Non-Interventional Study Protocol
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Registry of complete responses to Sunitinib in Spanish patients with Metastatic Renal Carcinoma (ATILA Study)

Statistical Analysis Plan (SAP)

Version: 1.0

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1 AMENDMENTS TO PREVIOUS VERSIONS

Not applicable, it is version 1.

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 ATILA study. This includes a brief summary of the main study characteristics and the aim of the SAP, which refers to the statistical analysis plan for this study.

CR to a tyrosine kinase enzyme inhibitor (TKI) is rarely achieved in clinical trials for the treatment of metastatic renal carcinoma, where the classic description of CR only provides for pharmacological treatment, and this response is evaluated either by the study investigator or by a centralized radiological committee (most common situation).

Since the eradication of all measurable lesions will be achieved in a small percentage of patients, the Sunitinib summary of product characteristics does not provide guidelines on the therapeutic strategy to be followed in these cases, i.e. continue the treatment and at what dose or discontinue it indefinitely.

The purpose of this registry is to shed some light on this issue, reviewing what was done in these patients in order to write useful recommendations for the clinician facing this dilemma.

- ***Data from phase III clinical trials***

In the Sunitinib pivotal clinical trial *(Motzer et al., 2007), the interim analysis, and according to RECIST criteria, no patient achieved CR to treatment according to the central radiological committee, whereas according to the researchers there was one patient with CR, which meant less than 1% of the subjects who participated in the clinical trial. However, in the final analysis published 2 years later (Motzer et al., 2009), 11 patients (3%) in the Sunitinib arm reached CR to treatment according to the investigator.*

In the Sorafenib clinical trial, TARGET study *(Escudier et al., 2007), there was no patient with CR according to the independent committee in the interim analysis, while one case of CR was described by investigator (<1%).*

In the phase III trial of Pazopanib versus placebo *(Sternberg et al., 2010), there was one patient in the interim analysis who achieved CR to treatment with Pazopanib (<1%) according to the independent radiological committee.*

In the COMPARZ study *(Motzer et al., 2013), according to an independent radiological committee, 3 patients achieved CR to treatment with Sunitinib versus 1 patient in the Pazopanib treatment arm.*

- ***Data from expanded access programmes:***

In the expanded access programme with Sunitinib *(Gore et al., 2015), in which the rate of tumour responses was evaluated by researchers, 1% of the patients achieved CR to treatment as best response.*

In the expanded access programme with Sorafenib in the US and Canada *(Stadler et al., 2010) less than 1% of the patients achieved CR to treatment with Sorafenib in the opinion of the investigator.*

- ***Retrospective data from real life studies:***

However, in real life this figure may be higher than when the evaluation is performed in the context of a clinical trial, because the definition of CR is looser, patient follow-up is greater and the opportunity to achieve CR is therefore more feasible, as there are late responders to the treatment.

In daily clinical practice, a CT scan is used for the evaluation of tumour response, while in clinical trials other complementary examinations are sometimes performed such as bone scintigraphy or brain resonances that can reveal metastases that would otherwise not be counted.

In the pool analysis of 3 prospective studies *published by Castellano (Castellano et al., 2017), 6.1% of patients achieved complete responses in the investigators' opinion.*

In the ***SULONG Spanish retrospective study****, in which 97 patients who had presented a PFS to Sunitinib of greater than 22 months were selected, the percentage of patients who achieved CR hit 21%, with a median of 33 months to CR (Puente et al., 2017).*

*I****n a retrospective series from the Gustav Roussy hospital****, Dr. Albiges analysed 64 patients who obtained CR to TKIs with the drug alone (36 cases) or in combination with a local treatment (28 cases); surgery, radiotherapy or radiofrequency ablation (Albiges et al., 2012).*

The definition of CR according to the RECIST 1.1 criteria was the disappearance of all known target lesions, the disappearance of all non-target lesions and the absence of new lesions.

The CR had to be confirmed with two consecutive CT scans separated by at least 4 weeks. Confirmation by the oncologist and radiologist from each site was required.

