Non-Interventional Study Protocol
A4061078

Axitinib In ADvanced / Metastatic Renal Cell CarcinOma - A Non-Interventional Study of Real-World Treatment Outcomes in Patients Receiving 2nd Line Axitinib after 1st Line Sunitinib (ADONIS)

Statistical Analysis Plan
(SAP)

Version: 1

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Date: 10-Nov-2021

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

2 INTRODUCTION

Note: in this document any text taken directly from the Non-Interventional (NI) study protocol is ***italicised***.

2.1 STUDY DESIGN

This study is a European, prospective (partly retrospective), non-interventional, non-controlled, observational multicenter study. It will be carried out with specialists in charge of patients with adv/mRCC, from several EU countries including Austria, Belgium/Luxembourg, France, Greece, Italy, Spain, Switzerland, The Netherlands and UK (non-exhaustive list, additional countries may be considered at a later stage).

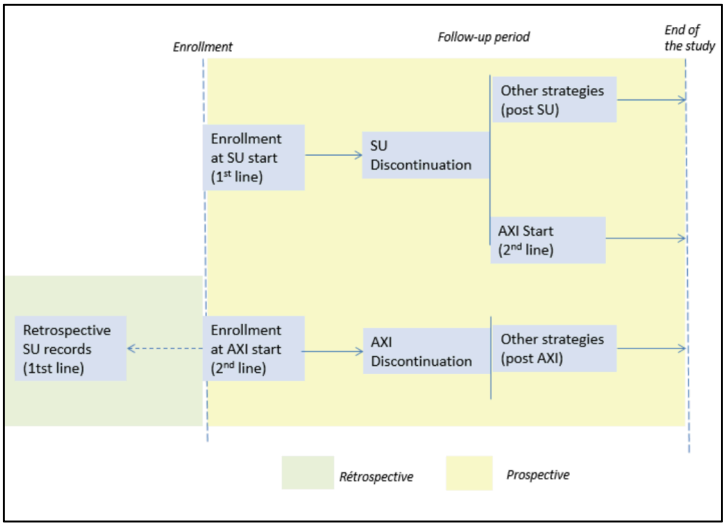
Study population:

Patients will be enrolled when they start a treatment with SU in 1st line or AXI in 2nd line post SU treatment (setting population). The possible sequences of treatment under investigation will be:

- *SU (prospective) – AXI*
- *SU (retrospective) – AXI*
- *SU (prospective) – no further active treatment (supportive care)*
- *SU (prospective) – other 2nd line treatment options (sorafenib, pazopanib, everolimus, temsirolimus, cabozantinib, nivolumab, other)*

*The study is designed to enrol approximately 750 patients. Out of these, 350 are expected to receive the combined SU-AXI sequence (**study population**: "SU-AXI patients") and to meet primary outcome objectives.*

Figure 1: Study Scheme



Inclusion and non-inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for the study:

- *Histologically confirmed diagnosis of advanced/metastatic renal carcinoma (clear cell RCC as well as non-clear cell RCC) with measurable disease according to RECIST1.1;*
- *Patients 18 years of age and over;*
- *Patients being treated with SU in 1st line according to the European therapeutic indication and/or being treated with AXI in 2nd line according to the European approved therapeutic indication (except post cytokines);*
- *Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.*

Patients meeting any of the following non-inclusion criteria will not be included in the study:

- *Patients being treated with cytokines or any other treatment outside of SU in 1st line;*
- *Patients receiving anti–tumor treatment beyond a 2nd line;*
- *Patients already under SU, already under AXI: enrollment must occur at the beginning of each line of treatment (before or at the first follow up visit).*

Data sources:

Data will come from medical records and will be collected in routine clinical practice. Because of the inclusion criteria (Patients being treated with SU in 1st line according to the European therapeutic indication and/or being treated with AX! in 2nd line according to the European approved therapeutic indication (except post cytokines)) the medication is prescribed within the regular practice of the physician. As a non-interventional study, there are no specific requirements with regards to the treatment process.

The study will include:

- *a retrospective data collection period consisting of SU 1st line treatment records for patients who start the study with AXI in 2nd line;*
- *A prospective data collection period for all patients enrolled in the study (socio-demographic, treatment and medical data).*

The medical data collection methods used will be:

- *eCRF (electronic Case Report Form) for physicians;*
- *Paper questionnaires for patients (assessment of the quality of life).*

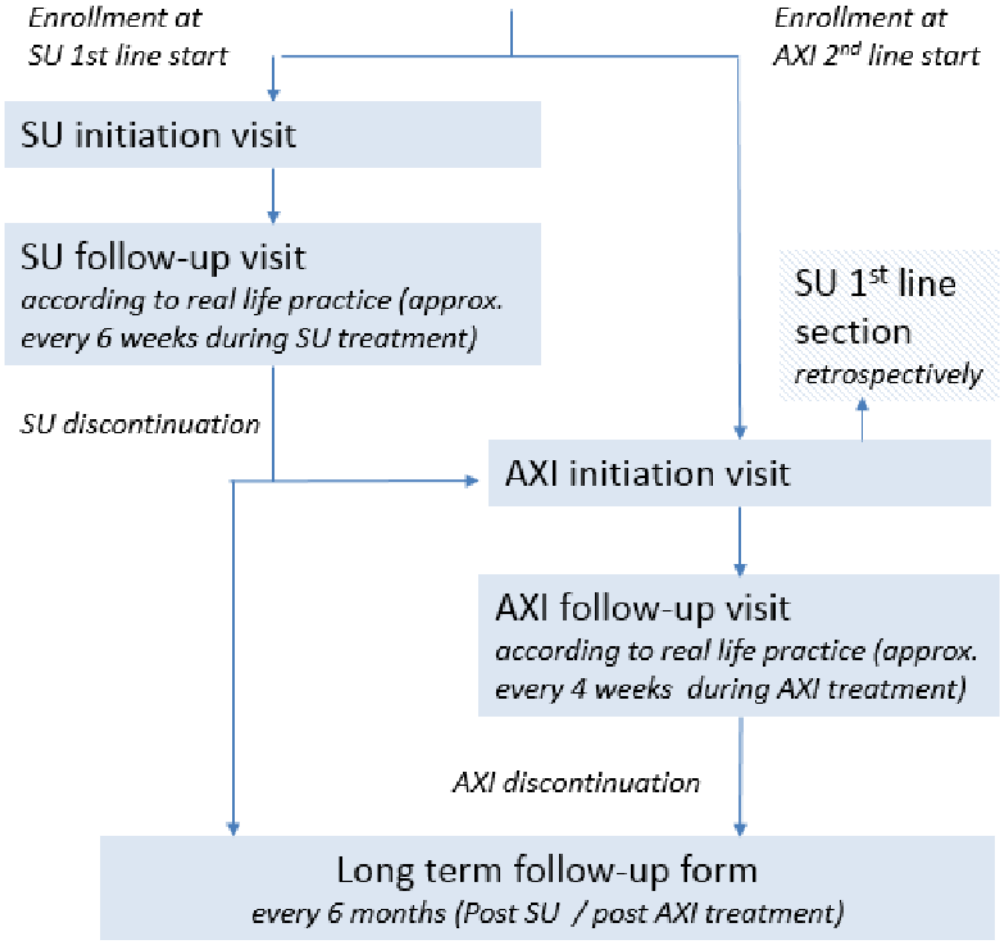
The Quality Of Life questionnaire will be completed at baseline and then every month for patients receiving AXI. QoL will also be measured at the discontinuation of AXI treatment. The physician will remit the QoL questionnaire to the patient and ask him/ her to complete it every month at home (i.e. Day 0 Day 30 Day 60 etc.). Patients will return it using pre-stamped envelopes. If not done before, the questionnaire will be completed at the site preferentially prior to the follow-up visit(s).

