previous treatment with Sunitinib
- Patients for whom the indication of Sutent® is retained in compliance with the text in the SmPC
- Platelets ≥ 100 x 10^9/l, hemoglobin > 9 g/dl, neutrophils >1.5 x 10^9/l
- Bilirubin < 2 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) ≥ 2.5 times upper limit of normal or ≤ 5 times upper limit of normal in the presence of hepatic metastases
- Patients of childbearing age must use a method of contraception
- Affiliated to a social security scheme
- Informed about the study methods and having given their consent

Exclusion criteria

- Previous systemic treatment
- Patients who are pregnant or breastfeeding
- Any contraindications to Sunitinib in accordance with the text in the SmPC

8.2.5. Detailed logistics

8.2.5.1. Initiation of the study

The oncologists who agreed to participate in the study during the feasibility study will receive a letter containing:

- A covering letter with a reply slip to be returned to Pfizer's logistics center
- A study synopsis
- The participating physicians' contracts, one copy of which should be returned to Pfizer's logistics center
- A pre-paid envelope

Physicians who did not respond to the emails will be contacted again by telephone fifteen (15) days later until the desired number of participating physicians has been reached.

Once the contract has been signed and returned to Pfizer's logistics center, it will be validated by Pfizer. The physician will be contacted by mail to know if he want a website monitoring visit for his center.

If the physician want a website monitoring visit so this one will be program with his disponibilities. The member of personal Pfizer of each department will be present :

- Post AMM study gestion
- Medical oncology
- Pharmacovigilance

The physician will receive the study website address and his access code. The physician will found on the website the following documents

- CCTIRS opinion
- EC opinion
- CNOM opinion
- CNIL opinion
- Authorization from the Ministry of Research
- The study protocol and protocol amendment
- The memorandum to physicians
- The serious adverse events (SAE) declaration form (Appendix 1)

In addition, data relating to the physician (year of registration, year of doctoral thesis, town where practicing etc.) can be uploaded to the website as well as the anonymized data regarding the patients.

Also, the physician receive by mail :

- A file containing all documents in the paper version of study (protocol, regulatory agreements, etc ...)
- briefings / patient consent
- CD / ROMs and pre postage for mailing envelopes at IGR
- aliquots pellets and pre-labeled and forms for the transport of blood samples
- envelopes sufficient to return the document
- Each physician investigator will be a single number (0001 to 00XX).

The physicians will be presented with a hotline number as well as an email address where they can ask questions about the conducting of the study.

8.2.5.2. Screening of patients

Before any gathering of personal data, the physician will invite the patient to participate in this research and will inform him/her about:

- The objective, the nature of the constraints
- The computer processing of his/her data that will be collected during this research and will also specify his/her rights of access, opposition and rectification of his/her data
- The storage of blood samples for scientific purposes at the end of the research

In addition, during this visit (screening visit), the physician will check the eligibility criteria.

Finally, an information leaflet summarizing these different points will be handed to the patient.

<u>If the patient with metastatic renal cell carcinoma in CR with Sunitinib (Cases) consents to participate in the research, the physician should during the screening visit:</u>

- Obtain his/her express written consent (Appendix 2)
- Complete the screening form and send it, along with the 2 CT scan burnet on 2 CD-ROM, to the IGR.
- Complete the inclusion questionnaire
- Draw 10 ml of blood into 2 EDTA tubes of 5 ml each and send the sample after centrifugation to the IGR
- Collection of a block or in the absence of 15 white slides from a histological sample

If the patient in CR presents disease progression during the 3 years of follow-up:

- Complete the disease progression questionnaire
- Draw 10 ml of blood into 2 EDTA tubes of 5 ml each and send the sample after centrifugation to the IGR
- Collection of a block or in the absence of 15 white slides from a histological sample

If the patient with metastatic renal cell carcinoma without CR with Sunitinib (**Controls**) consents to participate in the research, the physician should:

- Obtain his/her express written consent (Appendix 3)
- Complete the inclusion questionnaire
- Draw 10 ml of blood into 2 EDTA tubes of 5 ml each before starting Sunitinib, at 6 months, at 12 months and during disease progression and send the sample after centrifugation to the IGR.

Receipt and collection of case report forms
The Pfizer project managers will ensure monitoring of incomplete or inconsistent data (checking of inconsistencies, non-responses and omissions) and will be in permanent contact with the physicians.

During the patient screening phase, and based on the number of physicians (no patient enrolled), the project managers will be required to contact these physicians again and remind them about the study deadlines.

8.2.5.3. End of study

The project manager will inform the physician about the end of patient enrollment and will remind him/her again regarding possible missing documents required for remuneration or inconsistencies in the gathered data identified during data management.

8.2.5.4. Roles of those conducting the study

Via its project managers, the logistics center will ensure the telemonitoring as well as the centralized e-monitoring of the participating physicians (use of Pfizer's study management database and the dedicated study website).

The company responsible for the biometrics will ensure the configuration of the eCRF, the issuing of correction requests, the writing of the statistical analysis plan, the statistical report and the clinical report of the study.

The oncologists must ensure the screening of patients and the gathering of case report form data while observing the research protocol as well as the contract.

8.2.5.5. Logistical monitoring

The monitoring of the participating physicians will be done by a team of project managers specially trained for the study. This monitoring may be done in various manners: telephone call, email, specific letter and newsletter.

These contacts will be advantageous because they will promote the involvement of and the quality of the work done by the participating physicians. As far as possible, everyone will be monitored by the same project manager, from their recruitment to close-out of the study.

The project managers will ensure monitoring of incomplete or inconsistent data (checking of inconsistencies, non-responses and omissions) and will be in permanent contact with the participating physicians. During the patient screening phase and depending on the number of inactive participating physicians (no patient screened), the project managers may need to send them reminders.

In addition, a study-specific toll-free number will be provided for use by the participating physicians in order to be able to respond to their questions throughout the study.

In terms of traceability, all of the "incoming" and "outgoing" (screening call, reminder call etc.) calls to this toll-free number will be the subject of a written report (date, reason for call, action required etc.) and will be recorded in dashboards.

8.3. Variables

8.4. Data sources

Inclusion data

Descriptive statistics will be used to describe the patient population and the therapeutic treatment methods. More specifically, this will consist of the demographic profile of the patients, the associated diseases and concomitant treatments, data relating to the initial treatment of the cancer, data relating to disease progression, the kind of localized treatment received that led to the complete remission, data relating to the patient's health status and to the status of the disease at the start of Sunitinib, data relating to the complete remission and the treatment strategy after the complete remission.

End-of-study visit data

The number of deaths and the status of patients will be analyzed.

Supplementary data

Blood samples will be drawn from patients with metastatic renal cell carcinoma in CR with Sunitinib (**Cases**) during complete remission and in the case of disease progression.

Blood samples will be drawn from patients with metastatic renal cell carcinoma in the absence of CR with Sunitinib (**Controls**) before start of Sunitinib, at 6 months, at 12 months and during disease progression.

8.5. Study size

The primary objective of the study is:

To describe the characteristics of patients with metastatic renal cell carcinoma and presenting CR with Sunitinib (**Cases**) and to compare them with the characteristics of patients with mRCC and not presenting CR with Sunitinib (**Controls**) in order to identify factors associated with the occurrence of complete remission.

8.5.1. Complete justification of study population numbers (physicians/patients)

A sample size of N = 40 (**Cases**) and N = 80 (**Controls**) will give a statistical power of 80% in revealing:

• For a continuous variable with a normal distribution, an effect size (Cohen's d) ≥ 0.55;

• For a dichotomous variable, a difference in frequency between cases and controls corresponding to the ORs presented in the table below:

Frequency in the control	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

8.6. Data management

The contract research organization in charge of data management will process the research data for all patients.

The data may exist in paper and/or electronic format.

All of the data management operations will be performed in accordance with Pfizer's requirements and with the CRO's standard operating procedures.

A data management plan, defining and describing all of the biometric activities, will be developed by the CRO and submitted to Pfizer for validation

8.6.1. Processing of questionnaires

After validation of the physician's financial agreement by the logistics center, s/he will receive personalized access to the dedicated study website. This access will comprise the URL as well as the passwords required for secure access. Following their receipt, the participating physician will have access to the study. S/he will have the option to either save his/her data in order to be able to modify his/her questionnaire afterwards if s/he wishes, or to submit his/her questionnaire for a complete freeze of questionnaire data without the possibility of later modification.

During the recording of the questionnaires, the logistics center will be able to contact the physician again if data are incomplete or inconsistent (checking of inconsistencies, non-responses and omissions) in order that corrections can be made by the participating physician before submission of the questionnaires.

When the questionnaires are frozen, the data management company and the logistics center will receive the submitted and frozen questionnaires, which will then be directly integrated into the database as well as the "Pfizer study management" monitoring database.

8.6.2. Compiling of the database

An annotated questionnaire will be prepared by the CRO in charge of data management. This document will contain the name of the tables and the name of the variables. Each variable will be associated with its type, length and possible format. The annotated questionnaire will be sent to Pfizer for validation.

The CRO will then construct a database using their own software. The structure of the database will be documented and verified on listings by comparing the attributes of database variables with the specifications noted on the annotated questionnaire.

Before entering real data, the structure of the database and the entry screens will be tested and validated in accordance with the CRO's and Pfizer's standard operating procedures. To do so, fictitious questionnaires, generally 3 to 5, will be completed and captured. The validation will be done from scratch on lists of those data, then by comparison with the data recorded in the questionnaires. A validation report will be written and sent to Pfizer. The final structure of the database should be submitted for validation by Pfizer before entry of the actual data.

An audit sheet will be produced in order to record all changes made to the database. The original datum, the modified datum, the date and time of the change, the person who made the change and the reason for the change will be recorded on the audit sheet. The functioning of the audit sheet will be tested by making changes to the fictitious data. A report will be written and sent to Pfizer.

8.6.3. Data entry

After validation of the database by Pfizer, the participating physician will be able to commence entering the data collected during the patients' visits into the study website.

Periodic progress reports will be written by the CRO and sent to Pfizer for addition to the database.

8.6.4. Data checking

A list of consistency checks enabling the detection of inconsistencies and outlier responses present in the questionnaires will be compiled by the CRO and validated by Pfizer. These checks will be programmed using the CRO's own software, then tested using fictitious data. These fictitious data and the documentation relating to the tests will be kept in the study folder by the CRO and will be available for review by Pfizer.

After data entry, the checks will be executed continuously. A specific query for each inconsistency will be generated electronically by the data checking system.

The management of inconsistencies will be done in accordance with Pfizer's procedures.

In order to limit the number of queries to be submitted to the participating physicians, an obvious corrections guide, prepared by the CRO and validated by Pfizer, could be prepared.

Following a simple request from Pfizer, the CRO shall make available the documentation regarding data checks.

Periodic data check progress reports will be written by the CRO and sent to Pfizer.

8.6.5. Coding

This will be done using recognition software, a code and a preferred term, which will be allocated verbatim for coding. The dictionary chosen will be defined by Pfizer.

8.6.6. Final quality control

A final quality control will be conducted on a sample of $\sqrt{n} + 1$ patients selected at random. This quality control will be conducted in accordance with Pfizer's "CRF to database - QC guideline" guide. The acceptable error rate is 0.5%.

A new sample will be selected if the rate calculated exceeds this threshold value. The CRO will write a summary of this quality control and will send it to Pfizer for review.

8.6.7. Database freeze

The database freeze will not occur until the CRO has completed the entry and checking of data and final coding. The database freeze will be conducted in accordance with Pfizer's CT24 procedure. After validation by Pfizer, the database will be frozen by the CRO and prepared for statistical analysis.

8.6.8. Data management report

A data management report will be written by the CRO after the database freeze and sent to Pfizer.

8.6.9. Data transfer

There will be no partial intermediate transfer of the database. At the end of the project, all of the paper and electronic documentation (database, programs and documents) will be transferred to Pfizer via CD-ROM.

8.7. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term *DCT* should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A *DCT* is required and should be completed for each included patient. The completed original *DCT* are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the *DCTs* are securely stored at the study site in *encrypted electronic* form and will be *password protected or secured in a locked room* to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the *DCTs* and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The *DCTs* must be signed by the investigator or by an authorized staff member to attest that the data contained on the *DCTs* are true. Any corrections to entries made in the *DCTs* or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the *DCTs* must match those charts.

In some cases, the *DCT* may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the *DCT*, and for which the *DCT* will stand as the source document.

8.7.1. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., DCTs and hospital records), all original signed informed consent documents, copies of all DCT, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.8. Data analysis

A detailed statistical analysis plan (SAP) will be written and will constitute the frame of reference with regards to statistical analyses. **This analysis plan will be validated by the scientific committee and the study sponsor and will focus primarily on defining the populations studied as well as the statistical methods used.** Any modification of the statistical methods described in the SAP should be reported and documented in the clinical/statistical report.

Interim analysis

An interim analysis, based on the descriptive analysis of the patients included and on the data collected, will be performed during the study. This analysis will be performed as soon as 20 patients presenting a complete response (cases) have been included and followed for 6 months.