The treatment received was Sunitinib in 59 patients and Sorafenib in the remaining 5. The dose and regimen used for Sunitinib was 50 mg in 4/2 regimen and Sorafenib 800 mg/24 hours.

The majority of the patients had a favourable (22 cases) or intermediate (39 cases) prognosis. However, 3 patients were classified as having a poor prognosis.

Almost all patients had clear cell histology (60 of 64 patients) and they had all been nephrectomised.

There were 26 patients with a single metastasis site versus 23 who had 2 affected organs and 15 patients who had 3 or more sites.

The median time to eliminate all lesions from the beginning of exclusive treatment with TKI was 12.6 months, with a range of 2 to 28 months. The median time from CR to relapse was 7.9 months.

In the subjects in whom remission of the lesions with the TKI plus the local treatment was achieved, 18.5 months were needed (range of 5-45 months)

The median time from CR to relapse was 8.2 months.

The decision to interrupt treatment or not was as follows:

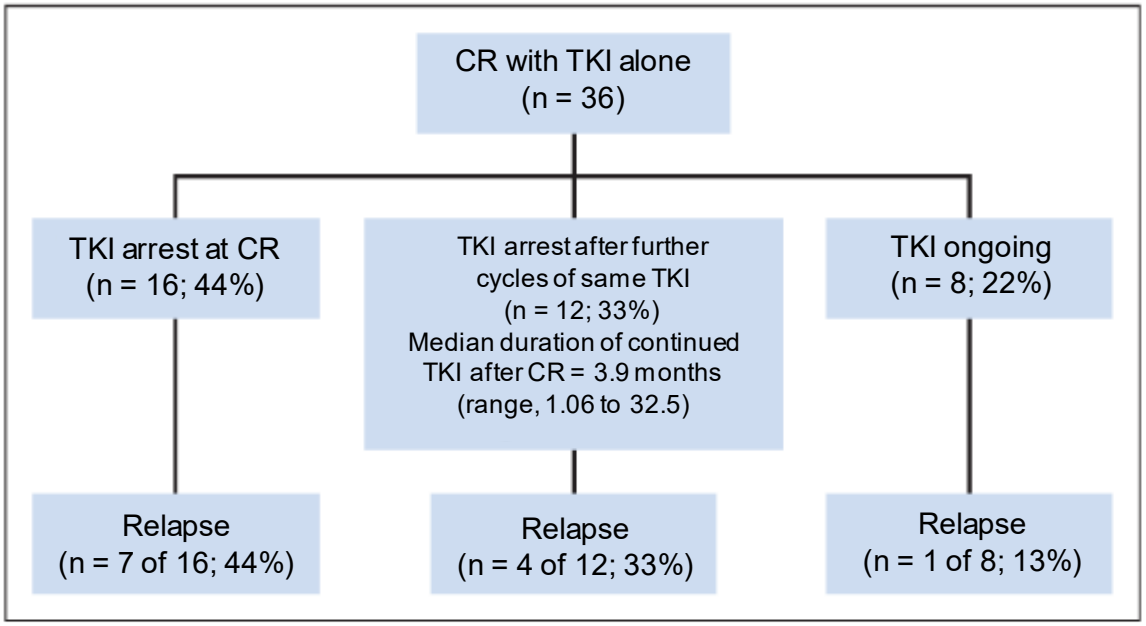

Fig 2. Outcome of patients who achieved complete remission (CR) with a tyrosine kinase inhibitor (TKI) alone.

The author's conclusion was that CR can be obtained in all prognostic groups and with metastases at any site.

In the retrospective analysis of the registry of the Czech renal cancer cooperative group (Buchler et al., 2016) (RENIS registry) covering 95% of patients treated outside clinical trials, of 2803 patients, 100 cases of CR were identified as best response (3.6% of the total) obtained exclusively with a TKI in first line:

- *84 patients treated with Sunitinib*
- *4 patients treated with Pazopanib*
- *9 with Sorafenib*
- *3 with Bevacizumab + Interferon alpha*

96% of the patients had been nephrectomized and the same percentage of tumours were clear cell histology.
Regarding the MSKCC classification of the prognosis group, 47% of the patients had a good prognosis, while 51% had been classified as intermediate prognosis and the prognosis was poor in 2%.

