Non-interventional (NI) study protocol
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Retrospective Study to Identify Clinical Factors Related to a High Benefit of Axitinib in metastatic Renal Cell Carcinoma (AXILONG Study)

Statistical Analysis Plan (SAP)

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LIST OF ABBREVIATIONS

AE: Adverse event.

CR: Complete response.

CRF: Case report form.

DB: Database.

DP: Disease progression.

EC: Exclusion Criteria.

FAS: Full Analysis Set.

IC: Inclusion criteria.

KPS: Karnofsky performance status.

LR: Long Responders

Max: Maximum.

Min: Minimum.

N: Number of cases.

NI: Non-interventionist.

ORR: Objective response rate.

PFS: Progression-free Survival.

PR: Partial Response.

PS: Performance status.

Q1: First quartile.

Q3: Third quartile.

RCC: Renal cell carcinoma.

SAP: Statistical Analysis Plan.

SD: Stable disease.

STD: Standard deviation.

TKI: Tyrosine kinase inhibitor.

Tmt: Treatment.

[redacted]

1 AMENDMENTS TO PREVIOUS VERSIONS

This is version 3 of the SAP.

Amendment No.	Date	Summary of change(s)	Reason(s)
1	9 August 2018	- Insertion of definitions and explanations for statistical analysis. - Specification of methodology and analysis to be performed. - Update of author and dates.	Review of the first version of the SAP.
2	24 October 2019	-Insertion of statistical analysis details, about the sob-groups of patients. Specifications of methodology and analysis to be perform.	Review after draft of results.

2 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical analyses that will be performed to generate the final report for the AXILONG study. This includes a brief summary of the main study characteristics and the aim of the SAP, which corresponds to the *statistical analysis plan for this study.*

The efficacy and safety profile of axitinib in patients with metastatic renal cell carcinoma (RCC) is scientifically documented in the pivotal phase III "AXIS" study, with a subgroup of patients who benefited from a longer progression-free survival, called "long-term responders" with a survival of greater than 9 months. However, due to the rigid inclusion criteria in a clinical trial, these data cannot be generalised to the population treated in normal clinical practice. Therefore, it is necessary to identify the clinical, tumour and response factors of these patients in "real-world" clinical practice compared to those patients with a below-average PFS.

These concepts underline the need for observational studies that respond to unsolved questions and complete the information obtained from clinical trials, helping to improve our understanding of the real-world use of medicines after they have been marketed and to confirm and reaffirm the data obtained in the development phase. So much so that, in the last few years, the European and local health authorities have started to include in their guidelines the application for real-world studies with authorised drugs that confirm these clinical data and allow for better patient screening.

Furthermore, studies carried out under routine clinical conditions allow us to establish whether clinicians' routine usage patterns correspond with the authorisation, which is based on information obtained from clinical trials.

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2.1 STUDY DESIGN

Post-authorisation, multicentre, observational study with retrospective follow-up.

In this study, the treatment with axitinib will have started before the enrolment of the patient, so the decision to treat and enrol these patients will be independent of the decision to carry out this study and will depend exclusively on the clinical judgement of the responsible doctor.

Study population

The eligible patient population for this study includes any patient with advanced or metastatic renal cell carcinoma who has been treated with axitinib for at least 9 months or whose best response to this treatment has been DP.

The requirements for a patient's inclusion are:

1. These patients had to receive axitinib as second-line treatment or further line, according to its Summary of Product Characteristics. Two groups exhibiting extreme responses to the drug will be compared: one group of patients showing no evidence of disease progression for at least 9 months after the start of treatment with axitinib versus a group of patients showing disease progression while taking the drug at the first response assessment.
2. Collection of clinical, safety and response data in patients with advanced renal cell carcinoma.

The study is expected to be conducted in at least 30 sites throughout Spain in order to reach the maximum number of study patients.

The study will start at each site after the agreement with the site is signed and all study documentation and information on the procedures and objectives of the study have been received by the person appointed by the sponsor.

Recruitment will be competitive between all participating sites. All the patients at a particular site who meet the inclusion criteria during the recruitment period may be enrolled. The recruitment period will have a maximum of three months from the opening of the last study site. No patient follow-up will be carried out after their inclusion in the study.

Patients will be considered evaluable if they meet the inclusion criteria and do not meet the exclusion criteria, and have received at least one dose of axitinib prior to their inclusion in the study.

[redacted]

Sample size

Given the low incidence of metastatic renal cell cancer, and thus the population to be included in the study, the number of patients expected to be included will be small, around 60 patients. However, as it is an observational and exploratory study, no hypotheses were specified and, therefore, the sample size calculation is not applicable.

Inclusion criteria

Patients must meet all the inclusion criteria below to be eligible for inclusion in the study:

1. IC1: Evidence of a personally signed and dated informed consent document indicating that the patient (or his/her legal representative) has been informed of all relevant aspects of the study. Informed consent will only be obtained from patients who are still alive.
2. IC2: Aged 18 or over.
3. IC3: Histologically confirmed diagnosis of advanced renal cell carcinoma, with at least one radiological evaluation of the disease according to RECIST 1.1 criteria.
4. IC4: Treatment with axitinib, as second-line or further line treatment and with progression-free survival PFS of 9 months or more or with disease progression at the first response assessment.

Exclusion criteria

Patients who meet any of the following criteria will not be included in the study:

1. EC1: Treatment with axitinib not specified in the summary of product characteristics.
2. EC2: Non-compliance with any of the study inclusion criteria.

[redacted]

Analysis population

All analyses will be performed with evaluable patients.

The CRF contains the information related to the eligibility criteria as binary variable (Yes/No) for each of the described items.

Several of these criteria can be verified with the data recorded in the CRF. This verification is performed in order to prevent the inclusion of non-evaluable participants in the statistical report and prior to the start of any analysis.

These patients will be considered screening failure, and in the statistical report they will thus be included in a table of patient disposition together with the patients screening failure initially confirmed by the sponsor.

The criteria to be verified in the patient CRFs to define the evaluable population are described below:

- An "evaluable" patient must have received at least one dose of axitinib prior to inclusion in the study: it must be verified that the "Starting dose" and the "Treatment start date with axitinib" have been specified in "Treatment with axitinib". This date must be prior to the date of signing the informed consent (for patients who are still alive at enrolment).

- Inclusion requirement *Patients must have received axitinib as second-line treatment or further line*: it must be verified that there is information concerning a first-line treatment in the “First-line treatment” section.

- IC1: *Evidence of a personally signed and dated informed consent document indicating that the patient (or his/her legal representative) has been informed of all relevant aspects of the study. Informed consent will only be obtained from patients who are still alive*.

