NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Study Information

Title	Retrospective analysis of clinical factors associated with greater benefit of Axitinib in metastatic renal cancer (AXILONG Study)
Protocol Code	A4061089 /PFI-AXI-2017-01
Protocol Version	V 1.2_Admin changes
Date of the latest Protocol version	21 March 2018
Active substance	Therapeutic group/ATC code: L01XE17 Active substance: Axitinib (A4061089)
Drug	Inlyta (axitinib)
Hypothesis and objectives	To describe the clinical characteristics of a population of patients with a long-term response to axitinib and to identify and analyse clinical factors which could be related to the long-term response to axitinib, through the comparison between two groups of patients with an extreme response to the drug.
Author	PPD Pfizer España Avda. de Europa, 20B Parque Empresarial la Moraleja 28108 Alcobendas (Madrid)

CONTENTS

CONTENTS

[redacted]

[redacted]

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	*Agencia Española del Medicamento y Productos Sanitarios* (Spanish Agency of Medicines and Medical Devices)
AEs	Adverse Events
AR	Autonomous Regions
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CTC	Circulating Tumour Cells
DFS	Disease-Free Survival
DMBS	Data Management & Biostatistics
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBP	High Blood Pressure
Hgb	Haemoglobin
HIF	Hypoxia-inducible Factor
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

[redacted]

IHC	Immunohistochemistry
IMDC	International Metastatic Database Consortium
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan Kettering Cancer Center
NR	No Response
OS	Overall Survival
PD	Progressive-Disease
PFS	Progression-Free Survival
PR	Partial Response
RCC	Renal Cell Carcinoma
RTK	Receptor Tyrosine Kinase
SD	Stable Disease
SOPs	Standard Operating Procedures
TMAs	Tissue Microarrays
VEGFR	Vascular Endothelial Growth Factor Receptor
VHL	Von Hippel–Lindau

2. PERSONS RESPONSIBLE FOR THE STUDY

Name	Title	Affiliation	Address
Dr PPD	Coordinating Investigator	PPD	PPD (Spain)
PPD	Medical Advisor	Pfizer Oncology	Pfizer España Avda. de Europa, 20B Parque Empresarial la Moraleja 28108 Alcobendas (Madrid)
PPD	Medical & Scientific Relations	Pfizer Oncology	Pfizer España Avda. de Europa, 20B Parque Empresarial la Moraleja 28108 Alcobendas (Madrid)

3. ABSTRACT

SPONSOR:
Laboratorios Pfizer
Avenida de Europa, 20 – B
Parque Empresarial La Moraleja
28108 Alcobendas (Madrid)

Contact person: PPD

STUDY TITLE: Retrospective analysis of clinical factors associated with greater benefit of Axitinib in metastatic renal cancer (AXILONG Study)

PROTOCOL CODE: A4061089/PFI-AXI-2017-01

COORDINATING INVESTIGATOR:
The scientific coordinator will be responsible for maintaining the methodological rigour of the study, both in the design phase and in the evaluation of results and writing of the final report. He/she will guarantee the ethical conduct of the study, maintaining the scientific support for all participating doctors until the publication of the study results:

Study coordinator:
Dr PPD
Madrid

STUDY SITES:
It has initially been considered optimal to include patients in the Medical Oncology Departments of approximately thirty to forty Spanish sites.

IEC ASSESSING THE STUDY
This protocol will be submitted to the IEC:

PPD
Madrid

[redacted]

PRIMARY OBJECTIVE

The primary objective of the study is:

- To describe the baseline clinical characteristics of the population of patients with a long-term response to axitinib and to identify clinical factors which could be related to the long-term response to axitinib (defined as progression-free survival after taking the drug of at least 9 months), through the comparison of two groups of patients with an extreme response to the drug: one group of patients who are progression-free of at least 9 months compared to a group of patients who are shown to have disease progression before the first response assessment.
- To analyse the association of some clinical factors with greater benefit from the drug.

SECONDARY OBJECTIVE

The secondary objectives of the study are:

- To describe the response to treatment with axitinib in the group of patients with a long-term response.
- To describe the efficacy per treatment line (second line of treatment and subsequent lines)
  - Best response to treatment (CR, PR, 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 titrated doses of axitinib of more than 5 mg twice daily
- To describe the percentage of patients who reduced doses of axitinib of less than 5 mg twice daily
- To describe the tolerability of axitinib
- To describe the treatments received at progression
- To describe the response to the treatments received at progression

DESIGN

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

STUDY CONDITION

Advanced renal cancer.

STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

[redacted]

Patients of both sexes with advanced renal cell carcinoma will be included, who have received axitinib as second line or subsequent lines in accordance with the conditions approved for use in this disease.

The aim is to include two groups of patients: one with a long-term response to the drug (a group of patients progression-free for at least 9 months) compared to a group of patients who are refractory to the treatment (group of patients who show disease progression at the first assessment after the initiation of treatment).

The maximum possible number of patients will be included, progression-free at 9 months after the initiation of treatment. The ratio of long-term responders (PFS ≥9 months) and primary refractory patients (PFS ≤3 months) is estimated to be around 2:1.

During the study recruitment period, the participating sites may include all patients who meet the study's inclusion criteria and who do not meet the study exclusion criteria. Given that this is an observational and exploratory study, no hypotheses have been established and the sample size will not be pre-determined.

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.

SCHEDULE

The administrative procedures of the study are expected to begin with the central IEC and the AEMPS in September/October 2017, with the first sites expected to open in the first quarter of 2018.

Patient recruitment will be carried out competitively for a maximum period of three months following the opening of the last participating study site. No follow-up of patients will be carried out after their inclusion in the study.

Regarding the observation period—given that it is an observational, retrospective study—this will always be prior to the inclusion of the patient in the study, with this starting at the time of diagnosis of the study condition (renal cell carcinoma) and ending at the time of inclusion in the study, or the death of the patient if this occurs first.

The study is expected to end when the data of all enrolled patients have been collected and analysed, which is estimated for 2019.

SOURCE OF FUNDING

Pfizer España, as Sponsor, is responsible for funding the study. This funding includes all the research materials, the cost of recording and controlling processes for the Committee and healthcare authorities, the design, maintenance and management of the database, the cost of the

[redacted]

statistical analysis of the information and reports generated and the fees of the professionals involved in the collection and analysis of the data.