Statistics

For the case and control groups, the quantitative data will be described by their population sizes, means, standard deviations, confidence intervals, medians and outlying values. The qualitative data will be described by their frequencies and percentages (95% bilateral confidence intervals will be provided where relevant). The number of missing data will also be recorded.

All of the characteristics of the variables collected from cases and controls will be compared by the Student's t test for Gaussian quantitative data, the Mann-Whitney test for non-Gaussian quantitative data and the chi-squared test for qualitative data. The threshold of bilateral significance is set at 5%.

Data will be analyzed using SAS software (version 9.1 - SAS Institute, North Carolina, USA).

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Patient consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative/parent(s) or legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

9.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.4. Institutional review board (IRB)/Independent ethics committee (IEC)

9.4.1. French Board of Physicians (CNOM)

Pursuant to article L4113-6 (formerly L365-1) of the French Public Health Code, the following documents were sent by the sponsor of the study to the CNOM:

- Final study protocol and amended version of 25/11/2013
- Data collection questionnaire
- List of physicians participating in the study and members of the scientific committee
- Financial agreement proposed to participating physicians and to members of the scientific committee
- Patient information leaflet and consent forms

The study sponsor must inform the CNOM by registered letter of all financial matters between the sponsor, the members of the scientific committee and the physicians participating in the study.

No response from the CNOM 2 months after receipt of the dossier indicates a favorable opinion. A copy of the proof of receipt will be sent by the sponsor to each participating physician. It is then the responsibility of each participating physician to send a copy of this proof of receipt and the financial agreement signed to the regional medical association to which s/he belongs.

In the context of this case-control observational study, CENGEPS - *Centre National de Gestion des Essais de Produits de Santé* (French National Center for the Management of Health Products Trials) contracts are not applicable and can only be used for settling hospital overheads paid directly to the institution to which the participating physician belongs.

9.4.2. Data protection French Data Protection Agency "CNIL"

In accordance with French law no. 78-17 of January 6, 1978 on data protection, as amended by French law no. 2004-801 of August 6, 2004 on the protection of individuals with regard to treatment of personal data, this protocol has been subject to a request for an opinion from the CCTIRS - *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (French Advisory Committee for Data Processing in Health Research), which issued a favorable opinion on 18/01/2012. Following receipt of the favorable opinion from this committee, the computer file used to conduct the present study will be subject to a request for authorization from the French Data Protection Agency (CNIL). This computer file will be implemented following receipt of the authorization from CNIL; i.e. after 12/06/2012.

9.4.3. Ethics Committee (EC) and declaration of the blood sample bank

In this research, all of the procedures practiced and products used to treat those patients with metastatic renal cell carcinoma (mRCC) are those to which oncologists normally have recourse to.

The conditions of use of Sunitinib and of other medication likely to be prescribed by the participating physicians during follow-up of the patients are compliant with their official indications and with their current methods of use, in accordance with the SmPC.

In addition to the normal treatment of this kind of patient, and in order to better characterize those presenting CR with Sunitinib (followed or not followed by a recurrence), the protocol provides for

specific follow-up methods that involve only negligible risks and constraints for the patient. These specific methods consist of a 10 ml blood sample during inclusion on the trial (to identify biomarkers of CR) and a second sample taken in the event of a recurrence (to identify biomarkers predictive of the recurrence) for the cases group; a 10 ml blood sample during inclusion on the trial (to identify biomarkers predictive of the response), a 10 ml blood sample during follow-up at 6 months (to identify biomarkers predictive of the response), a 10 ml blood sample during follow-up at 12 months (to identify biomarkers predictive of the response) and, finally, a 10 ml blood sample during disease progression (to identify biomarkers predictive of the recurrence) for the control group.

This bank of blood samples, collected for scientific research purposes, will help improve the therapeutic treatment of patients with metastatic renal cell carcinoma.

Pursuant to articles L 1121-1-2° and R 1121-3 of the French Public Health Code, the protocol for this observational research was submitted to the Ile de France VII EC for the session on 07/12/2011. On February 13, 2012, the EC concluded that it was not empowered to issue an official opinion, the study not falling within the law governing biomedical research. It is of the opinion, however, that:

- The rationale for this study is valid
- The study is conducted under the ethical rules in force in France
- The patient information leaflet is of good quality

The informing of the patient will be the subject of a written document submitted to the EC. Express consent should be obtained from the patient before the start of the research.

Moreover, as the blood is being collected to directly compile a collection of human biological samples, the provisions referred to in articles L 1243-3 and L 1243-4 apply, as well as the principles of compensation for injury and of insurance obligations as defined for biomedical research.

The collection of samples was the subject of a prior declaration by the ANSM, formerly the AFSSAPS, dated 25/11/2013.

9.4.4. Informing persons and obtaining their consent

Persons participating in research must be informed about the purpose of the study, its duration, the number of participants, the purpose and methods of collecting blood samples to establish the sample bank, the method of reporting adverse events as well as their right to withdraw from the study. They must also be informed about the nature of the data sent, the intended use of the data, the recipients of those data and their right of access and of rectification as well as their right of opposition, in accordance with French law no. 78-17 of January 6, 1978 on data protection, as amended by French law no. 2004-801 of August 6, 2004 on the protection of individuals with regard to treatment of personal data. This information will be provided to the patients in writing via the document entitled "Patient information leaflet" appended to the study protocol and an informed consent form will have to be signed by the patient.

The participating physician will countersign this consent form and will retain the original copy and provide the patient with a copy.

Similarly, if an amendment to the protocol were to result in a revision of the patient information leaflets and informed consent forms, it would be the participating physician's responsibility to have these new forms signed by each patient participating in the research. This does not apply to patients who have completed the study.

This personal information should be kept in the participating physicians file and be treated strictly confidential, but should be examinable by the competent authorities and duly authorized persons.

9.4.5. Ministry of research

The participating physicians must collect blood samples from their patients. According to current French regulations, the Ministry of Research must be approached for a request for authorization to compile a collection of human biological samples.

Before the end of the research, the storage of the collection of biological samples will be declared to the Ministry of Research and to the director of the regional health authority (and submitted to the EC for opinion in the event of a change to the purpose of the research).

9.4.6. ANSM - *Agence National de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety)

In the case of a collection of human biological samples, the ANSM - *Agence National de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety) wishes to be informed about the nature of the samples, the storage location as well as the purpose for compiling the collection. In order to do so, form FCEB280806 was sent to the ANSM on 25/11/2013.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The reference document to use during this observational study is the SmPC for the Sutent® range, version no.: 001-01/14.

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the electronic data capture and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the electronic data capture	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	**10.1.** *Poential reiks (PGR SUTENT V16.0)* Carcinogénicity Potential Other cardiac events: Trouble of the conduction, Ischemic events Tachycardia Retinal abruption *Missing important informations (PGR SUTENT V16.0)* Pédiatric population Pregnancy and lactation Severe hepatic insufficiency Cardiac insufficiency

Safety event	Recorded on the electronic data capture	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)
Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**.
In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the electronic data capture. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period
For each patient, the safety event reporting period begins at the time of the patient's first dose of Sutent or the time of the patient's informed consent signed date if s/he is already exposed to Sutent, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period.
If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.
Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to *<the named drugs under study>*, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Sutent, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Sutent caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Sutent caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Sutent did not cause the event, this should be clearly documented on the electronic data capture and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease; *<(Omit for Oncology and HIV studies)>*
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose Sutent:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.”

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An

emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Sutent or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Sutent (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure Sutent prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Sutent, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Sutent in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE :

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Communication problems

In case of prohibition or restriction (eg clinical hold) by a competent authority in any region of the world, or if the investigator is aware of any new information that may influence the evaluation of the benefits and risks of Sutent, Pfizer must be informed immediately.
In addition, Pfizer will inform the investigator immediately of any urgent safety measure taken by the investigator to protect patients in the trial against any immediate danger, and any serious violation of the Memorandum of NI study in which the investigator is aware.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Any information obtained from this research will be treated as confidential until the analysis and final review by Pfizer and by members of the scientific committee has been carried out.

The results of the study may be published or presented by members of the scientific committee after review and approval by Pfizer, such that confidential or proprietary information is not disclosed. Before publication or presentation, a copy of the final text should be sent by the member(s) of the scientific committee to Pfizer for comment. Such comments will aim to ensure the scientific content of proposed publications and/or presentations and to ensure that data and materials relating to Pfizer's products and activities are presented fairly, accurately and reasonably.

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13. APPENDIX

13.1. APENDIX 1. Sae form

Etude non-interventionnelle : Formulaire de notification d'évènements indésirables

Cadre réservé à Pfizer

Numéro AER	Date de notification à Pfizer

Ecrire toutes les dates au format JJ/MMM/AAAA

NUMÉRO DE PROTOCOLE / ÉTUDE	NUMÉRO DE CENTRE	IDENTIFICATION PATIENT/NUMERO DE RANDOMISATION

Titre du protocole :

☐ **Rapport initial** ☐ **Rapport de suivi**		**Pays de survenue de l'évènement :**	
Données Patient	Age ..... ☐ Homme ☐ Femme	Taille cm Poids kg	Origine ethnique : ☒ La réglementation locale interdit de poser la question
Si le patient est décédé:	Date de décès :	Cause du décès :	Autopsie réalisée ☐ OUI ☐ NON ☐ INCONNU *Si oui, quelle est la cause du décès déterminée à l'autopsie :*

Antécédents du patient
□☐ Aucun
□☐ Inconnu

Noter ci-dessous les antécédents médicaux pertinents. Inclure les autres pathologies présentes au moment de l'événement et les antécédents médicaux préexistants. Si la place prévue ici n'est pas suffisante, utiliser des exemplaires supplémentaires de la page.

Maladie (préciser)	Date de survenue	Date de fin	Cocher la case si maladie en cours	Informations pertinentes *incluant les interventions chirurgicales et leurs dates*
			☐	
			☐	
			☐	

Médicament à l'étude, Forme pharmaceutique, Voie d'administration	Cocher la case si produit Pfizer	Dosage	Unités	Fréquence	Date de début	Date de fin	Cocher la case si médicament en cours
	☐						☐
	☐						☐
	☐						☐

Médicaments concomitants

☐ Aucun ☐ Inconnu

Reporter ci-dessous les médicaments concomitants pris dans les 2 semaines précédant la survenue de l'évènement. Exclure tous les médicaments pris seulement plus de 2 semaines avant la survenue de l'évènement et tous les médicaments utilisés pour traiter l'évènement ou pris après l'apparition de l'évènement. Si vous manquez d'espace, veuillez utiliser plusieurs copies de cette page.

Nom du médicament (marque déposée et DCI)	Indication	Voie d'administration	Date de début	Date de fin	Cocher la case si médicament en cours
					☐
					☐
					☐

Examens complémentaires pertinents

Reporter seulement les résultats d'examens complémentaires pertinents par rapport à l'(aux) évènement(s), par exemple, analyse de laboratoire et résultat d'imagerie. Si vous manquez d'espace, veuillez utiliser plusieurs copies de cette page.

Examen	Date	Résultat	Unités	Valeurs normales		Commentaires
				Limite inférieure	Limite supérieure	

Etude non-interventionnelle : Formulaire de notification d'évènements indésirables

Cadre réservé à Pfizer
Numéro AER

Ecrire toutes les dates au format JJ/MMM/AAAA

NUMÉRO DE PROTOCOLE / ÉTUDE	NUMÉRO DE CENTRE	IDENTIFICATION PATIENT/NUMERO DE RANDOMISATION

EVENEMENTS INDESIRABLES GRAVES (si plus de 2, utiliser des copies supplémentaires de cette page)
S'il est connu, indiquer le diagnostic plutôt que les signes et symptômes.