It must be verified that the date of signing the informed consent is specified (for patients who are still alive at enrolment).

Noted that for patients already dead before the study inclusion, the CI1 could be “No”.

- IC2: *Aged 18 or over.*

It must be verified that the age calculated with respect to the date of the baseline visit is ≥18 years.

- IC3: *Histologically confirmed diagnosis of advanced renal cell carcinoma, with at least one radiological evaluation of the disease according to RECIST 1.1 criteria*.

It must be verified that the following data have been indicated: Date of first diagnosis, Tumour stage at disease diagnosis, Date of advanced disease diagnosis, Stage of advanced disease, Metastasis location, Best treatment response (first-line treatment).

[redacted]

- IC4: *Treatment with axitinib, as second-line or further line treatment and with progression-free survival PFS of 9 months or more or with disease progression at the first response assessment*.

It must be verified that in "Treatment with axitinib", "Treatment line in which it has been received" is ≥2.

It must be verified that the patient meets one of the following two conditions:

- "*Progression-free survival PFS of 9 months or more*": the time from the start of treatment with axitinib to disease progression or death by any cause is ≥ 9 months (see definition of PFS in section 7. Definition of variables).

or

- "*Disease progression at the first response assessment*": PD has been indicated in "Treatment with axitinib/ Best response to treatment".

If there is a contradiction between the binary variables and the information shown in the CRF, the latter shall be assumed valid.

A list of candidate patients who are non-evaluable must be made, and after approval or rectification by the study sponsor/coordinator, the list of non-evaluable patients who will be excluded from the analyses will be closed.

The sponsor will be informed of the number of non-evaluable study patients for the analysis and the reasons for non-inclusion, for consultation and confirmation prior to starting the analyses.

Origin of the data

The source document for this study will be the patient's medical records documented in his/her medical chart, including his/her surgical records, which will be kept at the study site. For special issues and/or queries or government inspection requirements, it will also be necessary to access the complete study file, if the patients' right to anonymity is protected.

The information collected in CRFs must match the data from the Medical charts.

[redacted]

Cohort treatment/labelling

For the study, “long-term responders to axitinib” have been defined as patients with a PFS for at least 9 months with the drug, and “refractory patients to axitinib” have been defined as patients with disease progression in the first assessment since the initiation of treatment (estimated PFS ≤3 months).

See point 5.2. *subgroups*, and in group 7 *Definition of variables and objectives,* how these groups are defined in terms of CRFs variables and algorithmic conditions of computer programming for the patient’s classification.

[redacted]

2.2 STUDY OBJECTIVES

The primary objective of the study is:

- To describe the baseline clinical characteristics of the long-term responders to axitinib and to identify clinical factors associated with a long-term response to axitinib (defined as progression-free survival of at least 9 months since the drug initiation), by comparing two groups of patients with an extreme response to the drug: one group of patients who are progression-free for at least 9 months versus a group of patients with disease progression before the first response assessment.
- To analyse the association of some clinical factors with greater benefit with the drug.

The secondary objectives of the study are:

- To describe the response to treatment with axitinib in the long-term responder's group.
- To describe the efficacy for each treatment line (second line treatment and further lines).
  - Best treatment response (Complete response [CR], Partial response [PR], Stable disease [SD]).
  - Progression-free Survival.
  - Objective Response Rate (ORR) and Clinical Benefit (sum of CR, PR and SD).
  - Time to progression.
  - Overall Survival.
- To describe the duration of treatment with axitinib.
- To describe the percentage of patients who increased axitinib doses to more than 5 mg twice daily.
- To describe the percentage of patients who reduced axitinib doses to less than 5 mg twice daily.
- To describe the axitinib tolerability.
- To describe the treatments received at progression.
- To describe the response to the treatments received at progression.

[redacted]

3 INTERIM ANALYSES

No interim analyses are planned.

4 HYPOTHESIS AND DECISION RULES

The level of significance will be α=0.05 two-tailed in all the statistical inference tests.

Adjustment by multiple comparisons is not planned.

5 ANALYSIS GROUPS/POPULATIONS

5.1 FULL ANALYSIS SET

The full analysis set [FAS] includes all evaluable patients, i.e. all patients who meet all the inclusion criteria and none of the exclusion criteria and have received at least one dose of axitinib prior to inclusion in the study.

5.2 SUBGROUPS

For some of the study objectives, the following two groups of patients with extreme responses to the drug are defined (see definition in point 7. Definition of variables):

- "Long-term responders to axitinib": Patients who have a PFS of at least 9 months with the drug.
- "Patients primary refractory to axitinib": Patients with disease progression at the first assessment after the initiation of treatment (estimated PFS $\leq$ 3 months). It means, patients with best response to axitinib=PD.

[redacted]

6 VARIABLES IN THE CRF

The following groups of variables will be recorded for this observational study: Demographic data, medical history, first-line treatments, other treatments prior to axitinib, treatment with axitinib, subsequent treatments and the patient's vital status. Details of all the variables recorded in the CRF are given below:

- Demographic data:
  - Date of birth
  - Gender
- Clinical history of renal cell carcinoma
  - Date of first diagnosis
  - Tumour stage at disease diagnosis (I/II/III/IV)
  - Non-systemic treatment
    - Nephrectomy (Yes/No/Unknown).
      - If yes, specify:
        - Date (Date/Unknown)
        - Type (Total/Partial/Unknown)
        - Kidney (Right/Left/Unknown)
      - Radiotherapy (Yes/No/Unknown).
        - If yes, specify:
          - Date (Date/Unknown)
    - Histological type (100% Clear cells/ Primarily clear cells/ Primarily non-clear cells/ 100% Non-clear cells)
      - If 100% Clear cells have not been marked, specify (Sarcomatoid/Chromophobe/ type 1 Papillary/ type 2 Papillary/ Other, specify/Not performed)
  - Diagnosis of advanced disease
    - Date
    - Stage (III/IV)
    - Metastasis site (multi-response question):
      - Lymph nodes
      - CNS
      - Liver
      - Lungs
      - Bone
      - Other, specify
    - Risk criteria before the initiation of the first line
      - Time from initial diagnosis to systemic treatment less than 1 year (Yes/No/Unknown)
      - ECOG/PS (Yes/No/Unknown)
      - LDH >1.5 x ULN (Yes/No/Unknown)
      - Haemoglobin < LLN (Yes/No/Unknown)
      - Corrected calcium >10 mg/dl (Yes/No/Unknown)
      - Presence of 2 or more metastatic sites (Yes/No/Unknown)

[redacted]

- Platelets > ULN (Yes/No/Unknown)
- Neutrophils > ULN (Yes/No/Unknown)- (current value)
- Lymphocytes (Yes/No/Unknown)- (value)
- Smoking habits (Smoker/Non-smoker/Former smoker)