Pfizer SLU, as Sponsor of the study, shall provide financial compensation to the sites/investigators participating in the study. Such compensation will be explicit and transparent, without prejudice to the internal rules of their employing agencies and in accordance with specific regulations in the ARs and at the sites where the study is conducted.

[redacted].

4. AMENDMENTS AND UPDATES

Amendment No.	Date	Substantial or administrative amendment	Amended protocol section(s)	Summary of change(s)	Reason
1	20 October 2017	Administrative.	Schedule/Milestones	Add clarification on patient observation period	Request from the AEMPS at the time of classification, to emphasise the retrospective nature of the study.
2	21 March 2018	Administrative.	- Format of data collection tool (CRF) - Schedule/Milestones - Annex 9 "list of planned sites and PIs in the study"	- Change in format of CRF (final CRF in paper format instead of electronic format) - Update of past or future expected dates in the schedule/milestones - Amendment of Annex 9 "list of planned sites and PIs in the study", to include two new sites and to change the name of the PI of one of them.	A decision has been made that the CRF format to be used in the study will be on paper because, with this being a retrospective study, it will be quicker and easier to use, and avoids delays in the start of the study caused by the scheduling and management thereof. Two new sites interested in participating in the study are also included, as well as the correction of the PI in one of the sites, following the request of his/her site.

[redacted]

5. MILESTONES

In order to obtain enough information to perform a proper analysis of the data, the proposed work plan is as follows:

Once the study is approved by the competent authorities and the contracts have been signed at each site, each study site will be opened and the investigator may start recording the requested data in the electronic case report form.

Before including the patient in the study, the investigator should review and verify the inclusion/exclusion criteria.

The observation period—given that it is an observational, retrospective study—will always be prior to the inclusion of the patient in the study, with this starting at the time of diagnosis of the study condition (renal cell carcinoma) and ending at the time of inclusion in the study, or the death of the patient if this occurs first.

The person appointed by the sponsor to monitor the study may request a face-to-face or remote visit from the site for the review of the data reported in the eCRF at any time after the first patient is included.

The site undertakes to fill in the data in the CRFs, and to resolve any discrepancies that may arise in them, on a regular basis and without interfering with the study's planned schedule.

The study sponsor will regularly inform the investigators involved in the study on its status by sending electronic monitoring reports.

The administrative procedures for the study with the central IEC and the AEMPS are expected to start in September/October 2017, so the following schedule is being considered:

Milestone	Expected date
Date of approval from the central IEC	*7 NOVEMBER 2017*
Start of data collection *Date of opening of the first site and start of study recruitment*	*15 MARCH 2018*
End of recruitment period *Expected date of study recruitment closure*	*30 SEPTEMBER 2018*
End of data collection	*30 DECEMBER 2018*

[redacted]

Expected date of closing of study data collection	
Final results report *Expected date for the final results of the study*	*31 MARCH 2019*

6. STUDY RATIONALE

6.1. Literature review

6.1.1. Epidemiology of kidney cancer

Kidney cancer accounts for approximately 5% and 3% of all new cases of cancer in men and women, respectively. This makes it the seventh most common cancer in men, and the tenth in women.[1] Metastatic disease is found in 20-30% of patients at diagnosis and the main sites of metastasis are: lung (50-60%), bone (30-40%), liver (30-40%), and CNS (5%), with a median survival before and after the introduction of targeted therapies of approximately 13 months and 29 months, respectively. In 2006, it was estimated that there were 63,300 new cases of kidney cancer and 26,400 deaths related to kidney cancer in the European Union, with 6,474 new cases being diagnosed in Spain in 2012.[2]

However, these data not only include renal parenchyma tumours, but also urothelial cancer of the renal pelvis. More specifically, renal cell carcinoma (RCC) is the most common solid lesion in the kidney, representing around 90% of all malignant renal tumours, with approximately 80% of these being clear cell RCC. Other less common cell types include papillary, chromophobe and Bellini duct tumours. It is most common in men (with a male/female ratio of 1.5:1), with the median age at diagnosis being 64.

Smoking and obesity are fully established risk factors for the development of kidney cancer, as well as several types of hereditary kidney cancer, with von Hippel-Lindau (VHL) disease—caused by an autosomal dominant mutation in the VHL gene which predisposes for renal carcinoma and other proliferative vascular lesions—being the most common.

Due to the more regular performance of imaging tests such as ultrasound and computed tomography (CT) scans, the number of incidentally-diagnosed cases of kidney cancer has increased, with incidence rates increasing by an average of around 1.1% each year, although death rates have fallen, by an average of 0.7% from 2004 to 2013.[3] Furthermore, the 5-year survival for localised cancer has increased from 88.4% (1992-1995) to 92.5% (2006-2012). In the case of advanced disease, this increase was from 7.3% (1992-1995) to 11.6% (2006-2012).[3]

Moreover, the stratification of these patients based on prognostic models has helped the oncology community in the interpretation and identification of patient groups at the highest risk of relapse. These nomograms or algorithms integrate a certain number of prognostic factors (anatomical, clinical and histological), obtaining predictive results regarding the evolution of the disease. Motzer, et al. developed one of the most important models, deriving from the analysis of 463 patients with advanced RCC treated with IFNα and with no previous systemic therapy, sequentially treated in clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York between 1982 and 1996, including the number and site of metastases, performance status, previous radiotherapy, previous nephrectomy, diagnostic interval at the start of treatment and specific baseline laboratory data (haemoglobin, albumin, alkaline phosphatase and LDH) as clinical factors for the univariate analysis. Of the multivariate analysis, five of these criteria were the best predictors of survival, of which three groups or risk models were developed, in which survival and probability of being disease-free are predicted. In the development of this model, the median survival was 13 months, with 18%, 62%, and 20% of the 437 patients considering themselves as having a good, intermediate and poor prognosis, respectively. Since the clinical trials conducted over the course of these years were carried out using a drug with very little efficacy, the results represent the natural history of patients previously treated for advanced RCC.

With the widespread use of new targeted therapies, it was necessary to develop prognostic models in patients reflecting the use thereof. Heng, et al. published a new prognostic model in 2009 based on the MSKCC model, with the addition of two additional factors, which was developed—thus proving useful—in patients treated with anti-VEGF targeted therapies. An important progression in this field was the development by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) of a model, implemented in patients with metastatic RCC, treated with a following drug line with targeted therapies, in progression after a first-line with these targeted therapies.[5, 6]

[redacted].