Observation period:

Patients will be enrolled for 3 years and followed-up for a minimum 2-year period, until the end of the study, whatever the therapeutic strategy post SU or post AXI. Visits will be naturalistic but follow-up visits are approximately expected:

- *during SU treatment: every 6 weeks (every cycle) with tumor assessment approximately every 3 months with respect to the clinical practice;*
- *during AXI treatment: every 4 weeks (every cycle) with tumor approximately assessment every 2 months with respect to the clinical practice;*

When patients come off SU treatment (i.e. are not receiving AXI) or come off AXI (after receiving the SU-INL sequence) they will be followed up every 6 months (separate form) for survival until the end of the study.



2.2 STUDY OBJECTIVES

Primary objectives:

In real life setting,

- *To assess the impact of AXI in 2nd line post-SU on progression free survival (PFS) and on time to treatment failure (TTF) for patients with adv/mRCC;*
- *To assess the impact of the SU–AXI sequence on combined PFS and TTF for patients with adv/mRCC*

Secondary objectives:

In real life setting,

- *To assess the Objective Response Rate (ORR) for adv/mRCC patients receiving AXI in 2nd line post SU;*
- *To describe usage of flexible dosing of AXI in these patients in terms of dosing change, dosing schedules and the average dose received during the AXI period treatment;*
- *3To assess the proportion of titrated patients within adv/mRCC patients receiving AXI in 2nd line post SU;*
- *4To assess the impact of titration on PFS for adv/mRCC patients receiving AXI in 2nd line post SU;*
- *To assess the Overall Survival (OS) (OS median and 24-month OS) for adv/mRCC patients receiving SU in first line followed by AXI in 2nd line;*
- *To assess the time to strategy failure (TSF) for adv/mRCC patients receiving the SU–AXI sequence;*
- *To assess PFS and OS for the combined 1st line SU – 2nd line sequences according to the second line post SU (TKI, mTOR) treatment;*
- *To describe safety and tolerability of patients receiving the SU–AXI sequence;*
- *To measure quality of life (QoL) in patients receiving AXI in 2nd line post SU.*

3 INTERIM ANALYSES

A final report will present the results of analyses concerning follow-up of the patient cohort and will address the study objectives.

Specific annual descriptive analyses will be realized before the final analyses.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

Not applicable.

4.2 STATISTICAL DECISION RULES

No statistical test will be performed. Whenever relevant, a two-sided 95% confidence interval will be provided.

5 ANALYSIS SETS/POPULATIONS

5.1 FULL ANALYSIS SET

The Full Analysis Set (FAS) refers to all **eligible** patients enrolled in the study, whatever the therapeutic strategy used during the observation period: i.e. patients enrolled when they start a treatment with SU in 1st line or AXI in 2nd line post SU treatment.

5.2 SAFETY ANALYSIS SET

The Safety Analysis Set (SAF) refers to all patients with **at least one treatment intake documented** (i.e. date of first intake available), whatever the treatment (Sunitinib or Axitinib).

5.3 OTHER ANALYSIS SET

Not Applicable

5.4 SUBGROUPS

Type of 2nd line treatment post SU:

- SU - AXI subgroup

  It refers to all patients from the FAS receiving the combined SU-AXI sequence during the observation period. It includes

  - patients enrolled at AXI initiation in 2nd line post SU treatment ("SU (retrospective) - AXI")
  - and patients enrolled at SU initiation with SU prospective part and receiving AXI in 2nd-line post SU ("SU (prospective)-AXI") (AXI declared as 2nd line at SU discontinuation)

  Two different baselines will be considered in the analyses of this subgroup: AXI initiation to explore only the AXI treatment period and SU initiation to consider the SU – AXI sequence.

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

6.1.1 Primary Endpoints

- Progression Free Survival (PFS) under Axitinib in 2nd line post Sunitinib

The PFS will be defined as the time from when the patient receives the first dose of AXI to the time of progression or death due to any cause, whichever occurs first.

PFS status and PFS time will be calculated as detailed below:

Variable name	Definition
PFS status	Patient will not be censored for the PFS analysis (PFS status = 1) in the following cases: 1) Tumor Assessment showing PD in at least one Axitinib follow-up visit (cf. CRF page 29) 2) Death within 3 months after treatment discontinuation / last Tumor Assessment. Death could be reported whether on Axitinib discontinuation page (cf. CRF page 35) or on Study Discontinuation visit (cf. CRF page 37) In all other cases, patient will be censored for the PFS analysis (PFS status = 0). Note: the following cases should be discussed at time of DRMs: - Patients with a PD not documented through a Tumor Assessment - Patients with no regular Tumor Assessments (i.e. not every 3/4 months)
PFS time (months)	The time to disease progression will be calculated in months as: • (Date of **first** Tumor Assessment showing PD in at least one Axitinib follow-up visit - Start date of Axitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death - Start date of Axitinib + 1) / 30.44, if case n°2 described above is reported Else, the time to disease progression will be censored as follows:

Variable name	Definition
	• (Date of Axitinib discontinuation - Start date of Axitinib + 1) / 30.44 if patient discontinued Axitinib for any reason other than PD • (Date of last follow-up visit - Start date of Axitinib + 1) / 30.44 if patient is lost to follow-up or still under Axitinib *Note; this could be adapted if necessary (to be discussed at time of DRMs)* Note: - Start date of Axitinib will be the one reported at time of Axitinib initiation visit (cf. CRF page 25 "Therapy started with Axitinib in 2nd line on") - Axitinib discontinuation date will be the Date of progression/intolerability or death reported at time of Axitinib discontinuation (cf. CRF page 35)

- Progression Free Survival (PFS) for the sequence Sunitinib-Axitinib

The PFS will be defined as the time from when the patient receives the first dose of SU in 1st line, until progression or death due to any cause with the 2nd- line treatment considered in the analysis, whichever occurs first.