The response was analysed according to RECIST 1.1 criteria, and only one image was needed to confirm the CR.

The median time to reach CR was 10.1 months, and the number of patients with CR increased linearly up to approximately 20 months after the start of treatment with the anti-angiogenic drug.

The patients had a median PFS of 3.8 years (45.6 months) and OS had not been reached in this cohort. 5-year survival was 80%.

The decision to continue the treatment or not once the lesions disappeared was shared by the clinician and the patient.

Patients who reached CR very quickly (before 10 months) were more likely to continue treatment, while a greater proportion of those in whom the lesions disappeared later decided to discontinue treatment.

Of the total cohort, 65 patients discontinued therapy in the absence of a documented relapse. The reasons were: medical or patient decision in 57 cases and 8 due to toxicity. Another 18 patients dropped out of the treatment due to disease progression at the time of the cut-off, while 17 patients were still on first-line treatment even although all their lesions had disappeared.

A second PFS was also defined as the time elapsed since the CR was obtained until the relapse of the disease or death from any cause; PFS from CR: it reached 2.3 years (27.6 months).

Of the 30 patients who discontinued treatment after reaching CR, 14 had progressed at the time of data cut-off, 12 of whom received a second-line treatment, including 4 subjects who were re-treated with the same drug. The median PFS of this second line was 14.5 months.
The authors' conclusions were that patients who achieved CR to an TKI had an excellent long-term prognosis, with very long PFS and OS.
No association was found between overall survival and progression-free survival after CR and the baseline prognosis group according to MSKCC.
There were no significant differences in survival between patients who decided to continue treatment after the disappearance of the lesions and those who discontinued it.

In the European Urology editorial, Dr. Alimohamed and Dr. Sridhar (Alimohamed and Sridhar, 2016), emphasised the importance of maintaining a balance between efficacy and toxicity in cases in which the decision is taken to continue treatment with TKIs after

the total eradication of the lesions. The patient's point of view is important. Discontinuing treatment may generate anxiety in some people.
On the other hand, continuing treatment once the CR is reached may promote resistance to it.

Observing the disappearance of lesions from the radiological point of view does not exclude the presence of viable tumour cells.

- ***Baseline characteristics associated with CR:***

Factors such as age do not seem to influence the impact of TKI on the tumour.
In a ***study*** *of metastatic renal carcinoma* ***by the Czech cooperative group*** *published by* ***Poprach*** *in 2016, where 1315 patients treated with sunitinib divided into two groups were retrospectively evaluated: 1016 individuals under 70 years of age versus 299 over 70 years, the percentage of patients <70 years of age that reached CR was 5.1% compared to 4.1% in those >70 years, with a smaller proportion of elderly nephrectomized patients and a greater interval between the diagnosis of metastatic disease and the beginning of systemic treatment, as well as initiation at a lower dose (Buchler et al., 2015).*

At ***SULONG study****, favorable baseline hematological values and a longer time from nephrectomy to the appearance of distant metastases were correlated with a longer SLP (Puente et al., 2017).*

- ***Data from phase III clinical trials with drugs that act on the immune system alone or in combination with an antiangiogenic.***

Before the introduction of targeted drugs, in the era of cytokines with interferon alpha or Interleukin 2, although the benefit of treatment for most patients was less than that which is obtained today, a group of patients achieved lasting CR to treatment. This occurred in 5-8% of treated patients (Fisher, Rosenberg and Fyfe, 2000; McDermott et al., 2005).

More recently, a significant percentage of complete responses have been obtained in the second generation of drugs acting on the immune system alone or in combination with an enzyme tyrosine kinase inhibitor (TKI).