- First-line treatment
  - Drug
  - Starting dose
  - Duration of treatment
    - Start date
    - End date
    - Reason for treatment withdrawal (DP/Toxicity/Other, specify)
    - Has there been disease progression? (No/Yes, specify date)
    - Best treatment response (CR, PR, SD, DP/Not evaluable).
      - Date of the best response obtained
- Other treatments prior to axitinib
  - Has the patient received other treatments prior to axitinib? (Yes/No/Unknown)
    - If yes, specify:
      - 2nd-line treatment
        - Drug
        - Starting dose
        - Reason for starting this treatment (DP in the 1st line treatment/Toxicity in the 1st line treatment/Other, specify)
        - Start date
        - End date
        - Reason for treatment withdrawal (DP/Toxicity/Other, specify)
        - Has there been disease progression? (No/Yes, specify date)
        - Best treatment response (CR, PR, SD, DP/Not evaluable).
          - Date of the best response obtained
      - 3rd-line treatment
        - Drug
        - Starting dose
        - Reason for starting this treatment (DP in the 2nd line treatment/Toxicity in the 2nd line treatment/Other, specify)
        - Start date
        - End date
        - Reason for treatment withdrawal (DP/Toxicity/Other, specify)
        - Has there been disease progression? (No/Yes, specify date)

[redacted]

        - Best treatment response (CR, PR, SD, DP/Not evaluable).
            - Date of the best response obtained

- Treatment with axitinib
    - Treatment line in which it was received.
    - Reason for starting treatment with axitinib (DP in previous treatment line/Toxicity in previous treatment line/Other, specify).
    - Risk criteria at the initiation of treatment with axitinib
        - Time from first diagnosis to systemic treatment less than 1 year (Yes/No/Unknown)
        - ECOG/PS (current status) (Yes/No/Unknown)
        - LDH >1.5 x ULN (Yes/No/Unknown)
        - Haemoglobin < LLN (Yes/No/Unknown)
        - Corrected calcium >10 mg/dl (Yes/No/Unknown)
        - Presence of 2 or more metastatic sites (Yes/No/Unknown)
        - Platelets > ULN (Yes/No/Unknown)
        - Neutrophils > ULN (Yes/No/Unknown) (value)
        - Lymphocytes (Yes/No/Unknown) (value)
        - Smoking habits (Smoker/Non-smoker/Former smoker)
    - Presence of comorbidities
        - Kidney failure (Yes/No)
            - If yes, specify, Creatinine Clearance (Mild, 60-89 ml/min/ Moderate, 30-59 ml/min/ Severe, 15-29 ml/min/ End Stage, <15 ml/min/ Dialysis)
        - Liver failure (Yes/No)
            - If yes, specify, Child Pugh (A/B/C)
        - Cardiovascular (Yes/No)
            - If yes, specify (multi-response question)
                - Decreased LVEF, specify %
                - Heart failure
                - Previous arrhythmia
                - Previous ischaemia
                - Controlled HTN, specify number of antihypertensive agents
                - Other, specify
        - Respiratory disease (Yes/No), specify
        - Other comorbidity (Yes/No), specify
    - Start date of treatment with axitinib
    - Has treatment with axitinib been discontinued? (Yes/No)
        - If yes, specify:
            - End-of-treatment date
            - Reason for suspension of treatment (DP/Toxicity/Other, specify)
    - Risk criteria at discontinuation of treatment with axitinib

[redacted]

- Time from first diagnosis to systemic treatment less than 1 year (Yes/No/Unknown)
- ECOG/PS (current status) (Yes/No/Unknown)
- LDH >1.5 x ULN (Yes/No/Unknown)
- Haemoglobin < LLN (Yes/No/Unknown)
- Corrected calcium >10 mg/dl (Yes/No/Unknown)
- Presence of 2 or more metastatic sites (Yes/No/Unknown)
- Platelets > ULN (Yes/No/Unknown)
- Neutrophils > ULN (Yes/No/Unknown) (value)

- Has there been disease progression? (No/Yes, specify date)
- Best treatment response (CR, PR, SD, DP/Not evaluable).
  - Date of the best response obtained
- Starting dose (5 mg/12 h; 2 mg/12 h; 3 mg/12 h; 7 mg/12 h; 10 mg/12 h)
- Has the dose been modified? (Yes/No)
  - If yes, specify:
    - Increased/Reduced
    - Dose modification date
    - Reason for dose modification
    - New dose (5 mg/12 h; 2 mg/12 h; 3 mg/12 h; 7 mg/12 h; 10 mg/12 h; other, specify mg/h)
- Adverse events
  - Adverse events (Anaemia; Asthenia; Fatigue; Diarrhoea; Dysphonia; Elevated ALT/GPT; Elevated AST/GOT; Elevated Bilirubin; Elevated Creatinine; Elevated Haemoglobin; Elevated Lipase; Hypercalcaemia; Hypertension; Hypocalcaemia; Hypophosphatemia; Hypothyroidism; Lymphopenia; Mucositis; Nausea; Neutropenia; Proteinuria; Rash; Hand-foot syndrome; Thrombocytopaenia; Vomiting, Other, specify).
  - Worst grade according to CTCAE
  - Cycle in which the worst grade occurred
  - Related to treatment (Yes/No)
  - Serious AE? (Yes/No), if yes, specify
    - Reason (Results in death/ Is life threatening/ Leads to hospitalisation or prolongation of hospitalisation/ Causes persistent or significant disability or incapacity/ Causes a congenital anomaly or birth defect/ Is medically significant).

- Subsequent treatments
  - Has the patient received any subsequent treatment? (Yes/No)
    - If yes, specify
      - Drug received
      - Starting dose
      - Treatment line
      - Start date

[redacted]

        - End date
        - Ongoing
        - Best response attained (CR, PR, SD, DP/Not evaluable)
        - Reason for discontinuation (DP/Toxicity/Other, specify)
- Vital status
    - Date of last follow-up
    - Status (Alive/Death)
        - If Death, specify
            - Date of death
            - Cause of death (DP, Other, specify)

[redacted]

7 DEFINITION OF VARIABLES AND OBJECTIVES

In addition, the following variables will be calculated from the CRF data:

NOTE: In patients with dates after the date of the IC visit / signature, the date of the IC visit / signature has been considered as the date of the last check. Due to the retrospective nature of the study, no data can be collected after the patient was included in the IC study / signature.