PFS status and PFS time will be calculated as detailed below:

Variable name	Definition
PFS status	Patient will not be censored for the PFS analysis (PFS status = 1) in the following cases: 1) Tumor Assessment showing PD in at least one Axitinib follow-up visit (cf. CRF page 29) 2) Death within 3 months after treatment discontinuation / last Tumor Assessment. Death could be reported whether on Axitinib discontinuation page (cf. CRF page 35) or on Study Discontinuation visit (cf. CRF page 37) In all other cases, patient will be censored for the PFS analysis (PFS status = 0). Note: the following cases should be discussed at time of DRMs:

Variable name	Definition
	- Patients with a PD not documented through a Tumor Assessment - Patients with no regular Tumor Assessments (i.e. not every 3/4 months)
PFS time (months)	The time to disease progression will be calculated in months as: • (Date of **first** Tumor Assessment showing PD in at least one Axitinib follow-up visit - Start date of Sunitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported Else, the time to disease progression will be censored as follows: • (Date of Axitinib discontinuation - Start date of Sunitinib + 1) / 30.44 if patient discontinued Axitinib for any reason other than PD • (Date of last follow-up visit - Start date of Sunitinib + 1) / 30.44 if patient is lost to follow-up or still under Axitinib *Note; this could be adapted if necessary (to be discussed at time of DRMs)* Note: - Start date of Sunitinib will be the one reported : - at time of Sunitinib initiation visit for patients enrolled at SU initiation (cf. CRF page 11 *"Therapy started with Sunitinib in 1st line on"*) - at time of Axitinib initiation visit for patients enrolled at AXI initiation (cf. CRF page 26 *"Therapy started with Sunitinib in 1st line on"*) - Axitinib discontinuation date will be the Date of progression/intolerability or death reported at time of Axitinib discontinuation (cf. CRF page 35)

- Time to Treatment Failure (TTF) under Axitinib in 2nd line post Sunitinib

The TTF will be defined as the time from when the patient receives the first dose of AXI to the date of AXI discontinuation (date completed by the physician), whatever the reason for discontinuation and whatever the following therapeutic strategy.

TTF status and TTF time will be calculated as detailed below:

Variable name	Definition
TTF status	Patient will not be censored for the TTF analysis (TTF status = 1) in the following cases: 1) Axitinib discontinued due to Progression, Intolerability or Death (cf. CRF page 35) 2) Study Discontinuation for any reason except lost to follow-up or patient's request whereas last treatment received is Axitinib (cf. CRF page 37) In all other cases, patient will be censored for the TTF analysis (TTF status = 0). Note: Other reasons for Axitinib discontinuation as well as other reason for study discontinuation (whereas last treatment received is Axitinib) will be reviewed at time of DRMs in order to decide whether corresponding cases should be censored or not for TTF analysis
TTF time (months)	The time to treatment failure will be calculated in months as: • (Date of progression/intolerability or death reported at time of Axitinib discontinuation - Start date of Axitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death reported on the Study Discontinuation form - Start date of Axitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is 'death' • (Axitinib end date reported on the Study Discontinuation form - Start date of Axitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is not 'death' and Axitinib status at last visit is 'discontinued' *Note: as only month and year of Axitinib end are reported in such cases, day of Axitinib end will automatically be "forced" to 01* • (Last visit date reported on the Study Discontinuation form - Start date of Axitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is not 'death' and Axitinib status at last visit is 'ongoing' • (Minimum of {Date of progression/intolerability or death reported at time of Axitinib discontinuation ; Date of death reported on the Study Discontinuation form ; Axitinib end date reported on the Study Discontinuation form ; Last visit date reported on the Study

Variable name	Definition
	Discontinuation form} - Start date of Axitinib + 1) / 30.44, if more than 1 case described above is reported Else, the time to treatment failure will be censored as follows: • (Maximum of { Date of last Axitinib follow-up visit ; Last visit date reported on the Study Discontinuation form whereas last treatment received is Axitinib } - Start date of Axitinib + 1) / 30.44 Note: Start date of Axitinib will be the one reported at time of Axitinib initiation visit (cf. CRF page 25 *"Therapy started with Axitinib in 2nd line on"*)

- Time to Treatment Failure (TTF) for the sequence Sunitinib-Axitinib

The TTF will be defined as the time when the patient receives the first dose with SU in 1st line to the time of AXI 2nd line treatment discontinuation (date completed by the physician), whatever the reason for discontinuation and whatever the following therapeutic strategy.

TTF status and TTF time will be calculated as detailed below:

Variable name	Definition
TTF status	Patient will not be censored for the TTF analysis (TTF status = 1) in the following cases: 1) Axitinib discontinued due to Progression, Intolerability or Death (cf. CRF page 35) 2) Study Discontinuation for any reason except lost to follow-up or patient's request whereas last treatment received is Axitinib (cf. CRF page 37) In all other cases, patient will be censored for the TTF analysis (TTF status = 0). Note: Other reasons for Axitinib discontinuation as well as other reason for study discontinuation (whereas last treatment received is Axitinib) will be reviewed at time of DRMs in order to decide whether corresponding cases should be censored or not for TTF analysis

Variable name	Definition
TTF time (months)	The time to treatment failure will be calculated in months as: • (Date of progression/intolerability or death reported at time of Axitinib discontinuation - Start date of Sunitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death reported on the Study Discontinuation form - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is 'death' • (Axitinib end date reported on the Study Discontinuation form - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is not 'death' and Axitinib status at last visit is 'discontinued' *Note: as only month and year of Axitinib end are reported in such cases, day of Axitinib end will automatically be "forced" to 01* • (Last visit date reported on the Study Discontinuation form - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported and reason for study discontinuation is not 'death' and Axitinib status at last visit is 'ongoing' • (Minimum of {Date of progression/intolerability or death reported at time of Axitinib discontinuation ; Date of death reported on the Study Discontinuation form ; Axitinib end date reported on the Study Discontinuation form ; Last visit date reported on the Study Discontinuation form} - Start date of Sunitinib + 1) / 30.44, if more than 1 case described above is reported Else, the time to treatment failure will be censored as follows: • (Maximum of { Date of last Axitinib follow-up visit ; Last visit date reported on the Study Discontinuation form whereas last treatment received is Axitinib } - Start date of Sunitinib + 1) / 30.44 Note: Start date of Sunitinib will be the one reported: - at time of Sunitinib initiation visit for patients enrolled at SU initiation (cf. CRF page 11 *"Therapy started with Sunitinib in 1st line on"*) - at time of Axitinib initiation visit for patients enrolled at AXI initiation (cf. CRF page 26 *"Therapy started with Sunitinib in 1st line on"*)

6.1.2 Secondary Endpoints

- Time to Strategy Failure (TSF) for the sequence Sunitinib-Axitinib

The TSF will be defined as the time from when the patient receives the first dose with SU in first line to the time of AXI 2nd line treatment discontinuation (date completed by the physician) without the time between discontinuation of SU and start of the 2nd line AXI treatment.