In the Checkmate 214 study *(Motzer, Tannir, et al., 2018), a phase III clinical trial of 1096 patients with naive renal cell carcinoma of intermediate or poor prognosis and clear cell histology in whom the overall survival and response rate of the combination of Ipilimumab (cytotoxic T-lymphocyte-associated protein 4 - CTLA-4 - at 1 mg/kg) + Nivolumab (PD 1 checkpoint inhibitor at 3 mg/kg) IV for 4 doses every 3 weeks (induction phase) followed by Nivolumab monotherapy every two weeks (maintenance phase) versus Sunitinib monotherapy at 50 mg on a 4/2 regimen was prospectively explored, 9% of the patients in the experimental arm (40 cases) versus 1% (5 cases) in the Sunitinib arm obtained CR according to a centralised radiological committee.*

Per researcher, in the combination arm, 11% of the patients achieved CR while a 1% they got it in the control arm.

The evaluation of the TACs /RMNs it was done every 6 weeks, after the 2-week rest of the Sunitinib cycle.

However, when the anti-tumoral activity is evaluated according to the expression of level of the programmed death ligand 1(PD-L1), in the tumour sample examined in a central laboratory and with the evaluation of the images by an independent radiological committee in patients with intermediate and poor prognosis, the percentage of complete responses in the Ipilimumab arm + Nivolumab falls to 7% in patients who do not express at least one 1% of this biomarker, with the patients treated with Sunitinib remaining at 1%.

In the positive group for PD-1, RCs reach 16% of patients and remained in the 1% of patients in the sunitinib arm (Motzer, Tannir, et al., 2018).

In the Checkmate 214 study, 26% of patients with medium or poor prognosis expressed PD-1 tumour ≥1%, while 74% of patients expressed it <1% (see table below)

Table S3. Antitumor Activity by PD-L1 Expression Level in Intermediate/Poor-risk Patients.

	PD-L1 <1%		**PD-L1 ≥1%**	
Outcome	**Nivolumab + Ipilimumab N=284**	**Sunitinib N=278**	**Nivolumab + Ipilimumab N=100**	**Sunitinib N=114**
Objective response rate,* % (95% CI)	37 (32-43)	28 (23-34)	58 (48-68)	22 (15-31)
	P=0.0252†		p < 0.001†	
Best overall response,* %				
Complete response	7	1	16	1
Partial response	30	27	42	21
Stable disease	36	47	19	40
Progressive disease	20	13	14	25
NA	7	12	9	13

* IRRC-assessed.
† Exploratory analyses.

In the IMmotion 151 study *(Motzer, Powles, et al., 2018), a phase III study of Atezolizumab plus Bevacizumab versus Sunitinib in treatment-naive patients with metastatic renal carcinoma, 915 patients were included, of whom 362 (39%) in the population by intention to treat expressed PD-L1 receptors ≥1% of immune cells that infiltrated the tumour.*

In this subgroup of patients, when tumour response was evaluated by the investigator in the experimental arm of patients treated with Atezolizumab + Bevacizumab, up to 9% of the total of 178 patients reached CR, whereas in the Sunitinib arm (184 patients) CR was reached by 4% of the patients who expressed PD-L1 ≥1%.

However, in the ITT population, i.e. subjects with or without PD-L1 +, the percentage of complete responses was 5% for the Atezolizumab + Bevacizumab combination and 2% for the Sunitinib arm.

When the analysis was performed by an independent radiological committee, the CR rates for the subgroup PD-L1 + were 15% for Atezolizumab + Bevacizumab and 8% for patients treated with Sunitinib.
However, for the PD-L1 patients - the percentage of RCs in the experimental arm was 8% while it was 6% in the comparator arm.

The researchers were blind to PD-L1 status.

PFS and ORR by IRC

	PD-L1 +		PD-L1–[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9,12.5)	7.2 (6.1.11.1)	11.0 (8.3,13.3)	8.4 (7.4,10.1)	9.6 (8.3.11.5)	8.3 (7.0,9.7)
Stratified HR (95% CI)	0.93 (0.72.1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26,40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15 %	8%	8%	6%	11%	7%

IRC and investigator assessment of PFS benefit was generally consistent in the ITT population; however, results differed from investigator assessment in patients with PD-L1 + disease

Investigators, IRC reviewers and the sponsor were blinded to PD-L1 status

[1] PD-L1 negative tumours had a PD-L1 IC IHC expression <1%. b n = 276 for ORR.