Evènement indésirable:	**Evènement indésirable:**
Date de survenue :	**Date de survenue :** .....
L'évènement est-il grave ? : ☐ OUI ☐ NON Si oui, préciser ci-dessous les critères de gravité :	**L'évènement est-il grave ? :** ☐ OUI ☐ NON Si oui, préciser ci-dessous les critères de gravité :
Critère de gravité (un ou plusieurs choix possibles) : ☐ A entraîné le décès ☐ Menace du pronostic vital ☐ Hospitalisation/Prolongation d'hospitalisation ☐ Invalidité/incapacité permanente ou importante ☐ Anomalie / malformation congénitale ☐ Evènement médicalement important	**Critère de gravité (un ou plusieurs choix possibles) :** ☐ A entraîné le décès ☐ Menace du pronostic vital ☐ Hospitalisation/Prolongation d'hospitalisation ☐ Invalidité/incapacité permanente ou importante ☐ Anomalie / malformation congénitale ☐ Evènement médicalement important
Evolution au moment de ce rapport ou au moment du décès : ☐ Guéri } Date de guérison : ..... ☐ Guéri avec séquelles } ☐ En cours de guérison ☐ Non Guéri ☐ Inconnu **Existe-t-il une possibilité raisonnable que l'événement soit lié au médicament à l'étude :** ☐ OUI ☐ NON **Si oui, préciser le médicament à l'étude :** ..... **Existe-t-il une possibilité raisonnable que l'événement soit lié à un médicament concomitant :** ☐ OUI ☐ NON **Si oui, préciser le médicament concomitant :**	**Evolution au moment de ce rapport ou au moment du décès :** ☐ Guéri } Date de guérison : ..... ☐ Guéri avec séquelles } ☐ En cours de guérison ☐ Non Guéri ☐ Inconnu **Existe-t-il une possibilité raisonnable que l'événement soit lié au médicament à l'étude :** ☐ OUI ☐ NON **Si oui, préciser le médicament à l'étude :** ..... **Existe-t-il une possibilité raisonnable que l'événement soit lié à un médicament concomitant :** ☐ OUI ☐ NON **Si oui, préciser le médicament concomitant :** .....
Dernière action entreprise pendant le ou les événements, préciser le nom du médicament : ..... ☐ Arrêt (temporaire ou permanent, ou prise décalée) ☐ Diminution de posologie ☐ Augmentation de posologie ☐ Posologie inchangée ☐ Inconnu ☐ Ne s'applique pas ☐ Arrêt (temporaire ou permanent, ou prise décalée) ☐ Diminution de posologie ☐ Augmentation de posologie ☐ Posologie inchangée ☐ Inconnu ☐ Ne s'applique pas	**Dernière action entreprise pendant le ou les événements, préciser le nom du médicament :** ☐ Arrêt (temporaire ou permanent, ou prise décalée) ☐ Diminution de posologie ☐ Augmentation de posologie ☐ Posologie inchangée ☐ Inconnu ☐ Ne s'applique pas ☐ Arrêt (temporaire ou permanent, ou prise décalée) ☐ Diminution de posologie ☐ Augmentation de posologie ☐ Posologie inchangée ☐ Inconnu ☐ Ne s'applique pas

Un EI/EIG est-il réapparu lors de la ré-administration du médicament ? ☐ Oui ☐ Non ☐ Inconnu ☐ Sans objet

Si oui, quel(s) EIG/EI :

Histoire de l'évènement (Narratif) : *Merci de bien vouloir fournir toute information concernant cet évènement qui ne serait pas rapportée dans un autre champ de ce formulaire (circonstances, chronologie, diagnostic et traitement symptomatique). Si vous manquez d'espace, veuillez utiliser plusieurs copies de cette page.*

Personne du centre effectuant la notification pour le centre :

Nom et prénom EN LETTRES CAPITALES _____ Date _____

Adresse : Rue _____ Ville _____ Code postal _____ Pays _____

N° de téléphone : _____ N° de fax : _____ E-mail : _____

Nom de l'investigateur si différent :

Signature de l'investigateur :

Date de prise de connaissance par l'investigateur (ou nidificateur) : ____-____-____ (JJ MMM AAAA)

13.2. Appendix 2: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

NCI CTCAE (version 4.0) are the reference criteria for this protocol.

The following link provides access to the NCI CTCAE criteria:

http://ctep.cancer.gov/reporting/ctc.html

13.3. Appendix 3: Information letter and consent form for patient with mRCC in CR with Sunitinib (Case)

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 1 of 8
PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016

Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

PART I

I NATURE AND AIM OF THE STUDY

This document is called a patient information letter and informed consent form. It contains detailed explanations about the observational study that you have been invited to participate in as well as a consent form, which you will be required to complete if you decide to participate. You have been invited to participate in this study conducted by Pfizer because you are currently receiving treatment for metastatic renal cell carcinoma.

You are being or have been treated with SUTENT® for your renal carcinoma and, thanks to the treatment, your disease is currently in complete remission, as has been confirmed by radiological examinations. Our aims are to identify the characteristics of patients (clinical or biological) who develop complete remission of renal cell carcinoma and to also search for factors that may favor a possible recurrence of the disease. Long-term, such research aims to improve the therapeutic management of patients with metastatic renal cell carcinoma.

It is a cross-sectional then longitudinal, comparative, multicenter, prospective, observational study with collection of blood samples.

II PROJECT ORGANIZATION

A STUDY PROCEDURES

The protocol for this research provides for you to be followed for 3 years and to have one blood sample taken (or two samples if there is a recurrence during this 3-year period) in order to assay certain substances in it the presence of which might be associated with the development of complete remission or a recurrence (these substances are called "biological and genetic markers"). Apart from these blood samples, this research does not affect the treatment of your disease.

Your participation in this study will involve:

- Authorizing the physician to collect personal data about the characteristics of your cancer, the treatments received to date and your possible associated diseases.
- Authorizing the physician to ask sending and collection of your histological sample before the initiation of Sunitinib
- Having a blood sample collected of approximately 2 x 5 ml for analysis of biological and genetic markers in association with the complete remission of your cancer. Your blood sample will be labeled anonymously.
- In the event of a recurrence of your renal cell carcinoma, completing a second questionnaire on the characteristics of the recurrence as well as having a second blood sample of 2 x 5 ml collected to identify the biological and genetic markers associated with this recurrence.
- As with all sample collection, these blood samples may cause a slight pain or cause a bruise to appear on your arm at the collection site.

During the research, all of the samples collected from subjects participating in the research will be sent and stored at the Institut Gustave Roussy laboratory (114 rue Edouard Vaillant, 94800 Villejuif, France) in order to perform the screening of biological and genetic markers. The storage of these samples will be the responsibility of the directors of those laboratories.

The biological and genetic samples collected will be used exclusively for the research.

By accepting to participate in this study, you'll validate your participation and will be included in the study

By accepting to participate in this study, you also consent to the future use of these samples for anything that concerns the objective of the study. Indeed, new markers will probably be identified as scientific knowledge advances.

At any moment, if you changed your opinion, you can ask the destruction of your samples in asking it to your physician. The sample will be destructed

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 2 of 8
PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016

Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**	
Name of participating physician	Telephone
Name of patient	

B PLANNED DURATION OF THE STUDY AND PLANNED NUMBER OF PATIENTS

If you decide to participate in this study, you will be one of 40 subjects with metastatic renal cell carcinoma treated with SUTENT®, and whose disease is in complete remission, included by one of the participating sites located in metropolitan areas throughout France.

This study will not change your relationship with your physician, who may prescribe any procedure during this consultation, if he deems it to be necessary.

C RESTRICTIONS ASSOCIATED WITH THE STUDY AND INFORMATION FOR THE PATIENT

This study does not have any restrictions that you need to observe.

Should the study result in any harm to you, in compliance with current French law, you will be covered during the entire study by insurance taken out by the sponsor Pfizer.

Contact details of the person to contact for additional information or in case of injury related to the study:

_____

_____

III RESPONSABILITIES, PATIENT'S RIGHTS AND CONFIDENTIALITY

A WITHDRAWAL FROM STUDY

The participating physician, i.e. the physician who suggests this study to you, or the sponsor may decide to discontinue your participation in this study, if:

a) You do not follow the participating physician's instructions

b) You develop a serious condition that would require discontinuation of treatment

c) The study is stopped by the sponsor or the health authorities

B RIGHTS

Your participation in this study is voluntary and entirely of your own free will. Please take the time to read this information leaflet and discuss it with your physician and your family, if you wish. Do not hesitate to ask your physician any questions if you require further information. If you decide not to participate or withdraw from the study for any reason whatsoever, this shall not affect your relationship with the physician who is monitoring you as part of this study, or with your attending physician. If you change your mind and decide not to participate in this supplementary study, you can ask for the destruction of your samples by approaching the study physician. The samples will then be destroyed.

If you have any questions during the course of the study, you should contact the physician monitoring you as part of this study. Pursuant to French law, the protocol describing the study in which you are participating received a favorable opinion from the CCTIRS - ***Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*** (French Advisory Committee for Data Processing in Health Research) on 18/01/2012. The committee is charged with verifying the scientific relevance of the trial, the conditions required for your protection and the upholding of your rights.

The drawing of blood samples was the subject of a prior declaration by the competent authority [ANSM - *Agence Nationale de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety)].

If you want, your attending physician will be informed about your participation in this study.

Following analysis of the data for all patients, you will be informed of the overall results of this study via the physician monitoring you as part of this study.

C DATA CONFIDENTIALITY

All medical records and documentation from this study that identify you will be kept strictly confidential and will not be subject to any disclosure to third parties, to the extent permitted by French laws and/or regulations currently in force. The data gathered regarding you that are identified by a code number will remain anonymous for the future analysis of study results. If the overall results from this study are likely to be communicated or published in the medical literature, only anonymized data will be presented.

In the context of the present study, you accept that designated representatives of the health authorities, representatives of Pfizer, other physicians, nurses and people participating in this study will have access to medical records about you. You agree that these documents shall be communicated under the conditions described above, even if you decide to withdraw from this study.

Data about you recorded during this study for epidemiological evaluation, including data about your lifestyle, will be subject to computer processing by or on behalf of Pfizer. In accordance with French law no. 78-17 of January 6, 1978 on data protection, as amended by French law no. 2004-801 of August 6, 2004 on the protection of individuals with regard to treatment of personal data, you may exercise your rights of access to and rectification of your data. You can exercise those rights at any time by contacting the physician monitoring you as part of the study.

Pfizer owns the data, will control their use and will take all necessary measures to ensure their protection.

IV PARTICIPATING PHYSICIAN'S COMPENSATION

The participating physician receives financial compensation from the sponsor for this study.

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 4 of 8

PATIENT IN COMPLETE REMISSION - CASES			
	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone
Name of patient	

CONSENT FORM FOR PARTICIPATION IN THE STUDY

Dr ..... invited me to participate in a study conducted by Pfizer on the treatment of metastatic renal cell carcinoma entitled: **"A PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA"**

I have reached the age of majority.

I belong to a social security scheme or am a beneficiary of such a scheme.

I have read the information above and have fully understood it. I was given the time and opportunity to ask any questions I wanted to about the study and this form.

I have read all pages of this consent form and have understood the risks and benefits described.

I have been informed that I will be covered by insurance taken out by the sponsor, Pfizer, pursuant to current French legislation.

I understand that data concerning me will remain strictly confidential. I consent to them being consulted only by members of Pfizer, their representatives, any service providers under contract to Pfizer and by the various regulatory authorities, provided that Pfizer is committed to respecting the confidentiality of the data pursuant to law no. 78-17 of January 6, 1978.

I accept that the data recorded during this study will be subject to computerization by Pfizer or on its behalf. I understand that my right of access and of rectification, as provided by law no. 78-16 of January 6, 1978 relating to data processing, data files and individual liberties, as amended by law no. 2004-801 of August 6, 2004 relating to the protection of individuals with regard to the processing of personal data, may be exercised at any time from Pfizer via the physician monitoring me during this study.

It was explained to me that I am free to accept or refuse to participate in this study and to withdraw from the study at any time without this changing my relationship with my physician. Signature of this consent form does not discharge Pfizer from its responsibilities and I retain all my rights as guaranteed by law.

I agree that the results of the study may be published and communicated to the authorities concerned and to Pfizer. I freely agree to participate in this study under the conditions specified in this document.

By signing this consent form I confirm that all of the information I have provided, particularly concerning my medical history, is accurate to the best of my knowledge.

I understand that I will be given a copy of this signed consent form.

The patient	***The participating physician***
Surname / First name in capital letters:	Surname / First name of participating physician in capital letters:
_____	Dr / Prof: ----------
Date: ----------	Date: ----------
Patient's signature:	Participating physician's signature:

Sponsor: PFIZER
23-25, avenue du Dr Lannelongue
75668 PARIS Cedex 14, France

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PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**
Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**		
Name of participating physician	Telephone	
Name of patient		

Part II

Study title: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Use and storage of blood samples for CCI research

Investigator's name:	Telephone number
Name of patient:	

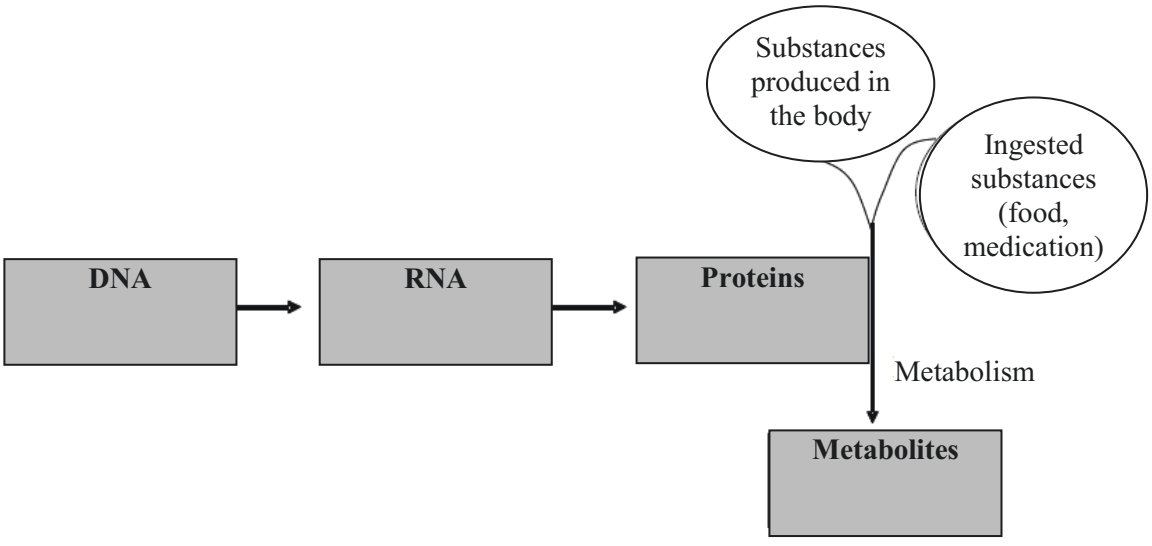
Part I of this consent form describes the main part of the biomedical research on SUTENT®.