6.1.2. Therapeutic approach

Until a few years ago, the only active systemic treatment available for metastatic RCC was based on immunotherapy with cytokines, IL-2 and IFNα, associated with a modest impact on overall survival, with a 5-year survival rate of less than 10%. However, this has dramatically changed with the development and marketing of the new targeted therapies, which have substantially modified the therapeutic approach and prognosis for these patients, from the average OS of 9.4 months described in the Motzer, et al. study to an average OS of 35.5 months in patients with anti-VEGF therapies, in progression after a first line with these targeted therapies.[4,6]

This substantial progress is based on the recent advances in the understanding of the genetics and biology of RCC, which has allowed the successful development of these targeted therapies aimed at VEGF and its receptors, and the target of the rapamycin pathway.[7,8] Regarding VEGF, several research lines support a unique dependence of RCC, in particular those with clear-cell histology, on this growth factor for carcinogenesis and progression.

Patients with a deletion in the VHL gene often develop multiple clear-cell tumours in their kidneys, at an early age. Similarly, the biallelic loss of the VHL gene occurs in the majority of patients who develop sporadic clear-cell RCC. This is because the VHL protein acts as a transcriptional activity regulator of the hypoxia-inducible factor (HIF), and its accumulation leads to the overexpression of multiple genes, including the gene that encodes for VEGF. VEGF binds to the receptor tyrosine kinases on the cell surface, located in the endothelial cells, to promote tumour angiogenesis and tumour proliferation.[9]

Thus, seven molecules designed to act against specific targets and angiogenic signalling pathways have been approved in Europe and the USA, five of which target the VEGF pathway, with two targeting the rapamycin (mTOR) pathways.

In addition to these molecules, there has been the recent approval from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) of *nivolumab*, a human-IgG4 monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus releasing the PD-1 pathway that mediates the inhibition of immune response,

[redacted]

including anti-tumour immune response; *cabozantinib*, a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) involved in tumour growth and angiogenesis; and *lenvatinib*, a selective RTK inhibitor of VEGF receptor kinase activity, approved in combination with everolimus, for the treatment of patients with RCC.

6.1.3. Therapeutic Management of Metastatic Disease

Angiogenesis is the key factor for the development and progression of RCC, given the high degree of vascularisation of these tumours, which is why it is considered to be a disease targeted by the VEGF pathway.[9] Both bevacizumab, a monoclonal antibody inhibitor of the VEGF receptor, and the TKIs sunitinib, sorafenib, pazopanib and axitinib have shown significant clinical benefits in patients with mRCC, thanks to their mechanism of action on the molecular target responsible for the development of the disease, vascular endothelial growth factors (VEGF) and their receptors.

For the treatment of the metastatic disease in first-line bevacizumab (in combination with interferon), sunitinib and pazopanib have been approved by the FDA and the EMA based on the improvement in PFS times, whether for interferon or placebo. Bevacizumab reported a PFS that was higher than the control group (10.2 m vs 5.4 m, HR 0.63 [95% CI: 0.52-0.75]; p=0.0001), independent of the risk group.[10] The sunitinib study, meanwhile, showed a statistically significant improvement in PFS compared to IFα (11 m vs 5 m; HR 0.42 [95% CI: 0.32-0.54; p<0.001).[11] Lastly, pazopanib demonstrated a statistically significant improvement in PFS, compared to the placebo control group, of 9.2 months in the overall population (HR: 0.48; 95% CI: 0.34-0.62; p <0.0001).[12]

In addition to axitinib, as second-line treatment, another three VEGFR inhibitors are authorised for use in the clinic, although none of them are authorised for the treatment of patients after failure of a previous line with a TKI: sunitinib, sorafenib, pazopanib. In two single-arm studies, sunitinib demonstrated an OS and PFS of 34-40% and 8.3-8.7 m, respectively.[13] Sorafenib (5.5 m vs 2.8 m) and pazopanib (7.4 m vs 4.2 m) showed improvements in the median PFS versus placebo.[12, 14]

[redacted]

In the group of mTOR inhibitors, temsirolimus and everolimus (authorised after TKI) are currently available in the therapeutic arsenal. Temsirolimus was approved in first line, based on the positive OS results versus placebo (10.9 vs 7.3 m).[8] Everolimus demonstrated an improvement in PFS compared with placebo (4.9 m vs 1.9 m), in patients who had progressed to a prior therapy that included sunitinib or sorafenib.[15]

Furthermore, indication of advanced RCC after treatment with a prior VEGF therapy has recently been authorised by the EMA for cabozantinib and lenvatinib, with the latter being in association with everolimus. Cabozantinib (7.4 m vs 3.8 m) and lenvatinib in combination with everolimus (14.6 m vs 5.5 m) showed a statistically significant improvement in PFS compared to the everolimus active comparator.[16, 17]

6.1.4. Axitinib in RCC

Axitinib was also evaluated in advanced renal cell cancer in a pivotal phase III study, with which it received approval for the treatment of advanced renal cell carcinoma after the failure of previous systemic therapy from the FDA (Federal Drug Agency) on 27 January 2012. Subsequently, on 3 September 2012, it was authorised by the EMA for the treatment of adult patients with advanced renal cell carcinoma after failure of a previous treatment with sunitinib or cytokines. On 1 June 2014, after evaluating the data of axitinib in kidney cancer, the AEMPS (Spanish Agency of Medicines and Medical Devices) issued a favourable opinion for the authorisation of axitinib in the treatment of adult patients with advanced renal cell carcinoma after failure of a previous treatment with sunitinib or cytokines (authorised on 01/06/2014).