In an analysis published by Lolli (Lolli et al., 2016), the prognostic and predictive value of the systemic immune inflammation index (SII) was analysed retrospectively in 335 patients treated with first-line Sunitinib, based on lymphocyte, platelet and neutrophil levels at the start of treatment and the changes after 6 weeks of treatment.
The patients were stratified into two levels according to these values (P<0.0001):
High level of SII and low level of SII with a cut-off value of 730.
SII values were associated with the objective tumour response, PFS and OS.

SII >730 (inflamed tumours):
. PFS 3.6 months
. OS: 13.5 months

SII < 730 (barely inflamed tumours):
. PFS 18.7 months
. OS: 43.6 months

Complete Response Rate			
TKI pivotal clinical trials			
Sunitinib	*Motzer 2007*	*Independent Committee*	*0%*

		By the Investigator	*< 1%*	
	Motzer 2009	*By the Investigator*	*3%*	
Sorafenib ***TARGET*** *Study*	*Escudier 2007*	*Independent Committee*	*0%*	
		By the Investigator	*< 1%*	
Pazopanib	*Sternberg 2010*	*Independent Committee*	*< 1%*	
Phase III clinical trial				
Comparz	*Motzer 2013*	*Independent Committee*	*3 Sunitinib patients*	*1 pazopanib patient*
Expanded access programmes				
Sunitinib	*Gore 2015*	*By the Investigator*	*1%*	
Sorafenib	*Stadler 2010*	*By the Investigator*	*< 1%*	
Retrospective real-life studies with Sunitinib				
Pool analysis	*Castellano 2017*	*By the Investigator*	*6.1%*	
SULONG *Long responders to Sunitinib > 22 months*	*Puente 2017*	*By the Investigator*	*21%*	
Gustav Roussy	*Albiges 2012*	*By the Investigator*	*64 Patients*	
RENIS registry	*Buchler 2016*	*By the Investigator*	*3.6%*	
Immunotherapy clinical trials alone or in combination with a TKI versus Sunitinib				
Checkmate 214 *Prognosis intermediate and poor*	*Motzer 2018*	*Independent Committee*	*9% Ipi Nivo*	*1% Suni*
IMmotion 151 *Powles 2018*		*By the Investigator PD-L1 ≥1% (39% of the population)*	*9% Atezo Beva*	*4% Suni*
		In ITT according to the investigator	*5% Atezo Beva*	*2% Suni*
		Total ITT population by independent committee	*11% Atezo Beva*	*7% Suni*
		ITT by independent committee *PD-L1 +*	*15% Atezo Beva*	*8% Suni*
		ITT by independent committee *PD-L1 -*	*8% Atezo Beva*	*6% Suni*

2.1 STUDY DESIGN

Observational, retrospective, multicentre study in spanish patients with metastatic Renal Cell Carcinoma (mRCC) treated with sunitinib as a first-line treatment (treatment with previous cytokine therapy is accepted) according to clinical practice who obtained a complete response (CR) to treatment in one of these 2 situations:

a) Complete response (CR) obtained exclusively with first-line sunitinib treatment (sunitinib CR).

b) Response obtained after a period of time on treatment with sunitinib in which local treatment was also performed (surgery of the residual metastasis/metastases, radiofrequency ablation or radiotherapy) to achieve the total macroscopic disappearance of the disease, according to the opinion of the physician responsible for the patient (CR + local treatment).

The patient population eligible for this study includes any patient with advanced or metastatic renal cancer treated with Sunitinib and who has achieved a CR to the tumour and its metastases at some point in the treatment and according to the usual evaluation criteria in daily clinical practice irrespective of whether it was obtained with Sunitinib alone or local treatment was required to eradicate all lesions: (residual metastasis(es), radiofrequency ablation or radiotherapy)

The requirements for a patient's inclusion are that:

1. These patients must have Sunitinib as first-line treatment in accordance with its Summary of Product Characteristics.

2. Collection of clinical, safety and response data in patients with advanced kidney cancer.

The study is expected to be conducted in at least 50 sites throughout Spain in order to reach the maximum number of study patients.