Part II below requires your consent in order to be able to use a blood and histological sample to study your genes, also called DNA and cellular biomarkers.

However, if you do not want to provide these additional samples, you can still participate in the main study described in Part I of the consent form.

WHAT IS THE PURPOSE OF THIS RESEARCH?

Blood contains genes. The genes provide instructions that govern different processes taking place in the body and physical characteristics such as eye color. Genes differ slightly from one person to another. Information on these differences between individuals allows researchers to learn more about diseases, the best way to treat them and to understand how each one responds to medication.



Pfizer	**Patient information leaflet and informed consent form**	**Page:** 6 of 8
PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**
Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**		
Name of participating physician	Telephone number	
Name of patient		

The objective of this study is to collect, store and use your blood sample to study the genes, RNA, proteins and metabolites. Your sample will be studied only with reference to the following:

- Analysis of genetic polymorphisms of VEGF-A (SNPs) in patients receiving Sunitinib in CR (cases) and selected as controls.
- To determine whether this polymorphism correlates with complete remission or progression.
- To determine whether polymorphisms of VEGF can reduce the response rate of patients receiving Sunitinib. All information enabling it to be identified as your sample will be deleted.

CCI [redacted]

[redacted]

This research could contribute to developing new treatments or improving existing treatments. The sample will be stored until it is used up or destroyed at Pfizer's discretion of, which may take several years. The information obtained following its analysis will be saved indefinitely. This will allow researchers to continue their investigations on genes in the future that have not yet been discovered today.

No genetic research in addition to the objectives described above will be carried out.

The samples will be stored by the Institut Gustave Roussy (IGR), 114 rue Edouard Vaillant, 94800 Villejuif, France.

Pursuant to current French legislation:

- The protocol describing this research:
  - Has received a favorable opinion from CCTIRS - *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (French Advisory Committee for Data Processing in Health Research).
  - Has been declared to the competent authority [ANSM - *Agence Nationale de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety)].
- Pfizer has taken out civil liability insurance covering any health problems in connection with your participation in this research.

WHAT WILL HAPPEN IF I PARTICIPATE IN THIS RESEARCH?

If you participate in this research, analyzes will be done on samples taken in the context of this observational study. ON :

- VGEF-A (SNPS) Genetic polymorphism
- Cellular marker

WHAT ARE THE BENEFITS ASSOCIATED WITH MY PARTICIPATION?

You are not expected to benefit from your participation in this supplementary research. On the other hand, the knowledge acquired thanks to this research may benefit other people.

WILL MY DATA BE CONFIDENTIAL?

As described in Part I, all data will remain strictly confidential and anonymized. The results of this part of the study are liable to be published for scientific purposes, but under no circumstances will your identity be revealed. Consequently, neither you nor any other person will be able to obtain the results of any genetic analysis performed on your sample.

Before being relabeled, your sample will be treated as "sensitive personal data".

By participating in this study, you agree that (1) the research team, (2) Pfizer's representatives and authorized companies, (3) the EC that approved this study and (4) national and international regulatory authorities can have access to and examine your medical records in order to (a) conduct the study, (b) check the accuracy of the data, (c) monitor that it is being conducted in accordance with good clinical practice and the law and (d) conduct other research associated with the study.

	Patient information leaflet and informed consent form	**Page:** 7 of 8
PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016

Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**	
Name of participating physician	Telephone
Name of patient	

WHO WILL HAVE OWNERSHIP OF MY SAMPLE(S)?

Pfizer will ensure that the samples are used in accordance with the objectives of this supplementary study, the associated informed consent form and the ethical approval received.

The study sponsor will not sell or transfer ownership of the sample to any third parties. The samples will only be used by Pfizer and/or researchers working with Pfizer, and only as part of the research study described above. Pfizer may use information from your sample in order to develop products or procedures from which it may make a profit. Pfizer intends to retain the exclusive rights to any products and processes that are developed using information from your sample. You will not receive any payments for products of any kind that are developed thanks to this research.

WHAT WILL HAPPEN IF I DECIDE TO NO LONGER PARTICIPATE IN THE STUDY?

If you change your mind and decide not to participate in this supplementary study, you can ask for the destruction of your samples by approaching the study physician (in this case, they will be destroyed). However, once your identity no longer appears on the sample (during the analyses), it will no longer be possible to have it destroyed.

Your participation in this biomedical research is voluntary and entirely of your own free will. If you decide not to participate in it or you withdraw from this research for any reason whatsoever, you will continue to receive the same advantages that you were able to before. This will in no way affect your relationship with the physician monitoring you as part of this research, as well as with your attending physician. If you so wish, you may be given time to reflect.

If you decide to withdraw from this research, you must inform the study physician. In the absence of this information from you, s/he will be required to contact you again in order to confirm your decision. If you withdraw from the study, no new information concerning you will be collected, however information that has already been collected may be used.

MY CONTACT DETAILS

Consenting to this supplementary part of the study is completely optional and separate from the consent given to participation in the clinical study on the medicinal product (Part I).

Before deciding to participate in this part of the study, you will be given time to study the information contained in this form. If you have any questions regarding this research and/or your rights, please contact:

NAME OF PHYSICIAN TO CONTACT	**Telephone number**
Dr / Prof:	Tel.: Email:

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 8 of 8
PATIENT IN COMPLETE REMISSION - CASES		
	Protocol no.: A6181209	**Date**: 11/04/2016

Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone
Name of patient	

CONSENT FORM FOR PARTICIPATION IN THE STUDY

Study title: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Dr Invited me to participate in an observational study organized by Pfizer.

This consent form relates to the supplementary pharmacogenomics study to describe the characteristics of patients with mRCC and presenting CR (Cases) with Sunitinib and to compare them with the characteristics of patients with mRCC and not presenting CR (Controls) with Sunitinib in order to identify factors associated with the occurrence of complete remission.

I have understood the information above. I was given the time and opportunity to ask any questions I wanted to about the research and this form and all of my questions were answered.

It was explained to me that I am free to accept or refuse to participate in this study and to withdraw from the study at any time without this changing my relationship with my physician. Signature of this consent form does not discharge Pfizer from its responsibilities and I retain all my rights as guaranteed by law.

By signing this consent form, I confirm that:

- I have reached the age of majority
- I belong to a social security scheme or am a beneficiary of such a scheme.

I was informed that:

- I will be covered during this biomedical research by the insurance taken out by Pfizer.
- Data pertaining to me will remain strictly confidential. I authorize access to the data to Pfizer, its representatives, any service provider under contract to Pfizer and the various regulatory authorities.

I accept that:

- The data recorded during this research will be subject to computerization by Pfizer or on its behalf. I understand that I may exercise my right of access and rectification from Pfizer at any time via the physician monitoring me for this research.
- The data will be collected, used and transferred in accordance with the conditions described.

I therefore freely agree to participate in this biomedical research under the conditions specified in this document and a signed copy of this patient information leaflet and informed consent form will be returned to me.

The patient (Surname / First name of patient in capital letters)	***The participating physician*** (Surname / First name of participating physician in capital letters)
----------	Dr / Prof ----------
Patient's signature: Date: ----------	Participating physician's signature: Date: ----------

The impartial witness * / legal guardian / family member ** / trusted person ** / guardianship judge
_____
Surname / First name in capital letters
_____ _____
Signature Date

* Impartial witness: a person who actually attended an event and can validly attest to this. S/he has no personal interest in the patient's consenting and is totally independent of the investigator and of the sponsor.

** Trusted person / Family member: person, freely chosen by the patient from his/her circle of family and friends and in whom s/he has complete confidence independent of the context of the clinical trial and who cannot be unfairly influenced. This person assists with informing the patient and with the obtaining of the informed consent if the patient or his/her legal guardian are unable to read. S/he reads the informed consent form and all other written information given to the patient.

* & ** pursuant to the articles of the French Public Health Code: article L 1122-1-1 and article L 1111-6.

13.4. Appendix 4: Patient information leaflet and consent form for patients with mRCC selected as controls and treated with Sunitinib

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 35 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

PART I

I NATURE AND AIM OF THE STUDY

This document is called a patient information letter and informed consent form. It contains detailed explanations about the observational study that you have been invited to participate in as well as a consent form, which you will be required to complete if you decide to participate. You have been invited to participate in this study conducted by Pfizer because you are currently receiving treatment for metastatic renal cell carcinoma.

You will be treated for metastatic renal cell carcinoma with a targeted therapy called SUTENT®. Our aims are to identify the characteristics of patients (clinical or biological) likely to favor complete remission (CR) of renal cell carcinoma with SUTENT® and to also search for factors that may favor a possible recurrence of the disease as well as factors that determine the response to treatments. Long-term, such research aims to improve the therapeutic management of patients with metastatic renal cell carcinoma.

II PROJECT ORGANIZATION

A STUDY PROCEDURES

The protocol for this research provides for you to be followed for 3 years and to have a blood sample drawn at inclusion, 6 months, 12 months and during disease progression, if it occurs.

These blood samples are collected in order to assay certain substances the presence of which might be linked to attaining complete remission or to the appearance of a recurrence (these substances are called "biological and genetic markers"). Apart from these blood samples, this research does not affect the treatment of your disease.

Your participation in this study will involve:

- Authorizing the physician to collect personal data about the characteristics of your cancer, the treatments received to date and your possible associated diseases.
- Authorizing the physician to request the sending and the preservation of your histological sample made before the initiation of sunitinib.
- Having a blood sample collected of approximately 2 x 5 ml for identification of biological and genetic markers present during your inclusion in the study. Your blood sample will be labeled anonymously.
- Having a blood sample collected of approximately 2 x 5 ml for identification of biological and genetic markers present during your 6-month and 12-month visits. Your blood sample will be labeled anonymously.
- In the event of a progression of your renal cell carcinoma, completing a second questionnaire on the characteristics of that progression as well as having a second blood sample of around 2 x 5 ml collected to identify the biological and genetic markers.
- In the event of a complete remission of your renal cell carcinoma, completing a second questionnaire on the characteristics of the complete remission as well as having a second blood sample of around 2 x 5 ml collected to identify the biological and genetic markers that are predictive of this CR.

As with all sample collection, these samples may cause a slight pain or cause a bruise on your arm at the collection site.

During the research, all of the samples collected from subjects participating in the research will be sent and stored at the Institut Gustave Roussy laboratories (114 rue Edouard Vaillant, 94800 Villejuif, France) in order to perform the screening of biological and genetic markers. The storage of this biological material will be the responsibility of the directors of those laboratories.

The biological and genetic samples collected will be used exclusively for the research.

By accepting to participate in this study, you also consent to the future use of these samples for anything that concerns the objective of the study. Indeed, new markers will probably be identified as scientific knowledge advances.

	Patient information leaflet and informed consent form	**Page:** 2 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

B PLANNED DURATION OF THE STUDY AND PLANNED NUMBER OF PATIENTS

If you decide to participate in this study, you will be one of 80 subjects with metastatic renal cell carcinoma treated with SUTENT® and included by 5 of the participating sites l'Institut Gustave Roussy de Villejuif, l'Hôpital Européen Georges Pompidou de Paris, l'Hôpital Civil de Strasbourg, l'Institut Calmette de Marseille and l'hôpital Nord de Marseille.

The maximum duration of your participating in this study will be 3 years (36 months).

This study will not change your relationship with your physician, who may prescribe any procedure during this consultation, if he deems it to be necessary.

C RESTRICTIONS ASSOCIATED WITH THE STUDY AND INFORMATION FOR THE PATIENT

This study does not have any restrictions that you need to observe.

Should the study result in any harm to you, in compliance with current French law, you will be covered during the entire study by insurance taken out by the sponsor Pfizer.

Contact details of the person to contact for additional information or in case of injury related to the study:

_____

_____

III RESPONSABILITIES, PATIENT'S RIGHTS AND CONFIDENTIALITY

A WITHDRAWAL FROM STUDY

The participating physician, i.e. the physician who suggests this study to you, or the sponsor may decide to discontinue your participation in this study, if:

a) You do not follow the participating physician's instructions

b) You develop a serious condition that would require discontinuation of treatment

c) The study is stopped by the sponsor or the health authorities

B RIGHTS

Your participation in this study is voluntary and entirely of your own free will. Please take the time to read this information leaflet and discuss it with your physician and your family, if you wish. Do not hesitate to ask your physician any questions if you require further information. If you decide not to participate or withdraw from the study for any reason whatsoever, this shall not affect your relationship with the physician who is monitoring you as part of this study, or with your attending physician. If you change your mind and decide not to participate in this supplementary study, you can ask for the destruction of your samples by approaching the study physician. The samples will then be destroyed.