6.1.5. Mechanism of action

Axitinib is a potent and selective second-generation tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors VEGFR-1, VEGFR-2 and VEGFR-3, which are located on the surface of the endothelial cells and are involved in pathological angiogenesis, tumour growth and the metastatic progression of cancer.[7, 9] Axitinib has a unique binding pattern and is more potent and selective against VEGF 1-3 than other multi-target TKIs such as sunitinib or sorafenib, and

[redacted]

has been proven to potently inhibit the proliferation and cell survival of endothelial cells mediated by VEGF. The neutralisation of VEGF biological activity produces a regression of tumour vascularisation, normalises residual tumour vasculature and inhibits tumour neovascularisation, thereby inhibiting tumour growth.[18]

6.1.6. Efficacy data

Three prior phase II studies showed that axitinib had significant clinical activity in advanced RCC, both in patients refractory to cytokines (A4061012, A4061035 [only in Japanese patients], and those refractory to sorafenib (A4061023).[19-21]

In the A4061012 study, which included 52 patients with metastatic RCC, the radiological objective response rate was 44.2% (95% CI: 30.5-58.7), with 4% achieving complete response. With a median follow-up of 5.9 years, the last analysis showed that 10 of the 52 patients were alive, with the 5-year OS rate being 20.6% (95% CI: 10.9%-32.4%), with a median OS of 29.9 months.[19,20]

The A4061035 study was a phase II trial in 64 Japanese patients with metastatic RCC who were refractory to cytokines. An independent radiological review committee found that, in the intention-to-treat population, axitinib reached a response rate of 50% and a median PFS of 11 months.[21]

In the A4061023 study by Rini, et al., which included 62 patients with metastatic RCC, the median PFS was 7.4 months (95% CI: 6.7-11.0), and the median OS was 13.6 months (95% CI: 8.4-18.8). Most patients included in this study also received prior treatment with sunitinib or other agents such as bevacizumab and temsirolimus, with 75% of patients treated with at least two previous treatment lines.[22]

Based on the results of these trials, a randomised (1:1), open-label pivotal phase III study compared axitinib with an active TKI—sorafenib—as a second line therapy ("*Axitinib (AG 013736) As Second Line Therapy For Metastatic Renal Cell Cancer: Axis Trial*"), and included 723 RCC patients with a clear-cell component, with progression to a treatment line based on sunitinib, bevacizumab plus interferon, temsirolimus or cytokine-based regimens.[23] The patients were treated with axitinib, 5 mg every 12 hours, versus sorafenib, 400 mg every 12 hours. Patients were

treated until disease progression or unacceptable toxicity occurred. Nevertheless, after the disease progression defined by RECIST v.1.0 criteria, patients could continue with the treatment assigned at random at the discretion of the investigator.

PFS—the primary study endpoint—was significantly greater in patients treated with axitinib (6.7 m vs 4.7 m; HR 0.665; [95% CI: 0.544-0.812], p<0.0001), and was also higher in the PFS analysis in the pre-specified groups, with all the HRs favouring axitinib, independent of the ECOG, performance status, previous therapies, race, gender, age, MSKCC status and geographic region. The benefit of axitinib in terms of PFS must also be pointed out in the subgroup of patients previously treated with cytokines (12.1 m vs 6.5 m; HR 0.484, [95% CI: 0.318-0.876], p<0.0001), and particularly in the subgroup who had progressed to one previous line with sunitinib (4.8 m vs 3.4 m; HR 0.741 [95% CI: 0.573-0.958], p<0.0001). Likewise, the overall response rate favoured axitinib (19.4% vs 9.4%), with a median response duration of 11 m vs 10.6 m for axitinib and sorafenib, respectively.

The median OS, the secondary study objective which had recently been updated, was similar in both groups (20.1 m vs 19.2 m (HR= 0.969, p= 0.374); although the study design did not take into account the collection of data on subsequent therapies after the first progression, in such a way that any possible effect of post-progression therapy on the OS could not be determined. When the patients previously treated with sunitinib were analysed, using the median duration of previous sunitinib treatment (9.7 months) as a cut-off point, axitinib was associated with a tendency towards greater OS in patients who received sunitinib for longer: 11.7 months vs 18.1 months, in the sunitinib group <9.7 months vs ≥9.7 months, respectively (HR: 1.24; 95% CI 0.88–1.75; p=0.220).[24]

From a regulatory point of view, sorafenib was considered to be a reasonable choice for the comparator because it had shown activity in patients with RCC refractory to sunitinib, bevacizumab, and ≥1 previous antiangiogenic agent. During the start of the study, everolimus had still not been evaluated and was not approved as second line.

[redacted]

6.1.7. Tolerability data

The overall safety profile of axitinib is similar to the profile of other drugs belonging to the same class of molecules that inhibit the VEGF pathway. However, the aforementioned greater selectivity of axitinib compared to other targeted therapies such as sorafenib gives it a better safety profile, with less toxicity caused by the off-target effect being seen with axitinib.[23] These adverse events (AEs) include common events such as diarrhoea, nausea, high blood pressure (HBP), tiredness and dermatological events, as well as fewer common toxicities such as thromboembolic events, hypothyroidism and proteinuria. However, it should be noted that axitinib does not appear to have the same degree of elevated liver enzymes and potential for liver failure as described with certain other VEGF-pathway inhibiting molecules. In view of the above, the EMA recommends monitoring specific safety events such as heart failure, HBP, thyroid function, embolic and thrombotic events, arterial and venous events, erythrocytosis, proteinuria, etc., before starting treatment and regularly throughout treatment. In the pivotal study, the most common grade ≥3 AEs (≥10%) were HBP (17%), diarrhoea (11%) and fatigue (10%), whereas in patients receiving treatment with sorafenib palmar-plantar erythrodysesthesia and hypertension were reported in 17% and 11%, respectively.[23] It should be pointed out that, in the axitinib arm, no deaths were reported that were related to the drug, while two deaths associated with sorafenib were reported: one case associated with retroperitoneal bleeding due to tumour necrosis and another associated with gastrointestinal bleeding, whereas the rate of withdrawals due to related AEs favoured axitinib (4% vs 8%).[3] In the COMPARZ study, which directly compared pazopanib and sunitinib, the common toxicity profiles were reflected in: the median duration of treatment (8.0 m vs 7.6 m), number of dose reductions (44% vs 51%), and rate of discontinuation due to AEs (24% vs 19%), for pazopanib and sunitinib, respectively.[25] By contrast, in the AXIS study, 31% of patients reduced their dose in the axitinib arm versus 52% in the sorafenib arm.[23]

In accordance with their authorised indication, it is recommended to maintain axitinib until progression or unacceptable toxicity, with no cumulative toxicity apparently being observed using this therapeutic approach, as shown in the Rini, et al. study in a cumulative analysis of data in 672

[redacted]

patients with metastatic RCC previously treated with axitinib, 108 patients (16%) had received axitinib for ≥2 years, and most of the adverse events occurred during the first 6 months of treatment. The authors concluded that a stable or decreasing rate of AEs supported the concept of an acceptable safety profile for axitinib.[26]

In summary, we can say that, although the safety profile of axitinib has a similarity to that of sorafenib and other approved agents targeting the VEGF pathway (based on indirect comparisons), some significant differences have been observed between axitinib and these other agents. Axitinib seems to be associated with a lower incidence of: skin reactions than those reported with sorafenib and sunitinib; myelosuppression than pazopanib and sunitinib; hypothyroidism than sorafenib and pazopanib; and changes in liver enzyme levels than with pazopanib and sunitinib. By contrast, axitinib appears to be associated with: a higher incidence of dysphonia than sorafenib and sunitinib; a higher incidence of hypothyroidism than sorafenib and pazopanib; and a higher incidence of HBP than sorafenib. These differences are partly derived from the higher specificity of axitinib, due to the inhibition of VEGFR, than other approved multi-target TKIs.