Case collection will start at each site after the contract with the site has been signed, all the study documentation is available and training in the procedures and objectives of the protocol has been provided by the person appointed by the sponsor.

Any number of patients that meet the inclusion criteria and no exclusion criteria may be recruited at the site.

This is an observational study designed to reflect routine clinical practice; there will be no interference with the daily routine of the medical care provided to kidney cancer patients.

The data collected will correspond to those usually collected in the medical record; patient demographic variables (never personal data that could lead the patient to be identified), age at start of treatment, routine laboratory values required in the diagnosis and control of this pathology, patient functional status and clinical status. Treatment compliance, tolerability and adverse events and treatment effectiveness will be collected.

Since this is an observational study, no additional material not provided for in routine practice will be required.

Any patient who meets the inclusion criteria and who does not meet any of the exclusion criteria and has received treatment with Sunitinib prior to participation in the registry will be considered evaluable.

No patient follow-up period is established and nor is there any interview with them, since there is only one moment in which the patient's data are reviewed; this will be when the investigator completes the case report form.

Analysis population

Patients above the age of 18 years with advanced carcinoma with a renal cell component who have received Sunitinib as a first line of treatment according to the indication of the drug and who have achieved a CR according to the criteria of the responsible medical team will be included.
During the study recruitment period, the participating sites may include all patients who meet the study's inclusion criteria and do not meet any of the exclusion criteria.
Since this is an observational and exploratory study, no hypothesis has been established and the number of subjects included will not be pre-established, although a sample of close to 90 cases is estimated in around 50 Spanish sites.
Treatment with Sunitinib will have begun before the patient is included in this registry, hence the treatment decision will depend solely on the treating physician's clinical criteria.

2.2 STUDY OBJECTIVES

Describe the compete responses in daily clinical practice in Spain in the 2007-October 30, 2018 period as the documented disappearance of all lesions in the investigator's opinion on at least 2 consecutive CT scans.

Seek associations between the CR from the macroscopic point of view and the baseline features of both patient and tumour, such as:

- Demographic characteristics (age at the start of treatment)
- Comorbidities: cardiovascular, renal, endocrine, autoimmune, intestinal, chronic dermatological, obesity, intestinal and hepatic.
- Previous nephrectomy
- Classification of the risk group according to Motzer and/or Heng criteria and of the association between each one of the prognostic variables, such as: patient baseline status, time elapsed from nephrectomy to the start of systemic treatment, presence of anaemia, corrected calcium, LDH levels, neutrophil and platelet levels.
- *Tumour data: histology, Fuhrman grade, presence of tumour necrosis and number and location of metastases (organs involved).*

The risk factors associated with the occurrence of CR from the macroscopic point of view will be sought.

SECONDARY OBJECTIVES

- *Develop recommendations to be followed in patients who obtain CR when treated with Sunitinib based on the case registry and the therapeutic strategy adopted that yielded the greatest clinical benefit.*
- *Define the median time of treatment with Sunitinib until complete remission of the lesions in the opinion of the patient's treating physician.*
- *Define the median duration of the CR.*
- *The time elapsed from the verification of the CR to disease to stabilisation/progression or change of treatment due to unacceptable toxicity or death from any cause will be collected.*
- *A record of the doses and treatment regimens used will be made. In the event of changes in the treatment dose (increase or reduction) the reason will be specified: toxicity, efficacy, decision taken after the disappearance of lesions or at patient's request.*
- *Description of local treatment techniques if used and when they were applied. In the pathological anatomy report of the resected piece, the percentage of necrosis and histology will be recorded, as will any surgical complications that presented.*
- *Safety profile of treatment with sunitinib: the highest grade adverse events presented by the patients will be recorded, as well as whether the treatment had to be discontinued at any point due to toxicity.*
- *In cases of discontinuation of systemic treatment after a period of treatment with maintained CR, the reason for the decision and the patient's participation in this decision (whether the patient was consulted, whether it was at the patient's request or the investigator's decision).*
- *Pharmacological group by mechanism of action used in patients in the second line after disease progression: another TKI, treatment with a drug acting on the immune system.*