- Age (years) of patient at time of visit= (Visit date – Date of birth) / 365.25
- Age (years) at first diagnosis= (Date of first diagnosis – Date of birth) / 365.25
- Age (years) at the initiation of axitinib= (start date of axitinib – Date of birth) / 365.25
- Number of metastatic locations = sum (Lymph nodes, CNS, Hepatic, Pulmonary, Bone, Other).
- • Neutrophil / lymphocyte ratio. It will be categorized as follows: ≤3,> 3. "Before the beginning of the first line" and "At the beginning of treatment with axitinib" will be analyzed. This ratio is not calculated on axitinib suspension because there is no current lymphocyte value data in that part of the CRF.
- Time (months) between first diagnosis and nephrectomy = (Date of nephrectomy – Date of first diagnosis) / 30.4375. A list with the information (site, patient, date of first diagnosis, date of nephrectomy and the calculated time) in cases in which the time is negative (with date of nephrectomy before or equal to date of first diagnosis) will be displayed, and these cases will not be included in the descriptive analysis
- Time (months) between first diagnosis and radiotherapy = (Date of radiotherapy – Date of first diagnosis) / 30.4375. A list with the information (site, patient, date of first diagnosis, date of radiotherapy and the calculated time) in cases in which the time is negative (with date of radiotherapy before or equal to date of first diagnosis) will be displayed, and these cases will not be included in the descriptive analysis.
- Time (months) between first diagnosis and 1st-line treatment = (Date of the initiation of 1st-line treatment – Date of first diagnosis) / 30.4375. A list with the information (site, patient, date of first diagnosis, date of 1st-line treatment and the calculated time) in cases in which the time is negative (with date of 1st-line treatment before or equal to date of first diagnosis) will be displayed, and these cases will not be included in the descriptive analysis
- Duration (months) of previous1st-line treatment = (Date of end of 1st-line treatment – Date of start of 1st-line treatment) / 30.4375. If a patient is detected in whom this duration cannot be calculated or a negative time is left, it will not be considered in the descriptive analysis, and a list will be shown with the information related to this calculation of said patient.

[redacted]

- Pre-treatment of 1st line: a descriptive table with the collected drugs will be shown (if necessary, a list will be sent to the sponsor for the grouping of these drugs). In addition, the registered drugs will be grouped into three groups: Sunitinib, Other iTK, and Others, and the descriptive table will be included in the report.
- Duration (months) of previous 2nd-line treatment = (Date of end of 2nd-line treatment – Date of start of 2nd-line treatment) / 30.4375. If a patient is detected in whom this duration cannot be calculated or a negative time is left, it will not be considered in the descriptive analysis, and a list will be shown with the information related to this calculation of said patient.
- Duration (months) of previous 3rd-line treatment = (Date of end of 3rd-line treatment – Date of start of 3rd-line treatment) / 30.4375. If a patient is detected in whom this duration cannot be calculated or a negative time is left, it will not be considered in the descriptive analysis, and a list will be shown with the information related to this calculation of said patient.
- Duration (months) of previous 4th-line treatment = (Date of end of 4th-line treatment – Date of start of 4th-line treatment) / 30.4375. If a patient is detected in whom this duration cannot be calculated or a negative time is left, it will not be considered in the descriptive analysis, and a list will be shown with the information related to this calculation of said patient.
- Duration (months) of previous 5th-line treatment or further= (Date of end of 5th-line treatment – Date of start of 5th-line treatment) / 30.4375. It will be analyzed only if there if an adequate sample (enough high) of patients with 5th or later previous o lines.
- Duration (months) of treatment with axitinib = (Date of end of axitinib treatment or of latest follow-up if not suspended – Date of start of axitinib treatment) / 30.4375
- Time (months) to increase or Time (months) to reduction of axitinib dose = (Dose increase date or Dose reduction date – Start date of treatment with axitinib) / 30.4375
- Duration (months) of subsequent treatments = (Date of end of subsequent treatment or of latest follow-up if not suspended – Date of start of subsequent treatment) / 30.4375. In the case of several subsequent treatments per patient, proceed as follows: the duration in months of each of the subsequent treatments will be calculated (from the start date to the end date or last check if it continues). This will be done for all subsequent treatments and then proceed to make the sum per patient of all durations of subsequent treatments

[redacted]

- Progression-Free Survival (PFS, in months) =
  (Date of Disease Progression on treatment with axitinib or death from any cause – Date of start of treatment with axitinib) / 30.4375
  If there is no progression or death, the case is censored as
  PFS (months) = (Date of latest follow-up – Date of start of treatment with axitinib) / 30.4375
- Time to progression (TTP, in months) =
  (Date of Disease Progression – Date of start of treatment with axitinib) / 30.4375
  If there is no progression, the case is censored as
  TTP (months) = (Date of latest follow-up – Date of start of treatment with axitinib) / 30.4375
- Overall Survival (OS, in months) = (Date of death – Date of start of treatment with axitinib) / 30.4375
  If death has not occurred, the case is censored as
  Overall Survival (OS, in months) =(Date of latest follow-up – Date of start of treatment with axitinib) / 30.4375
- Overall Survival since the start of first-line treatment (OS, in months) = (Date of death – Date of start of first-line treatment) / 30.4375

  If death has not occurred, the case is censored as
  Overall Survival (OS, in months) = (Date of latest follow-up – Start date of first treatment) / 30.4375
- Patient subgroups
  - A-Long-term responders: comprising patients with PFS ≥9 months.
  - B-Refractory (primary): comprising patients with best response to treatment = PD. This date is collected in the CRF form “axitinib treatment”.
- MSKCC risk group (described in appendix 11.1.). It will be analysed “Before the beginning of the first line". These calculations will be performed on patients who have data on all the variables involved (in the case of a patient who does not have data on all the variables but has> 2 factors, it will be classified in the “Poor” risk group.

  Risk groups are defined considering the following five factors (Favourable, Intermediate, Poor):
  - ECOG/PS <1 (related to KPS <80)
  - Time from first Diagnosis to Systemic Treatment less than 1 year
  - LDH >1.5 x ULN
  - Corrected calcium >10 mg/dl
  - Haemoglobin < LLN

[redacted]

The risk groups are as follows:

- Favourable: 0 factors
- Intermediate: 1 or 2 factors
- Poor: >2 factors

- Heng (or IMDC) risk group (described in appendix 11.1.). It will be analysed "at the beginning of the axitinib treatment" and "on the axitinib discontinuation". These calculations will be performed on patients who have data on all the variables involved (in the case of a patient who does not have data on all the variables but has> 2 factors, it will be classified in the "Poor" risk group.