6.1.8. Administration regimens

The recommended starting dose of axitinib is 5 mg twice daily, every 12 hours, with or without food (with a glass of water), with dose increases or decreases being recommended in accordance with patient safety and tolerability. Patients who tolerate the starting dose of axitinib of 5 mg twice daily for two consecutive weeks, without presenting any serious adverse reactions, may increase the dose to 7 mg twice daily, unless the patient's blood pressure is >150/90 mmHg or the patient is receiving antihypertensive treatment. Therefore, using the same criterion, patients who tolerate an axitinib dose of 7 mg twice daily may increase the dose to a maximum of 10 mg twice daily.

Control of some adverse reactions may require a temporary or permanent suspension and/or a reduction in the dose of the treatment with axitinib. When the dose reduction is necessary, the dose of axitinib may be reduced to 3 mg twice daily or even 2 mg twice daily.

[redacted].

Treatment should be continued as long as clinical benefit is observed, or until an unacceptable toxicity occurs that cannot be managed with concomitant medication or dose adjustment.

6.2. Study rationale

The efficacy and safety profile of axitinib in patients with metastatic 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" clinical practice compared to those patients with a below-average PFS.

These concepts underline the need for observational studies that respond to unresolved questions and complete the information on clinical trials, helping to improve the knowledge on the real use of drugs 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 the authorised drugs that confirm these clinical data and allow for better patient screening.

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

[redacted] al.

7. HYPOTHESIS AND OBJECTIVES

7.1. Primary objective:

- To describe the baseline clinical characteristics of the population of patients who are long-term responders to axitinib and to identify clinical factors associated with a long-term response to axitinib.

For the study, "long-term responders to axitinib" has been defined as patients with progression-free survival [PFS] of at least 9 months with the drug, and "patients refractory to axitinib" has been defined as patients with disease progression in the first assessment after the start of treatment [estimated PFS ≤3 months]

To meet the study objective, two groups of patients with extreme response to the drug will be compared: a group of patients with long-term responses to the drug (group of long-term responders to axitinib) compared to a group of patients with disease progression in the first assessment after starting treatment (group of patients refractory to axitinib), in which the association of the following clinical factors will be analysed with the benefit of the treatment;

- Age (≤65 years and >65 years)
- Baseline ECOG/PS at the start of treatment for each line (0, 1 and ≥2)
- Number of previous treatment lines (1, 2 and ≥3)
- Previous nephrectomy (yes and no)
- MSKCC risk group (favourable, intermediate and poor)
- IMDC risk group (favourable, intermediate and poor)
- Change in the MSKCC or the IMDC risk group with respect to the previous line (yes vs no);
- Histology (100% clear cells, main component of clear cells, main component of non-clear cells, 100% non-clear cells).

[redacted].

- Duration of first-line with a TKI (≥12 months, ≤6 months; ≤3 months)
- Better response with the TKI received in first-line (CR/PR, SD, DP)
- Number of metastatic locations (1, 2 and ≥3);
- 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])
- Baseline LDH levels ≤1.5xULN (yes vs no)
- Baseline Hgb levels >LLN (yes vs no)
- Baseline corrected Ca++ levels ≤10 mg/dl (yes vs no)
- Baseline neutrophil levels ≤ULN (yes vs no)
- Baseline platelet levels ≤ULN (yes vs no)
- Neutrophil/lymphocyte ratio ≤3 (yes vs no)
- Smoking habits (smoker, non-smoker or ex-smoker)

7.2. Secondary objectives:

- To describe the response to treatment with axitinib in the long-term responder group (defined as a PFS of at least 9 months with the drug)
- To describe the efficacy per treatment line (second line of treatment and subsequent)
    - Best response to treatment (CR, PR, 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 titrated doses of axitinib of more than 5 mg twice daily

[redacted].

- To describe the percentage of patients who have reduced doses of axitinib to below 5 mg twice daily

- To describe the tolerability of axitinib

- To describe the treatments received at progression

- To describe the response to the treatments received at progression

[redacted]

8. METHODS OF INVESTIGATION

The purpose of this study is to describe, in routine clinical practice, outside the context of a clinical trial, the clinical characteristics of patients with metastatic kidney cancer who have been treated with axitinib for at least 9 months and to identify clinical factors associated with a greater benefit from the drug. No hypotheses have been pre-specified, and all study data will be analysed using the statistical descriptive techniques.

8.1. 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.

8.2. Scope

The patient population eligible for this study includes any patient with advanced or metastatic kidney cancer who has been treated with axitinib for at least 9 months or who has had PD as the best response to this treatment.

The requirements for a patient's inclusion are that:

1. These patients must have received axitinib as second-line treatment or later, in accordance with its Summary of Product Characteristics. Two groups presenting 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 kidney cancer.

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

[redacted].

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

Recruitment will be competitive between all participating sites, and as many patients as there are at the site that meet the inclusion criteria during the recruitment period may be included.

This is an observational study designed to reflect routine clinical practice; there will be no interference with the daily routine medical care of patients with kidney cancer. The data collected will be consistent with those normally collected from the patient's medical record in routine clinical practice, including the patients' demographic data, routine laboratory values required in the diagnosis and control of this condition, performance status, clinical condition, and the assessments carried out according to the site's routine clinical practice, use of medication, tolerability, adverse events and compliance with treatment.

Given that this is an observational study, no additional material not included in routine practice will be required.

Patients will be considered assessable 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.