If you have any questions during the course of the study, you should contact the physician monitoring you as part of this study.

Pursuant to French law, the protocol describing the study in which you are participating received a favorable opinion from the CCTIRS - *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (French Advisory Committee for Data Processing in Health Research) on 18/01/2012. The committee is charged with verifying the scientific relevance of the trial, the conditions required for your protection and the upholding of your rights.

The drawing of blood samples was the subject of a prior declaration by the competent authority [ANSM - *Agence Nationale de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety)].

If you want, your attending physician will be informed about your participation in this study.

Following analysis of the data for all patients, you will be informed of the overall results of this study via the physician monitoring you as part of this study.

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PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

C DATA CONFIDENTIALITY

All medical records and documentation from this study that identify you will be kept strictly confidential and will not be subject to any disclosure to third parties, to the extent permitted by French laws and/or regulations currently in force. The data gathered regarding you that are identified by a code number will remain anonymous for the future analysis of study results. If the overall results from this study are likely to be communicated or published in the medical literature, only anonymized data will be presented.

In the context of the present study, you accept that designated representatives of the health authorities, representatives of Pfizer, other physicians, nurses and people participating in this study will have access to medical records about you. You agree that these documents shall be communicated under the conditions described above, even if you decide to withdraw from this study.

Data about you recorded during this study for epidemiological evaluation, including data about your lifestyle, will be subject to computer processing by or on behalf of Pfizer. In accordance with French law no. 78-17 of January 6, 1978 on data protection, as amended by French law no. 2004-801 of August 6, 2004 on the protection of individuals with regard to treatment of personal data, you may exercise your rights of access to and rectification of your data. You can exercise those rights at any time by contacting the physician monitoring you as part of the study.

Pfizer owns the data, will control their use and will take all necessary measures to ensure their protection.

IV PARTICIPATING PHYSICIAN'S COMPENSATION

The participating physician receives financial compensation from the sponsor for this study.

	Patient information leaflet and informed consent form	**Page:** 4 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

I CONSENT FORM FOR PARTICIPATION IN THE STUDY

Dr ..... invited me to participate in a study conducted by Pfizer on the treatment of metastatic renal cell carcinoma entitled: **"A PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA"**

I have reached the age of majority.

I belong to a social security scheme or am a beneficiary of such a scheme.

I have read the information above and have fully understood it. I was given the time and opportunity to ask any questions I wanted to about the study and this form. I have read all pages of this consent form and have understood the risks and benefits described.

I have been informed that I will be covered by insurance taken out by the sponsor, Pfizer, pursuant to current French legislation.

I understand that data concerning me will remain strictly confidential. I consent to them being consulted only by members of Pfizer, their representatives, any service providers under contract to Pfizer and by the various regulatory authorities, provided that Pfizer is committed to respecting the confidentiality of the data pursuant to law no. 78-17 of January 6, 1978.

I accept that the data recorded during this study will be subject to computerization by Pfizer or on its behalf. I understand that my right of access and of rectification, as provided by law no. 78-16 of January 6, 1978 relating to data processing, data files and individual liberties, as amended by law no. 2004-801 of August 6, 2004 relating to the protection of individuals with regard to the processing of personal data, may be exercised at any time from Pfizer via the physician monitoring me during this study.

It was explained to me that I am free to accept or refuse to participate in this study and to withdraw from the study at any time without this changing my relationship with my physician. Signature of this consent form does not discharge Pfizer from its responsibilities and I retain all my rights as guaranteed by law.

I agree that the results of the study may be published and communicated to the authorities concerned and to Pfizer. I freely agree to participate in this study under the conditions specified in this document.

By signing this consent form I confirm that all of the information I have provided, particularly concerning my medical history, is accurate to the best of my knowledge.

I understand that I will be given a copy of this signed consent form.

The patient	***The participating physician***
Surname / First name in capital letters:	Surname / First name of participating physician in capital letters:
_____	Dr / Prof: ----------
Date:----------	Date: ----------
Patient's signature:	Participating physician's signature:

Sponsor: PFIZER
23-25, avenue du Dr Lannelongue
75668 PARIS Cedex 14, France

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 5 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

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Name of participating physician	Telephone number
Name of patient	

Part II

Study title: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Use and storage of blood samples for exploratory research

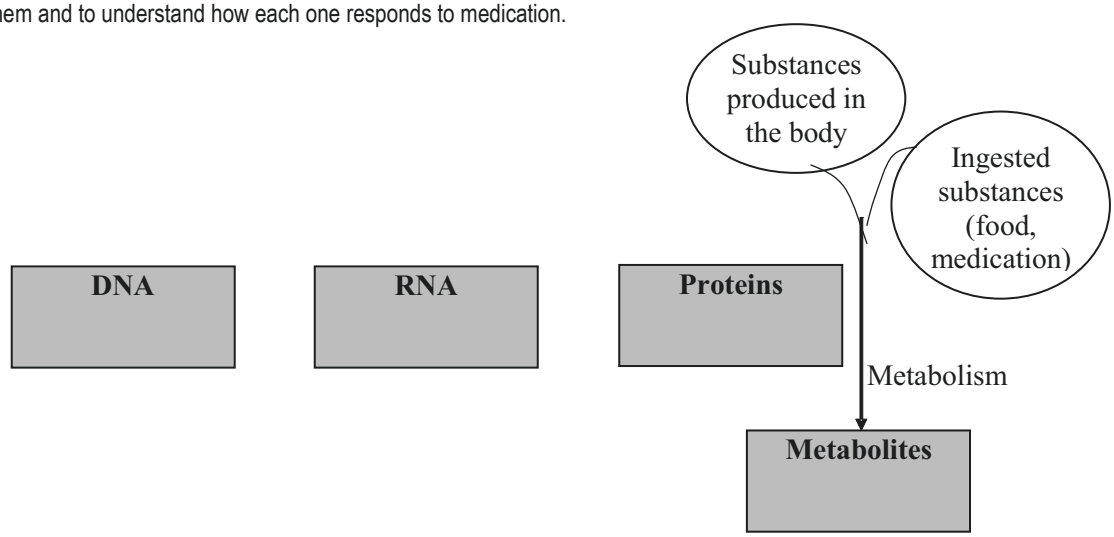
Investigator's name:	Telephone number
Name of patient:	

Part I of this consent form describes the main part of the biomedical research on SUTENT®.

Part II below requires your consent in order to be able to use a blood and histological sample to study your genes, also called DNA.and cellular markers.
However, if you do not want to provide these additional samples, you can still participate in the main study described in Part I of the consent form.

WHAT IS THE PURPOSE OF THIS RESEARCH?

Blood contains genes. The genes provide instructions that govern different processes taking place in the body and physical characteristics such as eye color. Genes differ slightly from one person to another. Information on these differences between individuals allows researchers to learn more about diseases, the best way to treat them and to understand how each one responds to medication.



The objective of this study is to collect, store and use your blood sample to study the genes, RNA, proteins and metabolites. Your sample will be studied only with reference to the following:

- Analysis of genetic polymorphisms of VEGF-A (SNPs) in patients receiving Sunitinib in CR (cases) and selected as controls.
- To determine whether this polymorphism correlates with complete remission or progression.
- To determine whether polymorphisms of VEGF can reduce the response rate of patients receiving Sunitinib.

CCI [redacted]

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 6 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

This research could contribute to developing new treatments or improving existing treatments. The sample will be stored until it is used up or destroyed at Pfizer's discretion of, which may take several years. The information obtained following its analysis will be saved indefinitely. This will allow researchers to continue their investigations on genes in the future that have not yet been discovered today.

No genetic research in addition to the objectives described above will be carried out.

The samples will be stored by the Institut Gustave Roussy (IGR), 114 rue Edouard Vaillant, 94800 Villejuif, France.

Pursuant to current French legislation:

- The protocol describing this research:
  - Has received a favorable opinion from CCTIRS - *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (French Advisory Committee for Data Processing in Health Research).
  - Has been declared to the competent authority [ANSM - *Agence Nationale de Sécurité du Médicament* (The French National Agency for Medicines and Health Products Safety)].
- Pfizer has taken out civil liability insurance covering any health problems in connection with your participation in this research.

WHAT WILL HAPPEN IF I PARTICIPATE IN THIS RESEARCH?

If you participate in this research, analysis will be performed on samples taken in the context of this observational study.

- VGEF-A (SNPs) polymorphisms genetic
- Cellular markers

WHAT ARE THE BENEFITS ASSOCIATED WITH MY PARTICIPATION?

You are not expected to benefit from your participation in this supplementary research. On the other hand, the knowledge acquired thanks to this research may benefit other people.

WILL MY DATA BE CONFIDENTIAL?

As described in Part I, all data will remain strictly confidential and anonymized. The results of this part of the study are liable to be published for scientific purposes, but under no circumstances will your identity be revealed. Consequently, neither you nor any other person will be able to obtain the results of any genetic analysis performed on your sample.

Before being relabeled, your sample will be treated as "sensitive personal data".

By participating in this study, you agree that (1) the research team, (2) Pfizer's representatives and authorized companies, (3) the EC that approved this study and (4) national and international regulatory authorities can have access to and examine your medical records in order to (a) conduct the study, (b) check the accuracy of the data, (c) monitor that it is being conducted in accordance with good clinical practice and the law and (d) conduct other research associated with the study.

WHO WILL HAVE OWNERSHIP OF MY SAMPLE(S)?

Pfizer will ensure that the samples are used in accordance with the objectives of this supplementary study, the associated informed consent form and the ethical approval received.

The study sponsor will not sell or transfer ownership of the sample to any third parties. The samples will only be used by Pfizer and/or researchers working with Pfizer, and only as part of the research study described above. Pfizer may use information from your sample in order to develop products or procedures from which it may make a profit. Pfizer intends to retain the exclusive rights to any products and processes that are developed using information from your sample. You will not receive any payments for products of any kind that are developed thanks to this research.

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 7 of 8
PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS		
	Protocol no.: A6181209	**Date**: 11/04/2016

Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

WHAT WILL HAPPEN IF I DECIDE TO NO LONGER PARTICIPATE IN THE STUDY?

If you change your mind and decide not to participate in this supplementary study, you can ask for the destruction of your samples by approaching the study physician (in this case, they will be destroyed). However, once your identity no longer appears on the sample (during the analyses), it will no longer be possible to have it destroyed.

Your participation in this biomedical research is voluntary and entirely of your own free will. If you decide not to participate in it or you withdraw from this research for any reason whatsoever, you will continue to receive the same advantages that you were able to before. This will in no way affect your relationship with the physician monitoring you as part of this research, as well as with your attending physician. If you so wish, you may be given time to reflect.

If you decide to withdraw from this research, you must inform the study physician. In the absence of this information from you, s/he will be required to contact you again in order to confirm your decision. If you withdraw from the study, no new information concerning you will be collected, however information that has already been collected may be used.

MY CONTACT DETAILS

Consenting to this supplementary part of the study is completely optional and separate from the consent given to participation in the clinical study on the medicinal product (Part I).

Before deciding to participate in this part of the study, you will be given time to study the information contained in this form. If you have any questions regarding this research and/or your rights, please contact:

NAME OF PHYSICIAN TO CONTACT	**Telephone number**
Dr / Prof:	Tel.: Email:

Pfizer	**Patient information leaflet and informed consent form**	**Page:** 8 of 8

PATIENT WITH MRCC AND TREATED WITH SUTENT - CONTROLS

	Protocol no.: A6181209		**Date**: 11/04/2016
Location	**Language: French**	**Site no.: All sites**	**Country: France**

Protocol title: **APERCU study: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA**

Name of participating physician	Telephone number
Name of patient	

CONSENT FORM FOR PARTICIPATION IN THE STUDY

Study title: PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Dr Invited me to participate in a biomedical study organized by Pfizer.

This consent form relates to the supplementary pharmacogenomics study to describe the characteristics of patients with mRCC and presenting CR (Cases) with Sunitinib and to compare them with the characteristics of patients with mRCC and not presenting CR (Controls) with Sunitinib in order to identify factors associated with the occurrence of complete remission.

I have understood the information above. I was given the time and opportunity to ask any questions I wanted to about the research and this form and all of my questions were answered.

It was explained to me that I am free to accept or refuse to participate in this study and to withdraw from the study at any time without this changing my relationship with my physician.

Signature of this consent form does not discharge Pfizer from its responsibilities and I retain all my rights as guaranteed by law.

By signing this consent form, I confirm that:

- I have reached the age of majority
- I belong to a social security scheme or am a beneficiary of such a scheme.

I was informed that:

- I will be covered during this biomedical research by the insurance taken out by Pfizer.
- Data pertaining to me will remain strictly confidential. I authorize access to the data to Pfizer, its representatives, any service provider under contract to Pfizer and the various regulatory authorities.

I accept that:

- The data recorded during this research will be subject to computerization by Pfizer or on its behalf. I understand that I may exercise my right of access and rectification from Pfizer at any time via the physician monitoring me for this research.
- The data will be collected, used and transferred in accordance with the conditions described.