  Risk groups are defined taking into account the following six factors (Low, Intermediate, High):

  - ECOG/PS <1 (related to KPS <80)
  - Time from first Diagnosis to Systemic Treatment less than 1 year
  - Corrected calcium >10 mg/dl
  - Haemoglobin < LLN
  - Neutrophils > ULN
  - Platelets > ULN

  The risk groups are as follows:

  - Favourable: 0 factors
  - Intermediate: 1 or 2 factors
  - Poor: >2 factors

- Risk group according to MSKCC Criteria for patients previously treated with a TKI (defined in appendix 11.1). It will be analysed "at the beginning of the axitinib treatment". Of note, all patients must have been previously treated with a TKI. These calculations will be performed on patients who have data on all the variables involved (in the case of a patient who does not have data on all the variables but has> 2 factors, it will be classified in the "Poor" risk group.

Risk groups are defined taking into account the following three factors (Low, Intermediate, High):

- ECOG/PS <1 (related to KPS <80)
- Haemoglobin < LLN
- Corrected calcium >10 mg/dl

The risk groups are as follows:

[redacted]

  - Favourable: 0 factors
  - Intermediate: 1 factor
  - Poor: 2 or 3 factors
- The Objective Response Rate (ORR) is the frequency of subjects with CR or PR.
- The Clinical Benefit Rate is the frequency of subjects with CR, PR or SD.
- Increase of the axitinib dose to above 5 mg twice daily. Defined as having specified "Increase" at least one time, and in this case having specified "New dose" >5 mg/12h.
- Reduction of the axitinib dose to below 5 mg twice daily. Defined as having specified "Reduction" at least one time, and in this case having specified "New dose" <5 mg/12h.

[redacted]

7.1 PRIMARY OBJECTIVE

In order to meet the study's primary objective, the baseline clinical characteristics of two patient groups with extreme response to the drug will be compared: A group of patients with long-term responses to the drug (long-term responders to axitinib) versus a group of patients with disease progression at the first assessment after the initiation of treatment (group of patients refractory to axitinib).

The classification (in long-term responders or refractory patients) will be based on PFS (in months), as indicated in section 5.2.

It will be shown the following descriptive tables:

- "Long responder" patient (Yes, No). "Long responding patient" is defined if he / she has an PFS ≥9 months (during axitinib treatment). The 95% CI will be displayed.
- PFS in long responding patients. Only the descriptive analysis of the time in months and the CI for the average, will be shown.
- "Refractory" patient (Yes, No). "Refractory patient" is defined if there is a better response to treatment = PE (to axitinib treatment). 95% CI will be shown.
- PFS in refractory patients. Only the descriptive analysis of the time in months and the CI for the average will be shown.
- Patient group (Long respondent, refractory). It is defined in section 5.2. IC95% will be displayed

At the same time, In addition to comparisons of baseline clinical characteristics between the groups (long-term responders, refractory patients), an association analysis of the following factors with the study groups will be performed:

- Age with respect to first visit (≤65 years and >65 years).
- Age with respect to first diagnosis (≤65 years and >65 years).
- Age with respect to start of axitinib (≤65 years and >65 years).
- Baseline ECOG/PS and at the initiation of first line treatment (0, 1 and ≥2).
- Baseline ECOG/PS and at the initiation axitinib treatment (0, 1 and ≥2).
- Baseline ECOG/PS and at the end of axitinib treatment (0, 1 and ≥2).
- Number of previous treatment lines
- Number of previous treatment lines (1, 2 and ≥3)
- Previous nephrectomy (yes and no)
- MSKCC (or IMDC) risk group in all moments in which it is analysed during the study (favourable, intermediate and poor)

[redacted]

- Histology (100% clear cells, primarily clear cells, primarily non-clear cells, 100% non-clear cells)
- Duration of first-line treatment
- Duration of first-line treatment:([0-3] months, [3-6] months, [6-9] months, [9-12] months, ≥12 months).
- Duration of first-line treatment: (≤9months, >9 months).
- Duration of first-line treatment: (≤12months, >12 months).
- Duration of first-line TKi treatment: ([0-3] months, [3-6] months,]6-9] months,]9-12] months, ≥12 months).

  It will be calculated the duration of the first line, if the drug was only a TKi.
- Duration of first-line TKi treatment: (≤9months, >9 months).
- Duration of first-line TKi treatment: (≤12months, >12 months).
- Duration of the first TKI treatment:([0-3] months, [3-6] months, [6-9] months, [9-12] months, ≥12 months.

  It will be calculated the duration of the first treatment with a TKi, in 1st or later line (always after axitinib).
- Patients treated with a TKi previous to axitinib other than first. It will be analysed the number of patients with a TKi previous to axitinib, different from the first TKi received.

  It will be analysed the duration of this treatment.
- Best response with the TKI received in the first-line (CR, PR, SD, DP)
- Best response with a TKi previous to axitinib with a TKi other than first line (CR, PR, SD, PD).
- Best response with line prior to axitinib with a TKI if a line prior to axitinib other than the first one has been received (CR/PR, SD, DP).
- Number of metastatic locations (1, 2 and ≥3); See this definition in section 7 Definitions of variables and objectives.
- Site of metastases (CNS metastases [yes vs no]; lymph nodes [yes vs no]; lung [yes vs no]; liver [yes vs no]; bone [yes vs no]). In addition to showing the descriptive and comparative table of metastatic locations between groups, another similar table will be shown but with the categories “Hepatic” and “Bone” united in a single.
- Neutrophil/lymphocyte ratio ≤3 (yes vs no). See this definition in section 7 Definitions of variables and objectives. It will be analysed in all moments included in the study.
- Line of treatment in which it was received.

[redacted]

- Presence of comorbidities.
- Suspension of treatment.
- Have you received any further treatment?
- Has there been disease progression?
- Best response to treatment (RC, RP, EE, PE).
- Best response to treatment (RC / RP, EE, PE).
- Duration of axitinib treatment.
- Vital status
- Baseline LDH levels >1.5xULN (yes vs no). At the beginning of 1st line
- Baseline Hgb levels ≤LLN (yes vs no). At the beginning of 1st line
- Baseline corrected Ca++ levels >10 mg/dl (yes vs no). At the beginning of 1st line
- Baseline neutrophil levels > ULN (yes vs no). At the beginning of 1st line
- Baseline platelet levels > ULN (yes vs no). At the beginning of 1st line
- Smoking habits (smoker, non-smoker or former smoker). At the beginning of 1st line
- Baseline LDH levels >1.5xULN (yes vs no). At the beginning of axitinib treatment
- Baseline Hgb levels ≤LLN (yes vs no). At the beginning of axitinib treatment
- Baseline corrected Ca++ levels >10 mg/dl (yes vs no). At the beginning of axitinib treatment
- Baseline neutrophil levels > ULN (yes vs no). At the beginning of axitinib treatment
- Baseline platelet levels > ULN (yes vs no). At the beginning of axitinib treatment
- Smoking habits (smoker, non-smoker or former smoker). At the beginning of axitinib treatment

A logistic regression model will then be carried out to study the association between belonging to each of the two extreme treatment response groups, with each of the possible clinical factors of interest, prior to axitinib treatment. That is, those baseline factors (prior to the start with axitinib) that have been studied in section 7 and that are significant (P <0.05) or close to significance (P <0.15).