TSF status will be the same as TTF status for the sequence Sunitinib-Axitinib.

TSF time will be equal to:

- For patients enrolled at SU initiation : TTF time - (Start date of Axitinib reported at time of Axitinib initiation visit – Date of progression/intolerability/death reported at time of Sunitinib discontinuation)
- For patients enrolled at AXI initiation : TTF time - (Start date of Axitinib reported at time of Axitinib initiation visit – Date of Sunitinib end reported at time of Axitinib initiation visit*)

  **cf. CRF page 26 "Therapy with Sunitinib in first line; therapy discontinuation on"*

- Overall Survival (OS) for the sequence Sunitinib-Axitinib

The OS will be defined as the time from date of first SU dose to the date of death of any cause. For patients not experiencing the event, their survival times will be censored at the last date they are known to be alive

OS status and OS time will be calculated as detailed below:

Variable name	Definition
OS status	Patient will not be censored for the OS analysis (OS status = 1) in the following cases: 1) Axitinib discontinued due to Death (cf. CRF page 35) 2) Death reported in Long term Follow-up (cf. CRF page 36) 3) Death reported on the Study Discontinuation form (cf. CRF page 37) In all other cases, patient will be censored for the OS analysis (OS status = 0).

Variable name	Definition
OS time (months)	The overall survival time will be calculated in months as: • (Date of death reported at time of Axitinib discontinuation - Start date of Sunitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death reported in Long term Follow-up - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported • (Date of death reported on the Study Discontinuation form - Start date of Sunitinib + 1) / 30.44, if case n°3 described above is reported Else, the overall survival time will be censored as follows: • (Maximum of {All visits dates reported} - Start date of Sunitinib + 1) / 30.44 Note: Start date of Sunitinib will be the one reported: - at time of Sunitinib initiation visit for patients enrolled at SU initiation (cf. CRF page 11 *"Therapy started with Sunitinib in 1st line on"*) - at time of Axitinib initiation visit for patients enrolled at AXI initiation (cf. CRF page 26 *"Therapy started with Sunitinib in 1st line on"*)

- Best Response under Axitinib in 2nd line post Sunitinib
Number and percentages of patients by best response (CR, PR, SD or PD) will be presented.

- Objective Response Rate (ORR) under Axitinib in 2nd line post Sunitinib
ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) according to RECIST from the start to the end of Axitinib treatment (cf. CRF page 29).

Patients who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR.

All assessments following an assessment of PD will be excluded from the derivation of ORR.

- Clinical benefice Rate (CBR) under Axitinib in 2nd line post Sunitinib
The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease according to RECIST criteria from the start to the end of Axitinib treatment (cf. CRF page 29).

Patients who die, progress, or drop out for any reason prior to reaching a CR, PR or SD will be counted as non-responders in the assessment of CBR.

All assessments following an assessment of PD will be excluded from the derivation of CBR.

- Objective Response Rate (ORR) under TKI in 2nd line post Sunitinib
ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) as best response under TKI treatment (cf. CRF page 36).

- Clinical benefice Rate (CBR) under TKI in 2nd line post Sunitinib
The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease as best response under TKI treatment (cf. CRF page 36).

- Objective Response Rate (ORR) under mTOR in 2nd line post Sunitinib
ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) as best response under mTOR treatment (cf. CRF page 36).

- Clinical benefice Rate (CBR) under mTOR in 2nd line post Sunitinib
The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease as best response under mTOR treatment (cf. CRF page 36).

- Objective Response Rate (ORR) under IO in 2nd line post Sunitinib
ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) as best response under IO treatment (cf. CRF page 36).

- Clinical benefice Rate (CBR) under IO in 2nd line post Sunitinib
The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease as best response under IO treatment (cf. CRF page 36).

- Objective Response Rate (ORR) for Sunitinib received in 1st line
ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) as best response under Sunitinib treatment (cf. CRF page 12 for patients included at time of Sunitinib initiation, cf. CRF page 26 for patients included at time of Axitinib initiation).

- Clinical benefice Rate (CBR) for Sunitinib received in 1st line
The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease as best response under Sunitinib treatment (cf. CRF page 12 for patients included at time of Sunitinib initiation, cf. CRF page 26 for patients included at time of Axitinib initiation).

OS status and OS time will be calculated as detailed below:

Variable name	Definition
OS status	Patient will not be censored for the OS analysis (OS status = 1) in the following cases: 1) Death reported in Long term Follow-up (cf. CRF page 36) 2) Death reported on the Study Discontinuation form (cf. CRF page 37) In all other cases, patient will be censored for the OS analysis (OS status = 0).
OS time (months)	The overall survival time will be calculated in months as: • (Date of death reported in Long term Follow-up - Start date of Sunitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death reported on the Study Discontinuation form - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported Else, the overall survival time will be censored as follows: • (Maximum of {All visits dates reported} - Start date of Sunitinib + 1) / 30.44 Note: Start date of Sunitinib will be the one reported : - at time of Sunitinib initiation visit for patients enrolled at SU initiation (cf. CRF page 11 *"Therapy started with Sunitinib in 1st line on"*) - at time of Axitinib initiation visit for patients enrolled at AXI initiation (cf. CRF page 26 *"Therapy started with Sunitinib in 1st line on"*)

- Progression Free Survival (PFS) for Sunitinib received in 1st line

PFS status and PFS time will be calculated as detailed below:

❖ Patients included at time of Sunitinib initiation (i.e. prospective group)

Variable name	Definition
PFS status	Patient will not be censored for the PFS analysis (PFS status = 1) in the following cases: 1) Tumor Assessment showing PD in at least one Sunitinib follow-up visit (cf. CRF page 12)

Variable name	Definition
	2) Death within 3 months after treatment discontinuation / last Tumor Assessment. Death could be reported whether on Sunitinib discontinuation page (cf. CRF page 17) or on Study Discontinuation visit (cf. CRF page 37) In all other cases, patient will be censored for the PFS analysis (PFS status = 0). Note: the following cases should be discussed at time of DRMs: - Patients with a PD not documented through a Tumor Assessment - Patients with no regular Tumor Assessments (i.e. not every 3/4 months)
PFS time (months)	The time to disease progression will be calculated in months as: • (Date of **first** Tumor Assessment showing PD in at least one Sunitinib follow-up visit - Start date of Sunitinib + 1) / 30.44, if case n°1 described above is reported • (Date of death - Start date of Sunitinib + 1) / 30.44, if case n°2 described above is reported Else, the time to disease progression will be censored as follows: • (Date of Sunitinib discontinuation - Start date of Sunitinib + 1) / 30.44 if patient discontinued Sunitinib for any reason other than PD • (Date of last follow-up visit - Start date of Sunitinib + 1) / 30.44 if patient is lost to follow-up or still under Sunitinib *Note; this could be adapted if necessary (to be discussed at time of DRMs)* Note: - Start date of Sunitinib will be the one reported at time of Sunitinib initiation (cf. CRF page 11 *"Therapy started with Sunitinib in 1st line on"*) - Sunitinib discontinuation date will be the Date of progression/intolerability or death reported at time of Sunitinib discontinuation (cf. CRF page 17)