Exploratory analysis:

Baseline neutrophil/leukocyte ratio and evolution of the neutrophil/lymphocyte ratio throughout treatment; at 4-6 weeks, 3 months, 6 months, 9 months, 12 months and then every 6 months in the available analyses close to these dates.

3 HYPOTHESIS TESTING

3.1 STATISTICAL HYPOTHESES

This being an observational and exploratory study, no hypothesis has been established.

3.2 STATISTICAL DECISION RULES

The statistical significance value is set to $p<0.05$ The SAS statistical software version 9.3 or later (SAS Institute Inc., Cari, NC, USA) will be used.

4 ANALYSIS POPULATION

4.1 FULL ANALYSIS SET

Since it is an observational and exploratory study, the number of subjects included will not be pre-determined, although a sample of close to 90 cases is envisaged in about 50 Spanish sites; taking the case collection period into account.

Any number of patients that meet the inclusion criteria and no exclusion criteria may be recruited at the site.

Any patient who meets the inclusion criteria and who does not meet any of the exclusion criteria and has received treatment with Sunitinib prior to participation in the registry will be considered evaluable.

4.1.1. Inclusion Criteria

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

1. Patients aged 18 years or older who have been treated for a metastatic renal carcinoma with first-line sunitinib in (prior cytokine treatment is admitted) between 2007 and October 30, 2018 and have obtained, as best response to treatment, total disease remission in the opinion of the treating physician from the clinical, radiological and/or macroscopic standpoint. This response must have been achieved through two possible strategies:
    a. Systemic treatment with Sunitinib alone.
    b. Treatment with Sunitinib and subsequent local treatment for one or several residual lesions that have not responded to the drug (traditional surgery, radiotherapy, SBRT (Stereotactic Body Radiation Therapy)).
2. The duration of the CR must have been confirmed by at least 2 consecutive imaging tests with no limit on the duration of this response. Patients with subsequent progression may be included in this registry.
3. Patients of any risk group.
4. Tumours of any histology.

4.1.2. Exclusion Criteria

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

1. Patients treated with another drug other than Sunitinib.
2. Patients without radiology reports that substantiate the CR.

3. Patients without a record of the dose and regimen of Sunitinib.
4. Patients who achieved complete remission after October 30, 2018.

4.2 SAFETY ANALYSIS

The safety analysis is the same as the full analysis.

4.3 OTHER ANALYSIS

NA

4.4 SUBGROUPS

NA

5 OBJECTIVES AND VARIABLES

The primary objective of the study is *to identify patients with metastatic renal cell carcinoma (mRCC) who obtained a complete response (CR) to treatment with Sunitinib exclusively or with Sunitinib and a local treatment to eliminate residual disease in the opinion of the clinician. Complete response (CR) is defined as the disappearance of all measurable lesions according to the investigator's criterion in at least 2 consecutive CT scans.*

The clinical baseline characteristics of these patients and the tumour will be described in order to look for predictive response factors.

The intention is to describe the therapeutic strategy used in patients who obtained the greatest clinical benefit in the cases described once the macroscopic lesions were eradicated in order to draft recommendations to be followed once the registry's statistical analysis is available.