I therefore freely agree to participate in this biomedical research under the conditions specified in this document and a signed copy of this patient information leaflet and informed consent form will be returned to me.

The patient (Surname / First name of patient in capital letters)	***The participating physician*** (Surname / First name of participating physician in capital letters)
----------	Dr / Prof ----------
Patient's signature: Date: ----------	Participating physician's signature: Date: ----------
The impartial witness * / legal guardian / family member ** / trusted person ** / guardianship judge	* Impartial witness: a person who actually attended an event and can validly attest to this. S/he has no personal interest in the patient's consenting and is totally independent of the investigator and of the sponsor.
_____ Surname / First name in capital letters	** Trusted person / Family member: person, freely chosen by the patient from his/her circle of family and friends and in whom s/he has complete confidence independent of the context of the clinical trial and who cannot be unfairly influenced. This person assists with informing the patient and with the obtaining of the informed consent if the patient or his/her legal guardian are unable to read. S/he reads the informed consent form and all other written information given to the patient.
_____ _____ Signature Date	* & ** pursuant to the articles of the French Public Health Code: article L 1122-1-1 and article L 1111-6

13.5. Appendix 5: Case report form for patients with mRCC in complete remission (Cases)

CASE REPORT FORM

PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

Cross-sectional then longitudinal, descriptive, multicenter, prospective study with 3-year patient follow-up and compilation of a biobank

APERÇU protocol

Identification no.: A6181209

Favorable opinion from CCTIRS on 18/01/2012

Patient code

Site no.: Patient number, allocated by the site

Investigator: Dr_____

CR SCREENING VISIT

Patient code: |___|___||___|___|___|

Consent form signature date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Screening visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

INCLUSION CRITERIA :

		YES	NO
1.	Adult patients (≥ 18 years)	☐	☐
2.	Patients with mRCC confirmed by histological analysis	☐	☐
3.	Treated with Sunitinib according to a regimen in the text of the SmPC	☐	☐
4.	Presenting a complete remission in the preceding 5 years (according to RECIST v1.1) with Sunitinib only or combined with localized treatment (surgery, radiotherapy, cryoablation or radiofrequency ablation)		
5.	Patients of childbearing age using a mandatory method of contraception		
6.	Affiliated to a social security scheme	☐	☐
7.	Informed about the study methods and having given their consent	☐	☐
		☐	☐
		☐	☐

EXCLUSION CRITERIA

		YES	NO
8.	Complete remission occurring in the absence of treatment with Sunitinib	☐	☐

Date of birth (mm/yyyy): |___|___| |___|___|___|___|

Date of diagnosis of initial renal cancer |___|___| |___|___| |_2_|_0_|_ _|___| (dd/mm/yyyy)

Date of diagnosis of metastatic renal cell carcinoma |___|___| |___|___| |_2_|_0_|_ _|___| (dd/mm/yyyy)

SUNITINIB start date |___|___| |___|___| |_2_|_0_|__|___| (dd/mm/yyyy)

Metastatic sites at start of SUNITINIB

LOCALIZATION OF METASTASES	YES	NO
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐

(please specify): ……..

NUMBER OF METASTATIC SITES: |___|

CR date |___|___| |___|___| |_2_|_0_|__|___| (dd/mm/yyyy)

Complete remission obtained by:	YES	NO	
- Medical treatment only	☐	☐	
- Combined with localized treatment	☐	☐	
If yes:			
o Surgery	☐	☐	Site: .....
o Radiotherapy	☐	☐	Site: .....
o Radiofrequency	☐	☐	Site: .....
o Cryoablation	☐	☐	Site: .....
o Metastasectomy	☐	☐	Site: .....
o Other	☐	☐	Site: .....

Radiological assessment of the complete remission (RECIST v 1.1 criteria)	YES	NO
- Disappearance of target lesions	☐	☐
- All target or non-target lymph nodes < 10 mm	☐	☐
- Disappearance of non-target lesions	☐	☐
- Absence of new lesions	☐	☐

SAMPLING DURING SCREENING VISIT		
	YES	**NO**
- Blood sample of 2 times 5 ml	☐	☐
Sampling date | __ | __ || __ | __ || 2 | 0 | 1 | __ | (dd/mm/yyyy)		
Histological sample of primitive tumor	☐	☐
Sampling date | __ | __ || __ | __ || 2 | 0 | 1 | __ | (dd/mm/yyyy)		

INCLUSION

DEMOGRAPHIC DATA

Consultation date	|___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)
DEMOGRAPHIC DATA	
Age	|___|___| years
Sex	☐ Male ☐ Female
Height (cm)	|___|___|___|
Weight (kg)	|___|___|___|. |___|

DATA RELATING TO THE STATUS OF A PATIENT IN COMPLETE REMISSION AT START OF SUNITINIB

Date of initial diagnosis of renal carcinoma |___\|___\| \|___\|___\| \|_2_\|_0_\|__\|___\| (dd/mm/yyyy)
Date of initial diagnosis of metastatic renal cell carcinoma
|___\|___\| \|___\|___\| \|_2_\|_0_\|_1_\|___\| (dd/mm/yyyy)

NEPHRECTOMY

Nephrectomy ☐ YES ☐ NO If yes, date |___\|___\| |___\|___\| |_2_\|_0_\|_1_\|___\| (dd/mm/yyyy)

- Type of nephrectomy:
  - ☐ radical
  - ☐ with adrenalectomy
  - ☐ with lymphadenectomy
  - ☐ open
  - ☐ partial
  - ☐ without adrenalectomy
  - ☐ without lymphadenectomy
  - ☐ laparoscopic

HISTOLOGY

	YES	NO
• Pathoanatomic classification:		
- Clear cell carcinoma	☐	☐
- Papillary cell carcinoma	☐	☐
- Chromophobe cell carcinoma	☐	☐
- Bellini's collecting duct carcinoma	☐	☐
- Medullary cell carcinoma	☐	☐
- Sarcomatoid contingent	☐	☐
- Other (please specify):		
• TNM classification: T |___| N |___| M |___|		
• Fuhrman nuclear grade: I |___| II |___| III |___| IV |___|		
	YES	NO
• Presence of necrosis?	☐	☐
• Vascular embolism	☐	☐

DATA RELATING TO THE STATUS OF A PATIENT IN COMPLETE REMISSION AT START OF SUNITINIB

Sunitinib start date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

METASTATIC SITES

LOCALIZATION OF METASTASES	YES	NO
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):	☐	☐

NUMBER OF METASTATIC SITES: |___|

MSKCC PROGNOSTIC CLASSIFICATION

☐ Good prognosis (0 pejorative factors)
☐ Moderate diagnosis (1 or 2 pejorative factors)
☐ Good diagnosis (more than 2 pejorative factors)

DATA RELATING TO COMPLETE REMISSION

Complete remission date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

• Complete remission obtained by:	YES	NO	
- Medical treatment only	☐	☐	
- Combined with localized treatment	☐	☐	
If yes:			
o Surgery	☐	☐	Site: .....
o Radiotherapy	☐	☐	Site: .....
o Radiofrequency	☐	☐	Site: .....
o Cryoablation	☐	☐	Site: .....
o Metastasectomy	☐	☐	Site: .....
o Other	☐	☐	Site: .....

RADIOLOGICAL ASSESSMENT OF THE COMPLETE REMISSION (RECIST v 1.1 criteria)

	YES	NO
- Disappearance of all known target lesions	☐	☐
- Disappearance of all non-target lesions	☐	☐
- No appearance of new lesions	☐	☐
- All target or non-target lymph nodes < 10 mm	☐	☐

TREATMENT STRATEGY FOLLOWING COMPLETE REMISSION

	YES	NO
- Continuation of Sunitinib treatment	☐	☐
- Discontinuation of Sunitinib treatment	☐	☐

SAMPLING BEFORE START OF SUNITINIB

*** A delay of 6 weeks is tolerated between initiation and sampling**

	YES	NO
- Blood sample of 2 times 5 ml	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		
Histological sample of primitive tumor	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

ANNUAL VISIT FOLLOWING A CR

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (jjmmaaaa)
If a Sunitinib complementary treatment (pseudo adjuvant) is realised since the CR, could you indicate the duration |___|___| (month)

Disease State

- Desease evolution : **- Complete Response** ☐
  - Partial Respsonse ☐
  - Progression ☐ **(Thanks to complete the disease progression follow-up visit)**
  - Stabilisation ☐
  - No evaluated ☐

Modification treatmentt.

- Sunitinib treatment always on going :

Actual dosage; |___|___| , |___|___| mg / j

Actual schema : 4/2 ☐
2 /1 ☐
Continuous ☐
Other ☐

- Sunitinib temporary cessation:

Sunitinib temporary cessation duration |___|___| (days)
Sunitinib cessation date: |___|___| |___|___| |_2_|_0_|_ _|___| (jjmmaaaa)
Temporary cessation Reason: Progression ☐
Intolérance ☐ **(Thanks to complete Adverse Event form)**
Complete Response ☐
Local treatment ☐
Other ☐
……

Has the sunitinib been taken back? Yes ☐ No ☐
If yes, Sunitinib recovery date |___|___| |___|___| |_2_|_0_|_ _|___| (jjmmaaaa)

Définitive Cessation
Sunitinib cessation date : |___|___| |___|___| |_2_|_0_|_ _|___| (jjmmaaaa)
Cessation reason : Progression ☐
Intolerance ☐ **(Thanks to complete Adverse Event form)**
Complete Response Retention ☐
Doctor / Patient choice ☐
Other ☐ **……**

DISEASE PROGRESSION VISIT FOLLOWING A CR

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)
If additional treatment with Sunitinib was given after the complete remission (pseudo-adjuvant), could you please indicate the duration |___|___| (months)

LOCALIZED OR DISTANT PROGRESSION

LOCAL PROGRESSION **YES** ☐ **NO** ☐

DISTANT PROGRESSION **YES** ☐ **NO** ☐

If yes: **Progression at a known metastatic site** Yes ☐No ☐

New metastatic site Yes ☐No ☐

METASTATIC SITES

LOCALIZATION OF METASTASES	**YES**	**NO**
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):.....	☐	☐

BLOOD SAMPLING DURING PROGRESSION

	YES	**NO**
- Blood sample of 2 times 5 ml	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

studyS OF SYSTEMIC TREATMENT OF THE PROGRESSION			
	Route of administration	Duration of administration	Daily dosage
Anti-VEGF - Bevacizumab (with interferon) ..... - Bevacizumab (without interferon)	 …… ……	 …… ……	 …… ……
Tyrosine kinase inhibitor - Restart of Sunitinib ..... - Sorafenib.....	 …… ……	 …… ……	 …… ……
mTOR inhibitor - Temsirolimus ..... - Everolimus.....	 …… ……	 …… ……	 …… ……
Other systemic treatment (please specify)	 …… …… ……	 …… …… ……	 …… …… ……
SURGICAL TREATMENT			
Please specify:			

DATA RELATING TO THE END OF STUDY VISIT
(36 months)

To be completed only if visit took place,

if not, complete the latest information or death form

Did the patient attend a visit at 36 months YES ☐ NO ☐

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Best objective response observed since progression

- Complete ☐

- Partial ☐

- Progression ☐

- Stable ☐

Duration of administration of the progression treatment |___|___| (months)

LATEST INFORMATION OR DEATH FROM

LATEST INFORMATION		
Did the patient withdrawn from study prematurely? YES☐ NO☐		
Latest information date: |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		
	YES	**NO**
- Complete remission persisting since the inclusion visit	☐	☐
- Complete remission after treatment of the recurrence	☐	☐
- Disease progression	☐	☐
Number of lines of treatment received after progression, post CR:		
DEATH		
☐ **YES**	☐**NO**	
Date of death: |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

13.6. Appendix 6: Case report form for patients with mRCC NOT in complete remission (Controls)

CASE REPORT FORM

PROSPECTIVE STUDY OF COMPLETE REMISSIONS OBSERVED WITH SUNITINIB IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

Cross-sectional then longitudinal, descriptive, multicenter, prospective study with 3-year patient follow-up and compilation of a biobank

APERÇU protocol

Identification no.: A6181209

Favorable opinion from CCTIRS on 18/01/2012

Patient code

Investigator: Dr_____

INCLUSION

Consent form signature date	|___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)
Consultation date	|___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

DEMOGRAPHIC DATA

Date of birth (mm/yyyy)	|___|___| |___|___|___|___|
Age	|___|___| years
Sex	☐ Male ☐ Female
Height (cm)	|___|___|___|
Weight (kg)	|___|___|___|. |___|

INCLUSION CRITERIA :

	YES	NO
1. Adult patients (≥ 18 years)	☐	☐
2. Life expectancy ≥ 3 months	☐	☐
3. Patients with mRCC confirmed by histological analysis	☐	☐
4. No previous treatment with Sunitinib	☐	☐
5. Patients for whom the indication of Sutent® is retained in compliance with the text in the SmPC	☐	☐
6. Platelets ≥ 100 x 10^9/l, hemoglobin > 9 g/dl, neutrophils >1.5 x 10^9/l	☐	☐
7. Bilirubin < 2 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) ≥ 2.5 times upper limit of normal or ≤ 5 times upper limit of normal in the presence of hepatic metastases		
8. Patients of childbearing age must use a method of contraception		
9. Affiliated to a social security scheme	☐	☐
10. Informed about the study methods and having given their consent	☐	☐