❖ Patients included at time of Axitinib initiation (i.e. retrospective group)

Variable name	Definition
PFS status	Patient will not be censored for the PFS analysis (PFS status = 1) in the following case: Sunitinib discontinued due to progression (cf. CRF page 27) In all other cases, patient will be censored for the PFS analysis (PFS status = 0).
PFS time (months)	The time to disease progression will be calculated in months as: • (Date of progression under Sunitinib - Start date of Sunitinib + 1) / 30.44, if case described above is reported Else, the time to disease progression will be censored as follows: • (Date of Sunitinib discontinuation - Start date of Sunitinib + 1) / 30.44 Note: - Start date of Sunitinib will be the one reported at time of Axitinib initiation visit (cf. CRF page 26 *"Therapy started with Sunitinib in 1st line on"*) - Date of progression under Sunitinib will be the one reported on CRF page 27 (Section "Reason for discontinuation of Sunitinib", item "Progression on …") - Sunitinib discontinuation date will the reported on CRF page 26 (Section "Therapy with Sunitinib in first line", item "Therapy discontinuation on …")

6.2 SAFETY ENDPOINTS

The analysis of safety will be realized thanks to following endpoints:

6.2.1 Incidence of Adverse Events (AEs)

- Incidence of AEs: Proportion of patients experiencing at least one AE of any grades by Body system (System Organ Class (SOC) MedDRA) ;
- Incidence of most common AEs of any grade (occurring in more than 10% of patients in either group) by preferred term (PT) (MedDRA);

  The following type of AEs will be described whatever the number and proportion of patients concerned: Diarrhea, hypertension, fatigue, asthenia, hand foot syndrome, nausea, stomatitis, neutropenia, lymphopenia and increased lipase

- Incidence of serious AEs;

- Incidence of non-serious AEs;
- Incidence of all AE per grade, especially grade 3 and 4 AE.

  Note: all grades should be considered for this analysis and not only worst grade.

AEs will be analysed separately for AEs related to SU or AEs related to AXI treatment

6.2.2 Discontinuation due to Toxicity

- Proportion of patients who discontinued the treatment of interest, because of AEs;

  Note: All discontinuations due to AE should be considered: those reported on SU/AXI follow-up forms and those reported on AEs form
- Treatment duration until discontinuation for AEs;

6.2.3 Deaths

- Proportion of patients who died due to any cause;
- Cause of death (tumor-related, other cause). In case of multiple cause of death, the cause from the Study Discontinuation form will be take into account in first.

6.3 OTHER ENDPOINTS

6.3.1 Axitinib Treatment

The real-life usage of AXI treatment will be analyzed with following endpoints:

AXI dose at initiation

- Proportion of patients with the recommended starting dose of AXI (5 mg BID)
- Proportion of patients with other starting doses

Dosing schedules over AXI treatment period

- Average/median total daily dose (mg) received over the AXI treatment period (i.e. at each study visit);
- Dose intensity of AXI: defined as the sum of AXI daily doses divided by the duration of AXI treatment in days (delay between the first AXI dose and the last dose, including temporary interruption).

  Note: Axitinib discontinuation date will the Date of progression/intolerability or death reported at time of Axitinib discontinuation (cf. CRF page 35)
- Proportion of patients with at least one modification of the dose during treatment.
- Proportion of patients with at least one modification of the dose or at least one temporary interruption during treatment.
- Proportion of patients with at least one temporary interruption during treatment.
- Among patients with at least one temporary interruption, sum of all durations of temporary interruption by patient.
- Proportion of patients for whom the dose was reduced
- Proportion of patients for whom the dose was increased

AXI interruption and discontinuation

- Proportion of patients with temporary interruption during the AXI treatment period and reasons (AEs, radiotherapy, surgery, other);

- (Median) duration of the first interruption (days) and of all interruptions together;
- Proportion of patients with AXI discontinuation and reasons (progression, intolerability, death or other reason).

6.3.2 Sunitinib Treatment

- Proportion of patients with the recommended starting dose of Sunitinib
- Proportion of patients with other starting doses
- Proportion of patients with at least one modification of the dose
- Proportion of patients with at least one modification of the dose or at least one temporary interruption during treatment.
- Proportion of patients with at least one temporary interruption during treatment.
- Among patients with at least one temporary interruption, sum of all durations of temporary interruption by patient

6.3.3 Quality of Life

The analyses of the quality of life will be realized thanks to following endpoints, assessed every month over the AXI treatment:

FKSI-19 score

The FKSI-19 score will result of completed answers from FKSI-19 questionnaire (Functional Assessment of Cancer Therapy Kidney Symptom Index-19) (version 4) (presented in appendix **Error! Reference source not found.**). This scale assesses symptoms of importance to patients with advanced kidney cancer, with 19 items:

- 12-item subscale about Disease Related Symptoms - Physical (DRS-P);
- 1-item subscale about Disease Related Symptoms - Emotional (DRS-E);
- 3-item subscale about Treatment Side Effects (TSE);
- 3-item subscale about Function/ Well-Being (FWB).

This score will be assessed for each subscale and overall, as sum of item scores. Scoring guidelines are presented in appendix **Error! Reference source not found.**.

Mental Health (MH) score of SF-36

The score of Mental Health (MH) domain of the Short Form (36) Health Survey (SF-36) will be defined as the sum of scores of items, divided by 5 (items presented in appendix 12.3). Scoring guidelines are presented in appendix **Error! Reference source not found.**.

Role-Emotional (RE) score of SF-36

The score of Role-Emotional (RE) domain of SF-36 questionnaire (presented in appendix 12.3) will be defined as the sum of scores of items concerned, divided by 3 (items presented in appendix 12.3). Scoring guidelines are presented in appendix **Error! Reference source not found.**.

Change in scores from baseline

This endpoint will be defined for the three scores mentioned above, as the difference between QoL score at visit every month over AXI treatment and the score at AXI initiation.

6.4 COVARIATES

In case of multivariate analyses, baseline characteristics will possibly be used as covariates.