The factors in this situation will be summarized below, and that potential prognostic factors of the response to axitinib treatment (long responding group vs refractory group) are considered.

[redacted]

The optimal model of prognostic factors will be constructed with the variables that are finally significant (P <0.05).

7.2 SECONDARY OBJECTIVES

- Response to treatment with axitinib in the long-term responder group (defined as a PFS of at least 9 months with the drug). The "Best treatment response" variable from the "Treatment with axitinib" form will be analysed in this group of patients.
- Efficacy of axitinib by treatment line (second line treatment and further lines). Note: in treatments following axitinib, the "Date of progression" is not available, so times to progression will not be done.

  o Treatment line in which axitinib is received (2, ≥3).

The following descriptive analyzes will be performed based on the treatment line on which axitinib has been received (2 vs. ≥3):

- o Best treatment response (CR, PR, SD, DP).
- o Duration of treatment.
- o Progression-free survival (this will not be performed for subsequent treatments).
- o Objective response rate (ORR) and clinical benefit (sum of CR, PR and SD).
- o Time to Progression (this will not be performed for subsequent treatments).
- o Overall Survival.

- Efficacy of axitinib per treatment line depending on the group (LR and Refractories)

A table will be displayed with the number of treatment line in which axitinib has been received in both groups of patients (2, ≥3). Depending on these groups (2, ≥3) the following analyzes will be performed in each of the groups (LR and PR):

- o Best treatment response (CR, PR, SD, DP).
- o Duration of treatment.
- o Progression-free survival
- o Objective response rate (ORR) and clinical benefit
- o Time to Progression
- o Overall Survival.

[redacted]

Likewise, a table will be shown with the number of patients with axitinib in the second line of treatment, and in ≥ 3 line in each group (long responders and refractories).

The following analyzes will be carried out by group (long responders / refractories):

- Best treatment response (CR, PR, SD, DP).
- Duration of treatment.
- Progression-free survival. PFS will be shown in all patients with axitinib in the second line of treatment, and PFS per group
- Objective response rate (ORR) and clinical benefit.
- Time to Progression
- Overall Survival. OS will be shown in all patients with axitinib in the second line of treatment, and OS per group
- Progression-free survival to sunitnib. PFS will be shown in all patients with axitinib in the second line of treatment, and PFS per group

It will be calculated as follows: Progression Free Survival to sunitinib (SLP, in months) = (Date of Progression of the Disease to treatment with sunitinib - Start date of treatment with sunitinib) / 30,4375. If there is no progression, the case is censored in SLP (months) = (Start date of treatment with axitinib - Start date of treatment with sunitinib) / 30,4375.

- **Majority sequence**

The number of patients receiving the second-line treatment will be shown, following the sequence that is most observed in all the patients included (SUT-AXI-NIVO).

The following analyzes will be carried out by group (long responders / refractories):

- Best treatment response (CR, PR, SD, DP).
- Duration of treatment (months).
- Progression-free survival. PFS will be shown in all patients with suntinib-axitinib sequence and PFS per group.
- Objective response rate (ORR) and clinical benefit.
- Time to Progression
- Overall Survival. OS will be shown in all patients with sunitnib-axitinib sequence and OS per group
- Overall Survival since the beginning of 1st line. OS will be shown in all patients with sunitnib-axitinib sequence and OS per group

It is defined as: Global Survival from the beginning of the first line (SG, in months) = (Exit date - Start date of first line treatment) / 30,4375. If there is no exitus the case is censored in Global Survival (SG, in months) = (Date of last control - Start date of the first treatment) / 30,4375.

[redacted]

- To describe the duration of treatment with axitinib.It will be described as it is described in section 7. Definition of variables and objectives
- To describe the percentage of patients who had increase the dose of axitinib above 5 mg twice daily. It will be described as it is described in section 7. Definition of variables and objectives
- To describe the percentage of patients who had reduce the dose of axitinib below 5 mg twice daily. It will be described as it is described in section 7. Definition of variables and objectives
- To describe the tolerability of axitinib (see point 9.2. Statistical analyses, Safety objectives).
- To describe the response to treatments received at progression. The treatments received will be described in cases of DP for first-line, 2nd line, etc.; that is, in treatments prior to axitinib.

- Overall survival based on post treatment

  o Overall survival. The OS will be displayed according to having received further treatment (Yes vs. No).

  o The following analyzes will be carried out in the patient population depending on whether or not they have had subsequent treatment;

  □ OS per group (LR vs RF).

  □ OS per axitinib line (2 VS ≥3).

  □ OS per group (LR vs RF) for patients with axitinib in line 2.

  □ OS per group (LR vs RF) for patients with axitinib online ≥3.

- Overall survival based on most recent subsequent treatment.

The following analyzes will be performed in this subpopulation of patients in the groups of patients who have had the 2 most common subsequent treatments:

- OS
- OS per group (LR vs RF)
- OS per axitinib line
- OS per group (LR vs RF) for patients with axitinib online 2
- OS per group (LR vs RF) for patients with axitinib online ≥3

• To describe treatments received at progression. The treatments received in the cases of PD for first line, 2nd line etc ... it means, in the treatments previous to axitinib will be described. The analysis of post-axitinib treatments will be shown as explained in section 9.2 Statistical analysis.

The responses of the previous treatments to axitinib initiated by PD in the different registered lines will be presented.

[redacted]

- Subpopulation of special interest

Patients with the sunitinib and axitinib sequence, without liver or bone metastases and MSKCC risk group at the beginning of favorable or intermediate axitinib will be analyzed.

In this group of patients, the following analyzes will be carried out by group (long responders / refractories):

- Best response to treatment (RC, RP, EE, PE).
- Duration of treatment with axitinib (months).
- PFS, PFS will be shown in all patients of this subpopulation, and this same SLP per group
- TRO, clinical benefit.
- Time to progression.
- Overall Survival. OS will be shown in all patients of this subpopulation, and OS per group.

[redacted]

8 MANAGEMENT OF MISSING DATA

In the event of incomplete dates, proceed as follows:

- If the year XXXX is known, but not the day or month, 15/06/XXXX will be entered.
- If the month YY and year XXXX are known, but not the day, 15/YY/XXXX will be entered.