8.2.1. Inclusion Criteria

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

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

2. *Aged 18 or over.*

3. *Histologically confirmed diagnosis of advanced kidney cancer, with at least one radiological evaluation of the disease in accordance with RECIST 1.1 criteria*

[redacted]

4. *Treatment with axitinib as second-line or later with a PFS equal to or greater than 9 months, or with disease progression in the first response assessment*

8.2.2. Exclusion Criteria

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

1. *Treatment with axitinib not accounted for in the Summary of Product Characteristics*
2. *Non-compliance with any of the study inclusion criteria*

8.3. Variables

For this observational study, the following variables will be recorded: demographic, medical history (including date and stage of disease at diagnosis and at progression), surgical treatment, histology, blood count and blood biochemistry, first-line treatments, associated adverse events, clinical efficacy and history of treatment with axitinib, including treatment line (second, third, etc.), dose, reason and date of start of treatment, disease risk criteria before onset, comorbidities, associated adverse events, concomitant medication and subsequent treatments, as well as the patient's condition (alive, deceased) and the last date on which contact was made.
A complete description of the variables, including the operational definitions, will be detailed in the Statistical Analysis Plan of the study.

8.4. Source documents

The investigator will, at all times, be fully responsible for the accuracy and authenticity of all clinical and laboratory data included in the CRFs.
The source document for this study will be the medical records of the patient documented in his/her medical record, including his/her surgical records, which will be kept at the site where the study is conducted. All data will be captured in a case report form (CRF). For particular problems and/or questions or governmental requirements for an inspection, it will also be necessary to access a complete study file, provided that the patient's right to anonymity is protected.

[redacted]

The information in the CRFs should be consistent with the data in the medical records.

8.5. 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, and it is expected that it will be around 60 patients. However, as it is an observational and exploratory study, no hypotheses were specified and, therefore, the calculations of the sample size are not applicable.

8.6. Data processing

The detailed software methodology for the handling of the data to be applied in this study will be documented in the Data Management Plan (DMP), which will be designed, filed and maintained by the sponsor. This document shall contain the details about which data (e.g. previous and concomitant medications, adverse events, etc.) will be encoded using the World Health Organization's (WHO) Drug Reference List (DRL), which will use the Anatomical Therapeutic Chemical (ATC) classification system, or the Medical Dictionary for Regulatory Activities (MedDRA). The specific versions of the coding dictionaries used will be documented in the DMP.

8.7. Data Analysis

The data will be analysed using descriptive statistics. A statistical summary will be provided including sample size, mean, standard deviation, median and range for the continuous variables, when applicable; frequency and percentages for the categorical variables. Depending on the results of interest, a stratified data analysis may be conducted. Additional exploratory analyses will be conducted, if necessary.

Details of the methodology for the summary and statistical analysis of the data collected in this study will be documented in the Statistical Analysis Plan (SAP), which will be prepared, filed and maintained by the sponsor. The SAP can modify the plans originally described in the protocol; any major change in the definitions of the study's primary objective or analyses will be reflected as an amendment to the protocol.

[redacted].

8.8. Quality control

As this is a post-authorisation study, the same procedures used in routine clinical practice will be followed by the investigator.

However, the investigators are responsible for ensuring that the protocol and Good Clinical Practice (GCP) standards are complied with.

Study sites might be subject to face-to-face or remote monitoring by the person appointed by the sponsor and a review by the Independent Ethics Committee (IEC) and/or quality assurance audits conducted by the relevant regulatory authorities and the study sponsor.

During the conduct of this study, Pfizer (or its representative) will monitor the activities of the collection of data by the sites, and can also carry out periodic monitoring visits at the sites in order to ensure the correct progress of the study. During visits at the sites, the monitors may review the source documents to confirm that the data recorded in the CRF are correct. All the information recorded in the CRF for this study must be consistent with the patient's source documentation (e.g. medical history).
Data included in the database, and some integrated data from third parties (if applicable), will be verified/validated as documented in the components of the DMP, which will be prepared, stored and maintained by the sponsor.

8.9. Limitations of the research methods

Due to the low incidence of patients with advanced clear-cell kidney cancer undergoing treatment with axitinib, and especially patients with the required response characteristics, it is difficult to estimate the number of patients who could be included throughout the course of the study.

[redacted].

8.10. Further aspects

- **Study procedures:**

For the inclusion of patients in the study, the Investigator must review the inclusion/exclusion criteria and, in the case of including patients who are alive and being followed-up at the site, the patient will be required to sign the ICF before inclusion in the study, as per the model appended to the protocol.

For patients who have already died at the time of inclusion in the study, the request for informed consent is not required, as is permitted in order SAS/3470/2009 of 16 December, on observational post-authorisation studies.

With the data available in the medical record, the requested information will be recorded in the electronic case report form in order to analyse the study variables. Lists of these variables, such as Annex I, are attached to the protocol.

- Review and confirmation of meeting the inclusion criteria and not meeting the exclusion criteria for the study.
- In the case of living patients who are subject to follow-up at the site, the patient must receive an explanation of the procedures and purpose of the study, and be requested to sign the ICF if he/she wishes to participate in the study.

- Data on demographic characteristics
- Disease history:
    - Patient's medical records
    - Data on the disease for which he/she is receiving treatment with axitinib
    - Data on previous treatments received for the disease.
- Data on the treatment with axitinib
    - Information on the patient's response to the treatment

[redacted].

- Information on the tolerability and management of treatment with axitinib
- Information on survival and dates of progression (if any)

- Information on subsequent treatment(s) received (if any).
- Information on the patient's vital signs in the last follow-up performed.

[redacted].

9. PROTECTION OF STUDY SUBJECTS

The study will be conducted in accordance with routine clinical practice as described in the protocol, standards of Good Clinical Practice, the International Conference on Harmonisation and applicable local laws and requirements (Order SAS/3470/2009, of 16 December). The sponsor undertakes to abide by current legislation regarding post-authorisation studies and the associated commitments.

9.1. Patient information and consent

All parties will ensure that personal data are protected and will not include patients' names on any of the sponsor's forms, reports, publications or any other text for disclosure, unless so required by law. For data transfer, Pfizer will maintain a high level of confidentiality and protection of patients' personal data.

Since this study is retrospective, a large number of patients will probably have died by the time they are included. In this case, and in accordance with order SAS/3470/2009 of 16 December on observational post-authorisation studies in which it is established that "In studies that require subjects to be interviewed or in those in which, using other sources of data, it is not possible to use a safe dissociation procedure that ensures that the information contains no personal data, subjects must be asked to provide informed consent, which must be granted in writing in accordance with current regulations", these patients will not be required to provide their signed informed consent. In the case of patients who are alive at the time of their inclusion in the study, the informed consent form must comply with the routine regulatory requirements, which should comply with ICH GCP, local administrative standards and legal requirements.