EXCLUSION CRITERIA

	YES	NO
11. Previous systemic treatment	☐	☐

12. Patients who are pregnant or breastfeeding	☐	☐
13. Any contraindications to Sunitinib in accordance with the text in the SmPC	☐	☐

INITIAL TREATMENT OF PATIENT WITH METASTATIC RENAL CELL

Date of initial diagnosis of renal carcinoma |___|___| |___|___| |_2_|_0_|__|___| (dd/mm/yyyy)

Date of initial diagnosis of metastatic renal cell carcinoma (date of initial discovery of the first metastases) |__|__| |__|__| |_2_|_0_|_ _|___| (dd/mm/yyyy)

Sunitinib treatment start date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

NEPHRECTOMY

Nephrectomy ☐ YES ☐ NO If yes, date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

- Type of nephrectomy:
  - ☐ radical
  - ☐ with adrenalectomy
  - ☐ with lymphadenectomy
  - ☐ open
  - ☐ partial
  - ☐ without adrenalectomy
  - ☐ without lymphadenectomy
  - ☐ laparoscopic

HISTOLOGY

	YES	NO
• Pathoanatomic classification:		
- Clear cell carcinoma	☐	☐
- Multilocular cystic clear cell carcinoma	☐	☐
- Papillary cell carcinoma	☐	☐
- Chromophobe cell carcinoma	☐	☐
- Bellini's collecting duct carcinoma	☐	☐
- Medullary cell carcinoma	☐	☐
- Sarcomatoid contingent	☐	☐
- Other*(please specify):*……	☐	☐

- Tumor size |___|___|___| mm
- TNM classification: T |___| N |___| M |___|
- Fuhrman nuclear grade: I |___| II |___| III |___| IV |___|

	YES	NO
• Presence of necrosis?	☐	☐
• Vascular embolism	☐	☐
• Sarcomatoïdis composante	☐	☐

BLOOD SAMPLING BEFORE START OF SUNITINIB

*** A delay of 6 weeks is tolerated between initiation and sampling**

	YES	**NO**
- Blood sample of 2 times 5 ml	☐	☐

Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Histological sample of primitive tumor	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

DATA RELATING TO THE STATUS OF A PATIENT WITH mRCC BEFORE START OF SUNITINIB

METASTATIC SITES

LOCALIZATION OF METASTASES	YES	NO
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):	☐	☐

NUMBER OF METASTATIC SITES: |___|

MSKCC PROGNOSTIC CLASSIFICATION

☐ Good prognosis (0 pejorative factors)
☐ Moderate diagnosis (1 or 2 pejorative factors)
☐ Good diagnosis (more than 2 pejorative factors)

DATA RELATING TO PATIENTS WITH mRCC AFTER 6 MONTHS OF TREATMENT WITH SUNITINIB

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Sunitinib Actual dose ☐50mg ☐37,5mg ☐25mg

Actual schema ☐ 4/2 ☐2/1 ☐ Continu

CLINICAL ASSESSMENT ACCORDING TO RECIST v 1.1

Partial response	Yes ☐	No ☐
Percentage tumor reduction: ..... %		
Complete response	Yes ☐	No ☐
If yes, the patient should move to the arm of patients in CR		
Stable disease	Yes ☐	No ☐
Progression		
	Yes	☐No ☐
If yes: Progression at a known metastatic site	Yes ☐	No ☐
New metastatic site	Yes ☐	No ☐

METASTATIC SITES		
LOCALIZATION OF METASTASES	**YES**	**NO**
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):	☐	☐

NUMBER OF METASTATIC SITES |__|

BLOOD SAMPLING AT 6 MONTHS		
	YES	**NO**
- Blood sample of 2 times 5 ml	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

DATA RELATING TO PATIENTS WITH mRCC AFTER 12 MONTHS OF TREATMENT WITH SUNITINIB

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Sunitinib Actual dose ☐50mg ☐37,5mg ☐25mg

Actual schema ☐ 4/2 ☐2/1 ☐ Continu

CLINICAL ASSESSMENT ACCORDING TO RECIST v 1.1

Partial response	Yes ☐	No ☐
Percentage tumor reduction: ..... %		
Complete response	Yes ☐	No ☐
If yes, the patient should move to the arm of patients in CR		
Stable disease	Yes ☐	No ☐
Progression	Yes ☐	No ☐
If yes: Date of progression |__|__| |__|__| |_2_|_0_|__|__| (dd/mm/yyyy)		
If yes: Progression at a known metastatic site	Yes ☐	No ☐
New metastatic site	Yes ☐	No ☐

METASTATIC SITES

LOCALIZATION OF METASTASES	YES	NO
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):	☐	☐

NUMBER OF METASTATIC SITES: |___|

BLOOD SAMPLING AT 12 MONTHS

	YES	NO
- Blood sample of 2 times 5 ml	☐	☐
Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)		

DATA RELATING TO PATIENTS WITH mRCC DURING DISEASE PROGRESSION

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

CLINICAL ASSESSMENT ACCORDING TO RECIST v 1.1

Date of disease progression |___|___| |___|___| |_2_|_0_|_1_|___|
(dd/mm/yyyy)

Progression at a known metastatic site Yes ☐ No ☐

New metastatic site Yes ☐ No ☐

METASTATIC SITES

LOCALIZATION OF METASTASES	YES	NO
- Lungs	☐	☐
- Bone	☐	☐
- Liver	☐	☐
- Adrenal glands	☐	☐
- Pancreas	☐	☐
- Brain	☐	☐
- Lymph nodes	☐	☐
o Supradiaphragmatic	☐	☐
o Infradiaphragmatic	☐	☐
- Recurrence at the nephrectomy renal bed	☐	☐
- Other	☐	☐
(please specify):	☐	☐

NUMBER OF METASTATIC SITES: |___|

BLOOD SAMPLING DURING PROGRESSION

	YES	NO
- Blood sample of 2 times 5 ml	☐	☐

Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Data relating to the end of study visit of patients NOT in CR (36 months)

Did the patient attend a visit at 36 months YES ☐NO☐

Visit date |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

Is the patient still being treated with Sunitinib? YES ☐NO ☐

If yes, is the patient presenting a:

PARTIAL RESPONSE	YES ☐	NO ☐
COMPLETE RESPONSE	YES ☐	NO ☐
STABLE DISEASE	YES ☐	NO ☐
PROGRESSION	YES ☐	NO ☐
If no, is the patient presenting disease PROGRESSION	YES ☐	NO ☐

Please specify the new treatment: .....

Sunitinib discontinuation date |___|___| |___|___| |_2_|_0_|_1_|___|

Number of previous lines of treatment……

LATEST INFORMATION

Did the patient withdraw from study prematurely? YES ☐NO ☐

Latest information date: |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

DEATH

YES ☐ NO ☐

Date of death: |___|___| |___|___| |_2_|_0_|_1_|___| (dd/mm/yyyy)

13.7. Appendix 7: Laboratory tests

	Conventional units	Conversion factor	SI units
Hematology			
Erythrocytes	10^6/mm3	x 10^6	10^{12}/l
Hemoglobin (Hb)	g/dl	x 10	g/l
Platelet count	10^3/mm3	x 10^9	10^{12}/l
Leukocytes	10^3/mm3	x 10^6	10^9/l
Leukocyte differential count	%	x 0.01	fraction
Schistocytes			
Haptoglobin			
Biochemistry			
Total bilirubin	mg/dl	x 17.1	µmol/l
Alanine aminotransferase (ALT)	U/l	ND	U/l
Aspartate aminotransferase (AST)	U/l	ND	U/l
Alkaline phosphatase	U/l	ND	U/l
Lactate dehydrogenase (LDH)	U/l	ND	U/l
Amylase	U/l	ND	U/l
Lipase	U/l	ND	U/l
Total protein	g/dl	x 10	g/l
Albumin	g/dl	x 10	g/l
Sodium	mEq/l	x 1.0	mmol/l
Potassium	mEq/l	x 1.0	mmol/l
Calcium	mg/dl	x 0.25	mmol/l
Phosphorous	mg/dl	x 0.323	mmol/l
Creatinine	mg/dl	x 88.4	µmol/l
Uric acid	mg/dl	x 0.059	mmol/l
Glucose	mg/dl	x 0.055	mmol/l
TSH	mU/l	ND	mU/l
Thyroxine T4	ng/dl	x 12.9	pmol/l
Coagulation			
Prothrombin time PT	seconds	ND	seconds
Activated partial thromboplastin time aPTT	seconds	ND	seconds
International normalized ratio INR	%	ND	%
Urinalysis (test strip)			
Protein	ND		
Glucose	ND		
Blood	ND		
Ketones	ND		
Albuminuria			
Creatinuria			

13.8. Appendix 8: Prognostic factors

- ECOG performance status

0 Fully active, able to carry on all predisease activities without restriction.

1 Patient restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work.

2 Patient ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of the waking hours.

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.

4 Patient completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 Patient is dead.

- Number of metastatic sites

- Length of time interval between diagnosis and start of systemic treatment

- Hemoglobinemia

- LDH

- Corrected calcium

- Alkaline phosphatases

13.9. Appendix 9: RECIST v 1.1 assessment criteria

This section presents the definition of the criteria used to determine the objective tumor response of target lesions.

- Assessment of target lesions

Complete response (CR): Disappearance of all target lesions Pathological lymph nodes (target or non-target) must show a reduction of the short axis to a size of < 10 mm.

Partial response (PR): Reduction of at least 30% of the sum of the diameters of the target lesions, taking the sum of the initial diameters as a reference.

Disease progression (DP): Increase of at least 20% of the sum of the diameters of the target lesions, taking the lowest sum in the study as the reference (including the initial sum if this is the lowest sum in the study). In addition the relative increase of 20%, the sum must also show an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable disease (SD): Absence of sufficient reduction for a PR or absence of a sufficient increase for DP, taking as reference the sum of the lowest diameters during the study.

- Assessment of non-target lesions

This section presents the definition of the criteria used to determine the tumor response of non-target lesions. Although some non-target lesions may actually be measurable, it is not necessary to measure them; they must only be assessed qualitatively at the times specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must have non-pathological dimensions (minor axis < 10 mm).

No CR/No DP: Persistence of one or more non-target lesions and/or maintenance of the level of tumor marker above normal limits.

Disease progression (DP): The appearance of one or more new lesions is also regarded as progression.

13.10. Appendix 10: Centralized reading CT SCANS

In this study, patients in CR (CAS) shall be granted prior to final inclusion in the study of a central review of two of their scanner :

• The baseline scan (performed at initiation of Sutent in the first line)

• The scanner showing complete response

This league will replay between the screening visit and the visit to include a patient .

For that scanners will be engraved on 2CD -ROM:

• 1 for the baseline scan (performed at initiation of Sutent in the first line)

• 1 for the scanner showing complete response

Scanners should be sent immediately after the screening visit at IGR accompanied by the screening sheet printed from the e -CRF . 2 CD- ROM by patient and envelopes will be provided by Pfizer .

Contact and address for sending CD- ROM

Contact:

PPD
PPD
PPD
France
Telephone: PPD

13.11. Appendix 11: Methods for collecting and transporting biological samples

For patients in complete remission (**Cases**)

- A whole blood sample will be collected during screening visit into two 5 ml EDTA tubes. These samples will be centrifuged and frozen to produce 2 aliquots (minimum) of plasma and 2 pellets of whole blood stored at -80 °C (see diagram below).
- A whole blood sample will be collected during disease progression (if it occurs) into two 5 ml EDTA tubes and processed in the same manner.

<u>For patients screened as controls (2 sites)</u>

- A whole blood sample will be collected before the start of Sunitinib into two 5 ml EDTA tubes and processed in the same manner.
- A whole blood sample will be collected **at 6 months** into two 5 ml EDTA tubes and processed in the same manner.
- A whole blood sample will be collected at 12 months into two 5 ml EDTA tubes and processed in the same manner.
- A whole blood sample will be collected **during disease progression** into two 5 ml EDTA tubes and processed in the same manner.

Storage and transport: These tubes will be stored at -80 °C and transported frozen to the laboratory by OCT Santé, accompanied by the form below.

IGR EXTERNAL SAMPLES HANDOVER FORM

APERÇU

CSET XXXX-XXXX

Investigator: Dr PPD Sponsor: IGR
Consultant CRA: ☎

Patient identification (Stick patient label here)

Patient's inclusion/randomization no.:

Enrolling site:

VISIT: Cases ☐ screening visit ☐ PROGRESSION

Or Controls ☐ Before treatment ☐ 6 months ☐ 12 months ☐ Progression

Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| _____ **Department**: .....