Possible, but not exclusive, baseline covariates related to SU initiation will be limited because of a retrospective part of the data collection, with:

- Age and sex
- ECOG (0, 1, 2, 3, 4), Karnofsky performance status
- MSKCC risk factors (first line) (Good, Intermediate, Poor)
- Heng risk factors (Favorable, Intermediate, Poor)
- Medical history of hypertension (Yes, No)
- Delay from diagnosis (< 1 year from diagnosis to first metastasis detection/ ≥ 1 year)
- Nephrectomy (Yes, No)
- Number of metastasic sites.

The covariates identified previously will be also explored if the baseline is the AXI initiation. In this case, other covariates will be:

- The response to SU treatment in 1st line
- Duration of SU treatment, PFS
- Previous treatments for primary tumor (surgery, radiotherapy, other);
- Additional anti-tumor treatments

7 HANDLING OF MISSING VALUES

The majority of data will be collected with a website (except for FKSI-19 and SF-36 questionnaires). In this website, the input of certain data will be obligatory, limiting the number of missing values, particularly for endpoints.

Regarding the descriptive analyses of each variable, it will be based on the available data ("observed-case analysis"), considering missing data as non-informative. The number of missing data will be documented for each analysis.

The analysis of the primary endpoint is a survival analysis which is known to efficiently handle missing data: all patients are included in the analysis and missing data are called right-censored data.

For continuous endpoints (QoL endpoints), a mixed model for repeated measures (MMRM) will be used to analyse longitudinal data. Missing data will not be imputed. However, this analysis will be performed on all patients having a baseline value and at least one post-baseline value. The model will be valid under the assumption of data missing at random (MAR).

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

Statistical analysis will be performed with SAS software (version 9.4 or higher, SAS Institute, North Carolina USA).

8.1.1 Descriptive Methods

Descriptive analysis of qualitative and ordinal variables will comprise the number and percentage of each category. Percentages will be calculated on the number of all available data, excluding missing data.

Descriptive analysis of quantitative variables will present the mean, the standard deviation (SD) as well as the median, quartile 1, quartile 3, min and max values.

The 95% confidence intervals will be presented for main endpoints. The 'exact' Clopper-Pearson confidence interval will be provided to assess 2-sided 95% confidence interval for main binomial proportions (e.g. ORR rate).

The number of missing values will be reported in the results table for each variable.

8.1.2 Survival Analysis Methods

The survival functions (for PFS, TTF, TSF, OS) will be estimated with the Kaplan-Meier method. The survival function S(t) is the probability that the event (treatment discontinuation, death or progression) does not occur before a specified time.

This method will be applied to derive, survival curves, median event time and a 95% confidence interval for the median survival time (time at which half the analyzed patients have presented the event). Survival curves will give an idea of whether or not the groups are proportional (i.e. the survival functions are approximately parallel). For OS, the share of patients alive at 24 months will also be measured.

The log-rank test of equality across strata will be used to compare survival curves for categorical variables (sub-groups of interest). For continuous variables, a univariate Cox proportional hazard regression will be used.

For analyses of prognostic factors of survival time, multivariate Cox proportional hazard regressions will be performed.

8.1.3 Strategy of Variable Selection in a Cox Model for PFS Analysis

The strategy of selection of variables in multivariate models will consist in:
Step 1: Selection of initial factor

In a first step, the association between the PFS and each potential factor will be analyzed using

- A Log-Rank test (PROC LIFETEST under SAS 9.4) for categorical factors. Kaplan-Meier curves will also be presented in order to give an idea of whether or not the corresponding groups are proportional (i.e. the survival functions are approximately parallel)
- a univariate Cox proportional hazard regression (PROC PHREG under SAS 9.4) for continuous factors

Only significant factors at the 25% threshold will be retained for the initial model.

The possible correlations between the factors selected will be investigated. This will be done using

- A Chi-2 or Fisher-exact tests (if at least one number is less than 5) for 2 categorical factors
- An Analysis of Covariance (ANCOVA) for 2 continuous factors or for a categorical and a continuous factor.

Since two highly correlated factors (p-value <5%) cannot be present in the same model, a clinical arbitration can be requested if necessary.

Step 2: Selection of final factors

For this step, a Cox model will be run (PROC PHREG under SAS 9.4).
In a first step, all the factors retained at the end of step 1 will be introduced to the model.

Then a backward elimination procedure will be used in order to retain only independently significant factors at the 5% threshold.

Step 3: Investigate possible interactions between final factors

When the final model has been reached, interactions will be introduced to verify their non-significance. The existence of an interaction between two variables means that the effect of one variable is different depending on the other variable; it will have to be taken into account in the interpretation.

8.1.4 Analysis of Longitudinal Data

Mixed models with Repeated Measures (MMRM) will be used to analyze longitudinal data (QoL over the AXI treatment). These models will allow to answer questions as "Are there significant changes in the endpoint from baseline?" or "Do any groups differ at any time point regarding the endpoint?".

In order to explore possible variations in time and the possible differences according to the best response observed under Axitinib treatment, each QoL score/subscore will be analyzed using a mixed model for repeated measures (MMRM) (using the SAS MIXED procedure) with:

- The absolute difference in score/sub score as endpoint (MODEL statement of the MIXED procedure)
- The time, the best response observed under Axitinib treatment, and the interaction between these 2 covariates as fixed effects (MODEL statement of the MIXED procedure). All these variables will be considered as categorical ones. Please refer to appendix **Error! Reference source not found.** of this document for the definition of monthly time windows
- The Baseline value and baseline-x-time interaction as covariates. This variable will be considered as continuous one
- A time repeated effect (REPEATED statement of the MIXED procedure) within each subject (SUBJECT = USUBJID as option of the REPEATED statement). This will permit to take into account the fact that for each subject, several measures are performed over time. The type of variance covariance matrix will be the unstructured one in a first time (TYPE = UN as option of the REPEATED statement). If the model with the unstructured covariance matrix fails to converge, other covariance structures including Toeplitz, compound symmetry, and spatial power will be considered. The covariance structure converging to the best fit, as determined by a minimal Akaike's information criterion (AIC), will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

In order to explore the validity of the model (and more precisely the assumption regarding independence, normality and constant variance of residuals), the following graphs will be provided:

- Q-Q plot of the residuals
- Distribution of residuals with its corresponding Normal density estimate
- Scatterplot of Residuals vs. Predicted values

8.2 STATISTICAL ANALYSES

8.2.1 Safety Analyses

Safety analyses will be provided in the safety population.

AEs will be presented overall and by period of treatment (Sunitinib, Axitinib).

They will be displayed in summary tables, by system organ class (SOC) and preferred term (PT).

The tables will present the number of subjects and the rate of occurrence within each period for which the events occurred. The rate of occurrence will be expressed as a percentage of the subjects from the Safety Analysis Set receiving the treatment concerned.