The informed consent form used in this study and any changes made during the course of the study must be prospectively approved by the IEC and by Pfizer prior to implementation.

[redacted]

The investigator must ensure that each study patient or his/her legal representative is informed of the nature and objectives of the study and possible risks associated with his/her participation therein. The investigator, or a person appointed by the same, will obtain written informed consent from each patient or his/her legal representative before performing any study-specific procedure. The investigator will retain the original of each patient's signed informed consent form.

9.2. Withdrawal of patients

Patients who are alive at the time of their enrolment in the study can withdraw at any time voluntarily, or may be withdrawn at the discretion of the investigator or the sponsor for safety, behaviour or administrative reasons. In any event, every effort should be made to document the results of any such patient. The investigator should inquire about the reason for the withdrawal and conduct follow-up on the patient in relation to any unresolved adverse event.

If the patient leaves the study and also withdraws his/her consent for future disclosure of information, no further data evaluation or collection should be performed. The sponsor may retain and continue to use any data collected before the withdrawal of consent.

9.3. IEC

The sponsor is responsible for obtaining the prospective approval of the study protocol, amendments and informed consent forms, and other relevant documents, if necessary, from the IEC. All correspondence with the IEC should be kept in the Investigator's File. Copies of the approvals from the IEC should be sent to Pfizer.

The requirements of current local regulations will be followed for the submission and management of initial approvals or amendments to the protocol.

9.4. Ethical considerations of the study

The study will be conducted in accordance with legal and regulatory requirements and scientific rigour, respect and responsibility and will follow the generally accepted research practices

[redacted]

described in the Guidelines for Good Pharmacoepidemiology Practices (GPP) published by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines published by the International Epidemiological Association (IEA), Good Practices for Outcomes Research published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research published by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

The study will be conducted in accordance with the protocol, Good Clinical Practice standards, the International Conference on Harmonisation and applicable local laws and requirements.

Additionally, the study will be governed by the basic ethical principles contained in the Declaration of Helsinki.

Data confidentiality

The highest levels of professional conduct and confidentiality will be maintained at all times, following national data protection legislation. The patient's right to confidentiality is fundamental. The patient's identity in the study documents will be encoded and only authorised persons will have access to personal details that could identify the patient if so required by data verification procedures. Personal details that could identify the patient will be kept confidential.

9.5. Interference with doctors' prescribing patterns

There will be no interference with the investigator's decision on the most appropriate treatment for the patient.

[redacted].

It is a non-interventional, retrospective study, and therefore decisions on treatment indications and inclusion in the study will be independent, and always based on routine clinical practice.

[redacted].

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/REACTIONS

REQUIREMENTS

This study protocol requires a manual review of unstructured patient data. The term "unstructured data" refers to literal medical data, including descriptions based on texts and visual representations of medical information, such as medical records, images of medical notes, neurological images, X-rays, or database narrative fields. The reviewer must report adverse events (AEs) that are explicitly attributable to any Pfizer drug that appear in the reviewed information (defined according to the study population and the study period specified in the protocol). The explicit attribution should not be deduced by a temporal relationship between drug administration and an AE, but should be based on a definite statement of causality by a healthcare professional, which links the administration of the drug with the AE.

The requirements for the reporting of safety events in the non-interventional study (NIS) adverse event monitoring (AEM) report form to Pfizer's Drug Safety Department are the following:

- All serious and non-serious AEs with explicit attribution to any Pfizer product that appear in the reviewed information should be recorded in the Case Report Form (CRF) and reported within 24 hours of knowledge thereof to Pfizer's Drug Safety Department using the NIS AEM Report Form.
- Situations involving exposure to a drug, including exposure during pregnancy, exposure during breast-feeding, medication errors, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product should be reported to Pfizer's Drug Safety Department within 24 hours of knowledge thereof using the NIS AEM Report Form.

Should these safety events be attributed explicitly or associated with the use of a Pfizer product, the data contained in the medical record will be all the known information regarding these adverse events. There will be no follow-up of these related adverse events.

All research staff will have to undertake the compulsory training in: "Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple

[redacted]

Languages)" and any supplementary training of Your Reporting Responsibilities that is considered to be relevant. This training will be provided to the research staff before the start of the study. All training modules include a Confirmation of Training certificate (which must be signed by the person who has received the training) as a record that he/she has completed the training, and must be stored in a recoverable format. Copies of all signed training certificates will be submitted to Pfizer.

Training must be completed annually, using the most recent version of: "Your Reporting Responsibilities".

[redacted].

11. PUBLICATION OF RESULTS

The investigator will send a written report of the study status to the sponsor, as described in the Study Agreement document. The investigator will also send regular interim progress reports to the sponsor, as required. A Clinical Study Report is also expected to be created. Periodic safety update reports will be provided on a yearly basis.
All information obtained as a result of this study will be considered confidential.

The Scientific Coordinator of the study, together with the sponsor, will undertake to disclose the results through the usual scientific means.
The authors listed in the publication of the study results must meet the following requirements:

•Substantial contribution to the proposal and design of the study or in the collection, analysis and interpretation of the study data AND
•Involvement or contribution in writing and/or reviewing the publications with regard to the intellectual content AND
•Contribution to the final approval of the published version AND
•Agreement to act responsibly in all aspects of the publication of the data to ensure that issues relating to the accuracy or integrity of any part of the work are investigated and appropriately addressed.

INCIDENT REPORTING

In the event that a ban or restriction (e.g. temporary suspension) is imposed by a competent authority in any part of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer must be immediately informed thereof.
The investigator will also inform Pfizer immediately of any urgent safety measures taken to protect the study patients from any danger and any violation of the protocol of which he/she is aware.

[redacted]

RESOURCES FOR THE CONDUCT OF THE STUDY

-Funding

Pfizer SLU, as sponsor of the study, will provide financial compensation to the sites/investigators participating in the study. Such compensation will be explicit and transparent, without prejudice to the internal rules of their employing agencies and in accordance with specific regulations at the sites where the study is conducted.

PRACTICAL CONSIDERATIONS

-Monitoring

There will be on-site monitoring at approximately 10% of sites with patients enrolled in the study. At the other sites, there will be telephone monitoring of the case report form. The sponsor will appoint the person in charge of monitoring the study.