➢ 2 x 5 ml EDTA tubes with "VIOLET" stopper_____Sampling time: __ :__

⇨ Instructions: (gently invert the tubes of blood 6 to 8 times)

Nurse's name and signature:

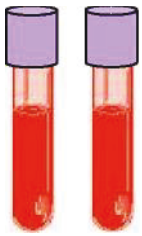
Comments:

Laboratory services

Comments:

Laboratory services

2 x 5.0 ml EDTA



Centrifuge at 2000 g for 10 min at +4 °C

LABELS ON CRYOTUBES

2 aliquots plasma 1.8 ml NUNC EDTA CRYOTUBES

2 whole blood pellets 1.8 ml NUNC EDTA CRYOTUBES

Freezing at -80 °C (-20 °C by default)

❖ Date and time of processing by the local laboratory: |__|__| |__|__| |_2_|_0_|_1_|__| at __ :__

❖ Technician's initials:

IGR EXTERNAL SAMPLES HANDOVER FORM
APERÇU
CSET XXXX-XXXX

Investigator: Dr PPD
Consultant CRA: ☎

Sponsor: IGR

Quickly send via OCT SANTE

The frozen cryotubes accompanied by this form to:

INSTITUT GUSTAVE ROUSSY
Laboratoire ET Extra PTL -1 pièce 1103
FAO: Lionel FOUGEAT
114 rue Edouard Vaillant
94806 Villejuif

Reception: Monday to Friday from 8:00 to 17:30 ☎ +33 (0)1 42 11 48 89
Please send an email to warn about the arrival of the samples to fougeat@igr.fr

BOX FOR IGR USE ONLY

- Date and time of receipt at the laboratory: |__|__| |__|__| |_2_|_0_|_1_|__|

at __ :__ Technician's initials:

- Compliant □ YES □ NO
- If NO, comments:

Aliquot 1 **supernatant** in box number: ---------- Position:
Aliquot 2 **supernatant** in box number: ---------- Position:
Aliquot 1 **pellet** in box number: ---------- Position:
Aliquot 2 **pellet** in box number: ---------- Position:

Laboratory address: Hematology laboratory
Institut Gustave Roussy
114 rue Edouard Vaillant
94805 Villejuif

Contacts: Dr PPD
Address: PPD
Telephone: PPD

IGR INTERNAL SAMPLES HANDOVER FORM
APERÇU
CSET XXXX-XXXX

Investigator: Dr PPD Sponsor: IGR
Consultant CRA: ☎

Patient identification (Stick patient label here)	Patient's inclusion/randomization no.: Patient's initials:

VISIT: Cases ☐ Screening visit ☐ PROGRESSION

Or Controls ☐ Before treatment ☐ 6 months ☐ 12 months ☐ Progression

Sampling date |___|___| |___|___| |_2_|_0_|_1_|___| _____ **Department**: ……

➢ 2 x 5 ml EDTA tubes with "VIOLET" stopper_____Sampling time: __ :__

⇨ Instructions: (gently invert the tubes of blood 6 to 8 times)

Nurse's name and signature:

Comments:

Immediately send the tubes accompanied by this form
To Sample Reception ET EXTRA (-1) via internal mail box no. 10 or 70
(Business hours: 8:00 to 17:30 from Monday to Friday)
In the event of any problems or delay, please contact 3649 or 4889

Laboratory services

- Sampling procedure Ref.: Labo préanalytique CSETXXXX-XXXX-APERçU.ppt
- Contract attached Ref.: CSETXXXX-XXXX-APERçU.xls
- Date and time of receipt at the laboratory: __/__/__ at __ :__ Technician's initials:
- **Time of freezing whole blood - EDTA "Violet" __ h : __ min at -80 °C**

  Aliquot 1 **supernatant** in box number: ---------- Position:

  Aliquot 2 **supernatant** in box number: ---------- Position:

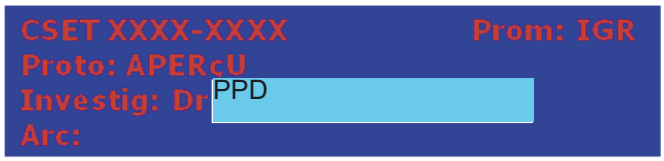
  Aliquot 1 **pellet** in box number: ---------- Position:

  Aliquot 2 **pellet** in box number: ---------- Position:

13.12. Appendix 12: Methods for collecting and transporting histological samples

For patients in complete remission (**Cases**) and screened as controls (Control)

A histological specimen, if available, will be sent during the screening or inclusion visit. These samples will be labeled (as indicated below) and sent by post to the IGR.



Storage and shipment: These slides will be stored at room temperature and transported by post to the laboratory accompanied by the sheet below.

14. EXTERNAL IGR SAMPLES HANDOVER FORM

15. APERÇU

16. CSET XXXX-XXXX

Investigator : Dr PPD Promotor : IGR
Referent RAC : ☎

Patient Identification
(past patient label)

inclusion/randomisation patient number:

recrutment site :

VISIT: « Cases »

☐ SCREENING VISIT ☐ INCLUSI

☐ BEFORE TREATMENT ☐ PROGRE

Or « **Control »**

Sample réalised |___|___| |___|___| |_2_|_0_|_1_|___| **Service** : ……

- 15 histological sample slides

Name and Sign of laboratory technician:

Comments :

Laboratory prestation

- Sample Date
- Local labortory Technical Date: |__|__| |__|__| |_2_|_0_|_1_|__|
- Shipment date : Le |__|__| |__|__| |_2_|_0_|_1_|__|
- Fixation Method …
- Technician initials :

17. EXTERNAL IGR SAMPLES HANDOVER FORM

18. APERÇU

19. CSET XXXX-XXXX

20. INVESTIGATOR : **DR** PPD
PROMOTOR : IGR

R.C.A. référent : ☎

Immediately send the slides by mail accompanied by this form
To the following address
INSTITUT GUSTAVE ROUSSY
Laboratoire ET Extra PTL – 1 piece 1103
A l'attention de Lionel Fougeat
114, rue Edouard Vaillant
94 806 VILLEJUIF
Business hours: 8:00 to 17:30 from Monday to Friday
Please send an email to alert sample arrival fougeat@igr.fr

BOX FOR IGR USE ONLY

- Date and hour for laboratory receipt: |__|__| |__|__| |_2_|_0_|_1_|__|

  H__ : _ Technician initials Technicien :
- Conformity ☐ YES ☐ NO
- If NO ; comments :

  Slide 1 in the box number : __ __ __ __ __ __ Location :

  Slide 2 in the box number : __ __ __ __ __ __ Location :

  Slide 3 in the box number : __ __ __ __ __ __ Location :

  Slide 4 in the box number : __ __ __ __ __ __ Location :

  Slide 5 in the box number : __ __ __ __ __ __ Location :

  Slide 6 in the box number : __ __ __ __ __ __ Location :

  Slide 7 in the box number : __ __ __ __ __ __ Location :

  Slide 8 in the box number : __ __ __ __ __ __ Location :

  Slide 9 in the box number : __ __ __ __ __ __ Location :

Slide 10 in the box number : __ __ __ __ __ __ Location :

Slide 11 in the box number : __ __ __ __ __ __ Location :

Slide 12 in the box number : __ __ __ __ __ __ Location :

Slide 13 in the box number : __ __ __ __ __ __ Location :

Slide 14 in the box number : __ __ __ __ __ __ Location :

Slide 15 in the box number : __ __ __ __ __ __ Location :

Laboratory adress : Laboratoire d'hématologie,
Institut Gustave Roussy
114 rue Edouard Vaillant
94805 Villejuif

Contact : Dr PPD

Adress : PPD

Phone number : PPD

13.13 Appendix 13: Sutent – product caracteristics summary

Summaries of product characteristics are available at the following links

http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=69225978
http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=65283820
http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=63841059

A printable version will be provided to participating physicians during the implementation of the study.

13.14 Appendix 14: Blood markers of angiogenesis: rationale, parameters analyzed and guidelines Rationale

On the one hand, angiogenesis involves a myriad of angiogenic growth factors and inhibitors synthesized by tumor and stromal cells and, on the other hand, endothelial cells (ECs) and their progenitors. The proliferation of ECs is activated by powerful stimulators, released by tumor cells, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).
It is important to remember that angiogenesis and hemostasis are linked to blood clotting and to fibrinolysis, which directly influence tumor angiogenesis. In fact, activated platelets release numerous angiogenic growth factors such as VEGF, bFGF, SDF-1 and platelet-derived growth factors (PDGFs) and they contribute to tumor angiogenesis within a potentially prothrombotic tumoral microcirculation [1,2].
Angiogenesis markers will be assessed in order to study the role they might play in the prediction of renewed disease progression.

Angiogenesis blood markers analyzed
The plasma levels of the following angiogenic factors will be quantified by ELISA:

- VEGF - prognostic factor of the angiogenesis pathway; target of the antiangiogenic treatment administered.
- bFGF - the levels of which correlate with the prognosis of certain solid tumors and whose proliferative
  action on endothelial cells in inhibited *in vitro* by
- SDF-1 - synthesized in response to hypoxia. It has a chemoattractive effect on endothelial cells
  and thus contributes to tumor angiogenesis [3].
- The soluble receptors of VEGF (sVEGFR1 and s VEGFR2), which reduce the angiogenic activity of VEGF.
- The 3 isoforms of PDGF (-AA, -BB and -AB) act on pericytes.

Objectives

- To assess the prognostic value of plasma VEGF in a complete response and progression context
- To study other angiogenesis markers as indicators of a complete tumor response to Sunitinib.

Schedule

The peripheral whole blood collected into EDTA tubes will be tested:
FOR CASES:
2 x 5 ml EDTA tubes will be collected during the screening visit or during the inclusion visit and in the event of disease progression.

FOR CONTROLS:
2 x 5 ml EDTA tubes will be collected before starting Sunitinib, at 6 months, at 12 months and during disease progression with Sunitinib.

Histological specimens (if available) will be tested:
For cases and for controls:
A histological block or 15 slides of histological sampling of the primary tumor performed before the screening visit.

Guidelines for the sampling, processing, storage and transport of blood samples. The assessment of blood markers of angiogenesis will be centralized at the IGR.

EDTA tubes: assessment of plasma markers of angiogenesis. After 2 rounds of centrifugation at 2000 g at 20 °C for 10 minutes, the plasma will be stored at a temperature of < -20 °C or, preferably, at -80 °C.

Delivery address: Biological Resources Center
Biopathology Department
Institut Gustave Roussy
114 rue Edouard Vaillant
94805 Villejuif
Telephone: +33 (0)1 42 11 42 11

References

1- Niedrodzik ML & Karpatkin S. Thrombin induces tumor growth, metastasis and angiogenesis: Evidence for a thrombin-regulated dormant tumor phenotype. Cancer Cell, 2006;10:355-362.
2. Lev EI, Estrov Z, Aboulfatova K, et al. Potential role of activated platelets in homing of human endothelial progenitor cells to subendothelial matrix. Thromb Haemost, 2006;96:498-504.
3. Jin DK, Shido K, Kopp HG, Petit I, Schmelkov SV, et al. Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4+ hemangiocytes. Nat Med, 2006;12:557-567.

13.15 Appendix 15: Analysis of genetic polymorphisms

Rationale

The isoforms of VEGF-A are encoded by a single gene at locus 6p12. Although no polymorphisms have been identified in the coding regions, several allelic polymorphisms located in the promoter region 5' of exon 1 or in the UTR region of exon 8 may explain the variations between individuals in the production of VEGF (1). It has been reported that significant variations in the blood levels of VEGF during hypoxia or during coagulation disorders correlate with polymorphisms (2, 3). Given the important pathophysiological role of angiogenesis in the development of clear cell carcinomas, it will be interesting to see whether these polymorphisms correlate with the occurrence of a complete response.
Sunitinib is an active treatment of renal cell carcinoma that acts by inhibition of the tyrosine kinases of VEGFR-1 and 2. Because elevated blood levels of VEGF, as well as significant quantities of VEGF bound to the extracellular matrix, can influence the efficacy of Sunitinib, it will also be interesting to examine the link between constitutional polymorphisms of VEGF and the occurrence of a complete response with Sunitinib.
Due to interference with one of the strongest targets of Sunitinib, VEGFR-2, polymorphisms may also perturb the level of response.

Polymorphisms analyzed

The non-exhaustive list of the polymorphisms that will be analyzed includes the analysis of the polymorphisms of the different VEGFRs and VEGF. The analysis of polymorphisms will be done by DNA sequencing after PCR amplification. The assessment of polymorphisms will be done at the end of the study.

Guidelines for the sampling, processing, storage and transport of blood samples.

2 EDTA tubes containing 5 ml samples (see Appendices 10 and 12) will produce 2 pellets of whole blood and allow the extraction of DNA for analysis of polymorphisms.

Delivery address: Biological Resources Center
Institut Gustave Roussy
114 rue Edouard Vaillant
94805 Villejuif

References

1. Watson CJ, Webb NJ, Bottomley MJ, et al: Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. Cytokine 12:1232-5, 2000

2. Schultz A, Lavie L, Hochberg I, et al: Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation. Circulation 100:54752, 1999

3. Webb NJ, Bottomley MJ, Watson CJ, et al: Vascular endothelial growth factor (VEGF) is released from platelets during blood clotting: implications for measurement of circulating VEGF levels in clinical disease. Clin Sci (Lond) 94:395-404, 1998