For the number of subjects and the rate of occurrence, the same classification (SOC and / or PT) in the same patient is counted only once.

In a first time, an overview of all AEs will be given overall and by period of treatment (Sunitinib, Axitinib) and will include the description of the number and the percentage of patients with the following criteria:

- At least one AE
- At least one SAE
- At least one non-serious AE
- At least one grade 3 AE
- At least one grade 4 AE
- At least one grade 3/4 AE

Same analysis will be repeated on related AEs only.

Then each of the following categories of AEs will be described by SOC and PT overall and by period of treatment (Sunitinib, Axitinib):

- All AEs
- Most common AEs (SOC or PT >= 10%)
- SAEs
- Non-serious AEs
- Grade 3 AEs
- Grade 4 AEs
- Grade 3/4 AEs

Same analysis will be repeated on related AEs only.

Proportion of patients who discontinued the treatment of interest because of AEs will be given with its 2-sided 95% 'exact' Clopper-Pearson confidence interval overall and by period of treatment (Sunitinib, Axitinib).

Treatment duration until discontinuation for AEs will be analyzed using descriptive statistics (mean, standard deviation, median and range) overall and by period of treatment (Sunitinib, Axitinib).

Proportion of patients who died due to any cause will be given with its 2-sided 95% 'exact' Clopper-Pearson confidence interval overall and by period of treatment (Sunitinib, Axitinib). Causes of deaths (tumor-related, other cause) will also be described.

8.2.2 Analyses of Efficacy Endpoints

Efficacy analyses will be provided in the FAS population.

Primary endpoints

PFS under Axitinib in 2nd line post Sunitinib will be described using the Kaplan Meier method in the SU-AXI subgroup:

- Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics: number of events, number of censored data, median survival time, Q1 and Q3 survival times and survival rates every 3 months.

  The confidence intervals for the median, Q1 and Q3 will also be provided according to Brookmeyer and Crowley (1982)

- The Kaplan-Meier curve will also be presented

Other primary endpoints will be analyzed according to the same methods:

- PFS for the sequence Sunitinib-Axitinib in the SU-AXI subgroup
- TTF under Axitinib in 2nd line post Sunitinib in the SU-AXI subgroup
- TTF for the sequence Sunitinib-Axitinib in the SU-AXI subgroup

Additionally a Cox regression model will run for the PFS under Axitinib in 2nd line post Sunitinib in the SU-AXI subgroup ***according to the method described in section 8.1 of this document (Strategy of selection of variables in multivariate models).*** Potential factors to be tested will be defined at time of Data Review Meetings among the ones mentioned in section 6.4 of this document.

Secondary endpoints

TSF for the sequence Sunitinib-Axitinib will be described using the Kaplan Meier method in the SU-AXI subgroup:

- Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics: number of events, number of censored data, median survival time, Q1 and Q3 survival times and survival rates every 3 months.

  The confidence intervals for the median, Q1 and Q3 will also be provided according to Brookmeyer and Crowley (1982)
- The Kaplan-Meier curve will also be presented

Following secondary endpoints will be analyzed according to the same methods:

- OS for the sequence SU-AXI in the SU-AXI subgroup
- PFS for Sunitinib received in 1st line
- OS for Sunitinib received in 1st line

ORR under Axitinib in 2nd line post Sunitinib will be given with its 2-sided 95% 'exact' Clopper-Pearson confidence interval in the SU-AXI subgroup.

Same analysis will be done for*:*

- CBR under Axitinib in 2nd line post Sunitinib in the SU-AXI subgroup
- ORR for Sunitinib received in 1st line
- CBR for Sunitinib received in 1st line

Additionally, following analysis will be performed according to MSKCC prognosis classification at Axitinib initiation (good/intermediate/poor) using the Kaplan Meier method:

- PFS under Axitinib in 2nd line post Sunitinib in the SU-AXI subgroup
- ORR under Axitinib in 2nd line post Sunitinib in the SU-AXI subgroup
- OS for the sequence SU-AXI in the SU-AXI subgroup
- For PFS and OS, the 3 Kaplan Meier curves corresponding to each MSKCC prognosis categories will be printed on a same graph.

Following analysis will be performed according to MSKCC prognosis classification at Sunitinib initiation (good/intermediate/poor) using the Kaplan Meier method:

- PFS for Sunitinib received in 1st line
- OS for Sunitinib received in 1st line
- ORR for Sunitinib received in 1st line
- CBR for Sunitinib received in 1st line
- For PFS and OS, the 3 Kaplan Meier curves corresponding to each MSKCC prognosis categories will be printed on a same graph.

If the number of patients who received IO in 2nd line is sufficient, following analysis will be performed according to MSKCC prognosis classification at Sunitinib initiation (good/intermediate/poor) using the Kaplan Meier method:

8.2.3 Analyses of Axitinib Treatment

Axitinib treatment analyses will be provided in the safety population.

Proportion of patients with the recommended starting dose of AXI (5 mg BID) will be given with its 2-sided 95% 'exact' Clopper-Pearson confidence interval in the SU-AXI subgroup.

Same analysis will be done for the proportion of patients:

- With other Axitinib starting doses. A listing of other doses reported will also be given.
- For whom the dose was reduced
- For whom the dose was increased
- With temporary interruption during the AXI treatment period. Description of corresponding reasons will also be provided.

- With AXI discontinuation. Description of corresponding reasons will also be provided.

AXI total daily dose (mg) received over the AXI treatment period will be analyzed using descriptive statistics (mean, standard deviation, median and range).

Same analysis will be provided for:

- The dose intensity (%) of Axitinib
- Duration (days) of the first Axitinib interruption
- Duration (days) of all interruptions together

8.2.4 Analyses of Quality of Life Endpoints

Quality of life analyses will be provided in the FAS population on the SU-AXI subgroup. According to the questionnaire date, time windows will be derived according to the rule explain in section **Error! Reference source not found.**. In case of missing or partial date, questionnaires will not be analyzed.

Quality of life will be analyzed using descriptive statistics at the treatment initiation, on the first 6 months and on AXI discontinuation overall and according to the best response observed under Axitinib treatment (CR, PR, SD, and PD):

- the FKSI-19 global score,
- the FKSI DRS-P subscore,
- the FKSI DRS-E subscore,
- the FKSI TSE subscore,
- the FKSI FWB subscore,
- the SF36 MH subscore,
- and the SF36 RE subscore.

Same analysis will be repeated on changes in scores/subscores from Baseline.

In order to explore possible variations in time and the possible differences according to the best response observed under Axitinib treatment, each changes in scores/subscores mentioned above will be analyzed using a mixed model for repeated measures (MMRM) according to the method described in section 8.1 of this document (Analysis of longitudinal data).