For all other variables, no criterion for substituting missing data will be used.

9 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSIS

9.1 STATISTICAL METHODOLOGY

Descriptive analysis:

Continuous numerical variables will be described using the principal measurements of centralisation and dispersion (mean, median, standard deviation, minimum Min., maximum Max., 25th percentile [Q1], 75th percentile [Q3], N)." 95% confidence intervals shall be given for the main quantitative variables for results associated with the primary objective and the main secondary variables.

There will be two percentage columns in the descriptive analysis of the qualitative variables: the total (%) and valid (% valid) percentages, that is, the percentage of the sum of valid responses plus missing values and the percentage of the total valid responses.

For questions with more than one response option (multi-response questions), multiple response tables will be displayed. These tables will show two percentage columns:

[redacted]

Inferential analysis:

When an inferential analysis is required, parametric tests will be used for continuous variables, and non-parametric tests will be used for ordinal, categorical or non-parametric variables. The hypothesis tests to be carried out will be two-tailed test in all cases with a significance level of 0.05. For variables that are not adjusted to a normal (or parametric) distribution, the Mann–Whitney U test (for unpaired data) or the Wilcoxon signed-rank test (for paired data) will be used. The Chi-squared test (or Fisher's exact test when applicable) shall be used for analysing the contingency tables and for the comparison of proportions and/or frequency distributions.

Survival analyses shall be performed using the Kaplan-Meier method, providing the median, mean, 95% confidence intervals, as well as number of events and number of censored cases.

When it is necessary to compare survival functions, the log-rank test will be used.

The assumptions of normality and homoscedasticity of the variables for the use of parametric tests will be studied.

The level of significance in all the statistical inference tests will be α=0.05, two-tailed.

Adjustment by multiple comparisons is not planned.

Estimates will be calculated with a 95% confidence level, the SPSS statistical analysis software package, V18.0 or later, will be used.

Logistic regression:

A logistic regression model will be used to study the association between membership to each of the two extreme treatment response groups with each of the possible clinical factors of interest (see the study factors in point 7.1. Primary objective).

[redacted]

9.2 STATISTICAL ANALYSES

Primary objective

A descriptive analysis will be performed of the baseline clinical characteristics (clinical history of renal cell carcinoma, first-line treatment, other treatments prior to axitinib) of the population of patients who are long-term responders with axitinib, in those patients refractories to treatment, and overall.

The baseline clinical characteristics will be statistically compared according to membership to each one of the two extreme treatment response groups.

Efficacy variables will be analyzed and compared between groups of long responders and refractory patients: PFS, time to progression, overall survival, overall survival from the beginning of the 1st line. These analyzes will be added in the statistical report in the sections in which these same analyzes are shown for the total N of patients.

In addition, the association of clinical factors of interest with the benefit of treatment will be analysed by logistic regression (see point 7.1. Primary objective).

Secondary objectives

A descriptive analysis will be performed on all secondary objectives.

Safety objectives

The number of patients with at least one AA, and the number of registered AAs will be analysed. The number of AAs per patient will be described

A descriptive analysis will be performed of the different adverse events reported during treatment with axitinib, their frequency, the worst grade according to CTCAE, the cycle in which the worst grade occurred, the relationship with the treatment, whether the AE was serious and, if so, the reason why it was considered serious.

section will be added indicating the number of patients with at least one AA related to the treatment, and the number of related AAs registered. The descriptive analysis of treatment-related AAs will be performed according to the worst grade according to CTCAE by patients.

A section will be added indicating the number of patients with at least one severe AA and the number of serious AAs registered. The descriptive analysis of the reason for the severity of AAs will be carried out and a list with the information of these serious AAs will be displayed (site, patient, AA, worse CTCAE grade, cycle in which it has been worse grade, relationship with treatment, reason for severity).

Other analyses

A descriptive analysis will be performed of all variables that do not cover any of the above objectives, and which have been recorded in the CRF.

Observations to the descriptive analyzes:

[redacted]

- SUBSEQUENT TREATMENTS: The section on subsequent treatments will be analyzed in patients who have indicated suspension of axitinib treatment.

And in this set, the number of lines after axitinib registered will be obtained on the total number of patients and on patients with Have you received any subsequent treatment? = Yes. On this set of patients, post-axitinib treatments will also be analyzed as follows:

- First post-axitinib treatment: the drug received, and the best response achieved will be analyzed if the treatment continues. If it does not continue, the reason for the discontinuation will be analyzed (specifying if there are other reasons).

- Second line and after suspension with axitinib: a list with the registered data of these treatments will be shown.

- DOSE MODIFICATION: It will be described how many patients have modified doses and how many modifications have been registered. In patients with modification, the following elements will be described:

- Type of modification (the variables included in the CRD will be analyzed. This analysis should not be confused with the definition included in section 7 definition of variables and objectives of this document).

- The changes registered will be ordered in order of occurrence (1st modification, 2nd modification ... until the last one), and for each order the following will be described: the type of modification, the new dose and the reasons for modification.

[redacted]

10 LIST OF TABLES AND TABLE TEMPLATES

Table/Graph number			Table/Graph title
1.			Distribution of patients
2.			Demographic data
3.			Medical records
3.	1.		Age at diagnosis
3.	2.		Tumour stage at diagnosis
3.	3.		Non-systemic treatment
3.	4.		Histological type
3.	5.		Diagnosis of advanced disease
3.	6.		Risk criteria before the initiation of the first line
4.			First-line treatment
4.	1.		Drug
4.	2.		Starting dose
4.	3.		Duration of treatment
4.	4.		Withdrawal of treatment
4.	5.		Disease progression
4.	6.		Best treatment response
5.			Other treatments prior to axitinib
5.	1.		2nd-line treatment
5.	1.	1.	Drug
5.	1.	2.	Starting dose
5.	1.	3.	Reason for starting
5.	1.	4.	Duration of treatment
5.	1.	5.	Withdrawal of treatment
5.	1.	6.	Disease progression
5.	1.	7.	Best treatment response
5.	2.		3rd-line treatment
5.	2.	1.	Drug
5.	2.	2.	Starting dose

[redacted]

5.	2.	3.	Reason for starting
5.	2.	4.	Duration of treatment
5.	2.	5.	Withdrawal of treatment
5.	2.	6.	Disease progression
5.	2.	7.	Best treatment response
6.	1.		Treatment with axitinib
6.	2.		Treatment line
6.	3.		Reason for starting
6.	4.		Risk criteria at the initiation of treatment
6.	5.		Presence of comorbidities
6.	6.		Duration of treatment
6.	7.		Withdrawal of treatment
6.	8.		Disease progression
6.	9.		Best treatment response
6.	10.		Dose and dose modification
6.	11.		Adverse Events
7.			Subsequent treatments
8.			Vital status

[redacted]

11 APPENDICES

11.1 APPENDIX 1: RISK GROUPS

A1.1 MSKCC risk group

Risk factors are defined to establish the patient's prognostic group at the initiation of mRCC treatment as follows.