-Follow-up and final reports

During the study and after its completion, the relevant reports will be sent to the Division of Pharmacoepidemiology and Pharmacovigilance of the Spanish Agency of Medicines and Medical Devices and the competent authorities for PASs under current regulations.

[redacted].

12. REFERENCES

1. Siegel RL, Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387. Epub 2017 Jan 5.

2. Incidencia del cáncer en España en 2012 y previsión para 2020: Sociedad Española de Oncología Médica (SEOM). http://www.seom.org/seomcms/images/stories/recursos/LAS_CIFRAS_DEL_CANCER_EN_ESP_2016.pdf

3. SEER Stat Facts Sheets: Kidney and Renal Pelvis Cancer. Available at: https://seer.cancer.gov/statfacts/html/kidrp.html

4. Motzer, R.J., Bacik, J., Murphy, B.A. et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002; 20: 289–296.

5. Heng DY, Xie W, Regan MM, Warren MA, 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. doi: 10.1200/JCO.2008.21.4809. Epub 2009 Oct 13.

6. Ko JJ, Xie W, Rini BI, Choueiri TK, Heng DY, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol. 2015 Mar;16(3):293-300. doi: 10.1016/S1470-2045(14)71222-7. Epub 2015 Feb 12.

7. Rini BI, Vascular endothelial growth factor-targeted therapy in renal cell carcinoma: current status and future directions. Clin Cancer Res 2007;13:1098-106

8. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356(22):2271-81

9. Rini BI, Rathnell WK. Biological aspects and binding strategies of vascular endothelial growth factor in renal cell carcinoma. Clin Cancer Res 2007;13:741s–746s

10. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind phase III trial. Lancet 370:2103-11, 2007

[redacted].

11. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Aug 1;27(22):3584-90

12. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J et al. Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial JCO Feb 20, 2010:1061-1068

13. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006; 295: 2516-2524.

14. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009; 27(20): 3312-33

15. Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma:a double blind, randomized, placebo-controlled phase III trial. Lancet 2008;372:449-456.

16. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, et al; METEOR Investigators.. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1814-23. doi: 10.1056/NEJMoa1510016. Epub 2015 Sep 25

17. Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol. 2016 Jan;17(1):e4-5. doi: 10.1016/S1470-2045(15)00543-4. Epub 2015 Dec 23.

18. Hu-Lowe DD, Zou HY, Grazzini ML, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008 Nov 15;14(22):7272-83. doi: 10.1158/1078-0432.CCR-08-0652

19. Rixe O, Bukowski RM, Michaelson MD, Rini BI, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol. 2007 Nov;8(11):975-84. Epub 2007 Oct 2

20. Rini BI, de La Motte Rouge T, Harzstark AL, et al. Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. Clin Genitourin Cancer. 2013 Jun;11(2):107-14. doi: 10.1016/j.clgc.2012.12.004. Epub 2013 Feb 4

21. Tomita Y, Uemura H, Fujimoto H, Kanayama HO, et al; Japan Axitinib Phase II Study Group. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy:

[redacted]

a phase II study in Japanese patients with cytokine-refractory metastatic renal cell Carcinoma. Eur J Cancer. 2011 Nov;47(17):2592-602. doi: 10.1016/j.ejca.2011.07.014. Epub 2011 Aug 31.

22. Rini BI, Wilding G, Hudes G, Stadler WM, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. J Clin Oncol. 2009 Sep 20;27(27):4462-8. doi: 10.1200/JCO.2008.21.7034. Epub 2009 Aug 3.

23. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. Lancet 2011;378:1931-1939

24. Escudier B, Michaelson MD, Motzer RJ, Hutson TE, Rini BI, et al. Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial Br J Cancer. 2014 Jun 10;110(12):2821-8. doi: 10.1038/bjc.2014.244. Epub 2014 May 13

25. Motzer R, Hutson TE, Reeves J, Hawkins R, Guo J, Nathan P et al. Randomized, open-label, phase iii trial of pazopanib versus sunitinib in first-line treatment of patients with metastatic renal cell carcinoma (mrcc): results of the COMPARZ Trial. Proceedings of the European Society for Medical Oncology 2012 Congress LBA8 PR

26. Rini BI, Escudier B, Motzer RJ, et al. Long-Term Safety With Axitinib in Previously Treated Patients With Metastatic Renal Cell Carcinoma. Clin Genitourin Cancer. 2015 Dec;13(6):540-7.e1-7. doi: 10.1016/j.clgc.2015.07.001. Epub 2015 Jul 20.

27. Puente J, Laínez N, Dueñas M, Méndez-Vidal MJ, Esteban E, et al Novel potential predictive markers of sunitinib outcomes in long-term respondersversus primary refractory patients with metastatic clear-cell renal cell carcinoma. Oncotarget. 2017 May 2;8(18):30410-30421. doi: 10.18632/oncotarget.16494

28. Tam S, de Borja R, Tsao MS, McPherson JD. Robust global microRNA expression profiling using next-generation sequencing technologies. Lab Invest. 2014 Mar;94(3):350-8. doi: 10.1038/labinvest.2013.157. Epub 2014 Jan 20.

[redacted]

13. LIST OF TABLES

N/A

14. LIST OF CHARTS

N/A

[redacted].

ANNEX 1. LIST OF INDEPENDENT DOCUMENTS

List of Annexes to the Protocol:

Number	Date	Title
Annex 1	N/A	List of Annexes to the Protocol
Annex 2	N/A	List of variables to be included in the CRF.
Annex 3	N/A	Coordinating investigator's Statement of commitment
Annex 4		Agreement of the central IEC
Annex 5	Version 1.0 of 5Sep2017	Patient Information Sheet/Informed Consent Form
Annex 6	Version 1.0	Schedule of Payments/Financial Report
Annex 7	N/A	Summary of product characteristics
Annex 8	-	AEs Report Form
Annex 9	Version 1.1	List of planned Sites and PIs in the study

[redacted].

ANNEX 2. CASE REPORT FORM (VARIABLES)

ANNEX 3: COORDINATING INVESTIGATOR'S STATEMENT OF COMMITMENT

ANNEX 4. IEC APPROVAL

ANNEX 5. PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

ANNEX 6. FINANCIAL REPORT

ANNEX 7. SUMMARY OF PRODUCT CHARACTERISTICS FOR STUDY MEDICATION.

ANNEX 8. AE REPORT FORM

ANNEX 9. LIST OF PLANNED SITES AND PIS IN THE STUDY

[redacted].