Estimated mean changes in scores/subscores from baseline will be provided and represented graphically with their 95% confidence interval:

- monthly (on the first 6 months),
- for each best response observed under Axitinib treatment (CR, PR, SD, and PD),
- in case of a statistically significant interaction between time and best response observed under Axitinib treatment, monthly estimated means will also be provided according to best response observed under Axitinib treatment (CR, PR, SD, and PD)

8.2.5 Analyses of Patients Characteristics at Time of SU Initiation

This analysis will be provided in the FAS population.

All patients' characteristics collected at SU initiation will be analyzed using descriptive statistics overall and according to treatment received at time of study inclusion: patients included in the study at time of Sunitinib initiation (Prospective group/SU in first line at inclusion) vs. patients included in the study at time of Axitinib initiation (Retrospective / prospective group/AXI in 2nd line at inclusion).

Note: some baseline characteristics related to SU initiation will be limited because of a retrospective part of the data collection. Whereas other ones, identified previously, will also be explored if the baseline is the AXI initiation (i.e. if patient was included in the study at time of Axitinib initiation).

These descriptions will be provided in the overall FAS population in a first time. Then they will be repeated on the SU-AXI subgroup.

Additionally, MSKCC prognosis classification (good/intermediate/poor) at SU initiation will be analyzed in patients who had PD as best response to 2nd line treatment and that for all 2nd line treatments (mainly for Axitinib and Nivolumab).

8.2.6 Analyses of Patients Characteristics at Time of AXI Initiation

This analysis will be provided in the FAS population on the SU-AXI subgroup.

All patients' characteristics collected at AXI initiation will be analyzed using descriptive statistics overall and according to treatment received at time of study inclusion: patients included in the study at time of Sunitinib initiation (Prospective group/SU in first line at inclusion) vs. patients included in the study at time of Axitinib initiation (Retrospective / prospective group/AXI in 2nd line at inclusion).

Additionally, MSKCC prognosis classification (good/intermediate/poor) at AXI initiation will be analyzed in patients who had PD as best response to Axitinib in 2nd line treatment.

9 LIST OF TABLES AND TABLE SHELLS

List of Tables and Table Shells will be provided in separate documents.

10 REFERENCES

Not Applicable.

11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and Use of Visit Windows in Reporting

Endpoint	Target Date	Target Day	Definition [Day window]
QoL	Baseline	1	Day-6 to Day 1
QoL	Month 1	30	Day 15 to Day 44
QoL	Month 2	60	Day 45 to Day 74
QoL	Month 3	90	Day 75 to Day 104
QoL	Month 4	120	Day 105 to Day 134
QoL	Month 5	150	Day 135 to Day 164
QoL	Month 6	180	Day 165 to Day 194

Day 1 corresponds to the Axitinib start date.

In case of multiple observations falling within a given window, the observations selected for analysis will be identified as follows:

1. The observation closest to the target day will be used.
2. If the observations are at equal distance from the target day in absolute value, the latest observation within the analysis window will be used.

A1.2 Further Definition of Endpoints

FKSI-19 questionnaire

NCCN-FACT FKSI-19

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	GF1	I am able to work (include work at home)	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

CCI

FKSI-19 scoring guidelines

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, and then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

If >50% of items were completed, the FKSI scores were calculated as the sum of the item responses divided by the number of items completed multiplied by the total number of items in the scale (eg, 19 in the case of the FKSI-19). If fewer than 50% of the items were completed, the scores were considered missing.

Scale	Item Code	Reverse item		Item response	Item Score
FKSI-19	GP1	**4**	-		=
Total	GP4	**4**	-		=
Score range: 0-76	C2	**4**	-		=
	HI7	**4**	-		=
	B1	**4**	-		=
	BRM3	**4**	-		=
	BP1	**4**	-		=
	L2	**4**	-		=
	HI12	**4**	-		=
	RCC2	**4**	-		=
	C6	0	+		=
	GF5	0	+		=
	GE6	**4**	-		=
	GP2	**4**	-		=
	C5	**4**	-		=
	GP5	**4**	-		=
	GF1	0	+		=
	GF3	0	+		=
	GF7	0	+		=

Sum individual item scores:

Multiply by 19:

Divide by number of items answered: **=FKSI-19**

Subscale	Item Code		Reverse item	Item response	Item Score
FKSI-DRS-P	GP1	**4**	-		=
(Disease Related	GP4	**4**	-		=
Symptoms-Physical)	C2	**4**	-		=
Score range: 0-48	HI7	**4**	-		=
	B1	**4**	-		=
	BRM3	**4**	-		=
	BP1	**4**	-		=
	L2	**4**	-		=
	HI12	**4**	-		=
	RCC2	**4**	-		=
	C6	0	+		=
	GF5	0	+		=

Sum individual item scores:

Multiply by12:

Divide by number of items answered: **=FKSI-DRS-P**

Subscale	Item Code	Reverse item	Item response	Item Score
FKSI-DRS-E				
(Disease Related				
Symptoms-Emotional)	**GE6**	4	-	= ___ **=FKSI-DRS-E**

Score range: 0-4

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-TSE	GP2	4	-		=
(Treatment	C5	4	-		=
Side Effects)	GP5	**4**	-		=

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____ **=FKSI-TSE**

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-F/WB	**GF1**	**0**	+		= _____
(Function/	**GF3**	**0**	+		= _____
Well-Being)	GF7	**0**	+		= _____

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: **=FKSI-F/WB**

RE and MN domains of SF-36 questionnaire

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

- Items of Role-Emotional (RE) domains

5.	During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)? **(Please circle one number on each line.)**	**Yes**	**No**
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

- Items of Mental-Health (MH) domains

9.	These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item. **(Please circle one number on each line.)**	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6

CCI [redacted]

SF-36 scoring guidelines

Step 1: For ease of interpretation each scale is then transformed to a 0-100 scale (see table below). This transformation converts the lowest and highest possible scores to zero (poor quality of life) and 100 (best quality of life) respectively.

Score of items for each item of RE and MH domains of SF-36 questionnaire

Items	Observed Score of items	
	Answer	(out of 100)
5a, 5b et 5c	1	0
	2	100
9d, 9h	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
9b, 9c, 9f	1	0
	2	20
	3	40
	4	60
	5	80
	6	100

Step 2:

The score of Role-Emotional (RE) domain of SF-36 will be defined as the sum of scores of items 5a, 5b and 5c, divided by 3.
The score of Mental Health (MH) domain of SF-36 will be defined as the sum of scores of items 9b, 9c, 9d, 9f and 9h, divided by 5.

For each domain:

- if >50% of items were missing, the missing values will be replaced by the average score of other completed items,
- If fewer than 50% of the items were completed, the scores were considered missing.

11.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

A2.1 Further Details of the Statistical Methods

Not Applicable.