Extract from Motzer et al. *Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma*. JCO 2001. Vol 20. No1. (JHanuary 1 (2002) pp 289-296.

"The Memorial Sloan–Kettering Cancer Center (MSKCC; NY, USA) criteria, first published in 1999, defined pretreatment clinical features that were predictive of survival in untreated patients with mRCC who were going to receive cytokine therapy, particularly IFN-α. The MSKCC risk system stratifies patients with mRCC into poor-, intermediate- and favorable-risk categories based on the number of adverse clinical and laboratory parameters present. Poor prognostic factors include a Karnofsky performance status (KPS) of less than 80, time from diagnosis to treatment less than 12 months, serum lactate dehydrogenase (LDH) more than 1.5-times the upper limit of normal (ULN), corrected serum calcium >10.0 mg/dl and hemoglobin less than the lower limit of normal (LLN).[21] Patients in the ***favorable-risk*** *group have no poor prognostic factors, those in the* ***intermediate-risk*** *category have one or two adverse prognostic factors, and patients with* ***poor-risk*** *RCC have more than two poor prognostic factors."*

Table 6. Results of Multivariate Analysis

	Parameter Estimate	SE	χ^2	P	Risk Ratio	95% CI
Lactate dehydrogenase	1.1715	0.1734	45.65	.0001	3.23	2.30-4.53
Hemoglobin	0.4232	0.1053	16.14	.0001	1.53	1.24-1.88
Corrected calcium	0.6561	0.1459	20.23	.0001	1.93	1.45-2.57
Karnofsky performance status	0.4153	0.1283	10.48	.0012	1.52	1.18-1.95
Interval from initial RCC diagnosis to IFN-α treatment*	0.3914	0.1184	10.93	.0009	1.48	1.17-1.87

*Less than 1 year versus ≥ 1 year.

A1.2 Heng risk group

Risk factors are defined to establish the patient's prognostic group at the initiation of mRCC treatment, in accordance with the Heng classification, as follows.

Extract from Heng et al. *Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study*. J Clin Oncol. 2009 Dec 1;27(34):5794-9

"A multivariate analysis identified a Karnofsky-PS score of <80 at the initiation of treatment, the period from the RCC diagnosis to metastasis treatment of <1 year, anemia, hypercalcemia (corrected Ca > 10), neutrophilia and thrombocythemia as independent poor prognostic factors. Patients were classified into a ***favorable-prognosis*** *group (with 0 poor prognostic factors),* ***intermediate-prognosis*** *group*

[redacted]

(with 1–2 poor prognostic factors) and ***poor-prognosis*** *group (with 3–6 poor prognostic factors)."*

Table 3. Multivariable Analysis and Final Model

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

NOTE. Total number of patients = 564.
Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.

A1.3 MSKCC risk group modified for the 2nd line

Extract from Motzer et al. *Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma*. J Clin Oncol. 2004 Feb 1;22(3):454-63.

"The seven variables included in the multivariate analysis were Karnofsky performance status, liver metastases, alkaline phosphatase, hemoglobin, lactate dehydrogenase, corrected calcium, and the time interval from diagnosis to treatment. Because corrected calcium is a linear combination of levels of albumin and calcium, among these three variables, only corrected calcium was included in the multivariate analysis. Using a significance level of 0.15 for entering and removing a variable in a stepwise analysis, five variables were retained: Karnofsky performance status, hemoglobin, corrected calcium, lactate dehydrogenase, and liver metastases. However, when fitting the final model with these five variables to obtain parameter estimates and SEs, it was noted that lactate dehydrogenase and liver metastases had P values of more than .10. Therefore, lactate dehydrogenase and liver metastases were not included in the final model.

To confirm this decision, a bootstrapping technique was applied. The percent inclusion among the 300 samples created by the bootstrapping technique for Karnofsky performance status, hemoglobin, and corrected calcium were 96%, 93%, and 84%, respectively. The percentage inclusion for each of the other four variables was lower than 65% (range, 33% to 61%). The results of the bootstrap procedure confirmed the variables chosen for the final model. Therefore, the three independent

[redacted]

risk factors predicting survival are corrected calcium, hemoglobin, and Karnofsky performance status.

…

*Low Karnofsky performance status (< 80%), low serum hemoglobin, and high corrected calcium were identified as risk factors. Corrected calcium and hemoglobin were dichotomized using previously defined cut-points (corrected calcium, < 10 v ≥ 10 mg/dL; hemoglobin, ≤ 13 v > 13 g/dL for males and ≤ 11.5 v > 11.5 g/dL for females [45]), and the univariate association of these dichotomized variables with survival is given in the right side of Table 4. A multivariate Cox model was then fit using the categoric forms of the variables (Table 5). Each patient was then assigned to one of three risk groups: those with zero risk factors (**favorable risk**), those with one risk factor (**intermediate risk**), and those with two or three risk factors (**poor risk**).”*

Table 5. Multivariate Survival Analysis

Parameter	Parameter Estimate	SE	χ^2	*P*	Risk Ratio	95% CI
KPS	1.26	0.26	23.4	< .001	3.5	2.1 to 5.9
Corrected calcium	1.21	0.28	18.7	< .001	3.4	1.9 to 5.8
Hemoglobin	0.50	0.21	5.5	.02	1.7	1.1 to 2.5

No. of Risk Factors	No. of Patients* (%)	No. of Patients Alive	Median Survival (months)	95% CI	1-Year Survival	3-Year Survival
0	56 (42)	13	22.1	17.7 to 26.3	76%	25%
1	46 (35)	8	11.9	8.3 to 16.2	49%	11%
2 or 3	30 (23)	3	5.4	4.8 to 6.5	11%	0%

NOTE. Analysis performed for patients enrolled after 1/1/1990.
Abbreviation: KPS, Karnofsky performance status.
*Five patients are missing data on one of the risk factors.

11.2 APPENDIX 2: RELATIONSHIP BETWEEN KPS AND ECOG.

KPS is not recorded in the CRF, but it is related to ECOG in line with the following table.

KPS	ECOG
100 - 90	0
80 - 70	1
60 - 50	2
40 - 30	3
20 - 10	4

This table is an adaptation of that which appears in:

http://oncologypro.esmo.org/Oncology-in-Practice/Practice-Tools/Performance-Scales

[redacted]

Moreover, which is based on that published in Am J Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

[redacted]