The variables to be analysed for this study will be obtained from the patients' medical records and case report forms according to the protocol. The data will be recorded on the paper CRF designed for this study where the following patient information will be included:

DEMOGRAPHIC AND DISEASE INFORMATION

1) Age at the start of treatment for metastatic disease
2) Functional status, measured by the ECOG scale (0, 1, 2, 3, 4) and/or by means of the KPS (Karnosfsky Performance Status) scale, at the start of treatment (see annex I)
3) Motzer and Heng prognostic criteria
4) Laboratory data (haemoglobin, leukocytes, corrected calcium, LDH levels, lymphocytes, platelets, neutrophils, lymphocytes)
5) Comorbidities
6) Date the disease was diagnosed
7) Metastasis site(s) and number
8) Furhrman grade (I, II, III, IV)

9) Tumour stage (TNM)
10) Previous nephrectomy
11) Necrosis

TREATMENT

1) Start date of treatment with first-line Sunitinib
2) Initial dose and treatment regimen
3) Type of treatment received (monotherapy or in combination with local treatment) and technique used in the case of local treatment
4) Response to treatment.
5) Date of completion of the treatment after CR if treatment is interrupted
6) Modification of dosage and/or treatment regimen, number of changes in the dose, reason, date and new dose
7) Dose interruptions, number of interruptions, reason, date of interruption and restart and new dose
CCI [redacted]
9) Adverse reactions

POST-TREATMENT

1) Continuation of treatment in 1st line
2) End date and reason
3) Date of progression
4) Date of and reason for death
5) Post-Sunitinib treatments (another TKI, mTOR, immunotherapy)

The following aspects will be assessed using the variables collected:

- **Time from nephrectomy to the start of systemic treatment:** defined as the time interval from the day of the nephrectomy to the day treatment with Sunitinib started.

  Time to CR: defined as the time interval from the day treatment with Sunitinib started until the day the complete response is documented in the first CT scan without lesions.

- **Duration of treatment with Sunitinib once CR is reached:** defined as the time interval from the day on which the complete response is documented until the day that the definitive discontinuation of the treatment is confirmed, either at the patient's own decision or at the doctor's decision.

- **Time to progression (TTP):** defined as the time interval from the day on which the complete response is documented until the first day that objective tumour progression, if any, is observed.

- **Time to change of treatment:** in patients who continue treatment with Sunitinib once the lesions have disappeared, it is defined as the time interval from the day on which the complete response is documented until the first day on which the change of treatment due to unacceptable toxicity is documented, as applicable.

- **Time to death:** defined as the time interval from the day on which the

complete response is documented to the day on which death from any cause is documented, if it occurs.

- **Duration of complete response (DOR):** defined as the time interval from the date on which the complete response to Sunitinib is identified until the date of the CT scan conforming tumour progression, the change of treatment due to unacceptable toxicity, death from any cause or until the date of the last follow-up at the close of the study. It represents the time that the patient survives without signs of disease.

5.1 EFFICACY/EFFECTIVENESS OBJECTIVES

Efficacy is assessed by describing the complete responses in daily clinical practice in Spain in patients with metastatic renal carcinoma treated with first-line Sunitinib, defined as the documented disappearance of all lesions in the investigator's opinion in at least 2 consecutive CT scans. The treatment may be with Sunitinib alone (CR Suni) or Sunitinib plus a local treatment to eliminate residual disease (CR + local treatment).

The baseline characteristics of both patient and tumour will be described to seek predictive response factors. The following variables will be considered:

- Demographic characteristics (age at the start of treatment)
- Comorbidities: cardiac, renal, endocrine, autoimmune and hepatic.
- Previous nephrectomy
- Classification of the risk group according to Motzer and/or Heng criteria and of the association between each one of the prognostic variables, such as: patient baseline status, time elapsed from nephrectomy to the start of systemic treatment, presence of anaemia, corrected calcium, LDH levels, neutrophil and platelet levels.
- Tumour data: histology, Fuhrman grade, presence of tumour necrosis and number and location of metastases (organs involved).

Secondary efficacy objectives evaluated will be time on treatment with Sunitinib until CR, duration of complete response and the time elapsed from CR to disease stabilisation/progression or change of treatment due to unacceptable toxicity or death from any cause.

The subjects with the greatest clinical benefit will be evaluated on the basis of the therapeutic strategy adopted in order to develop recommendations to be followed in patients who obtain CR. Moreover, the decision to discontinue treatment after a period of maintenance of CR and the pharmacological group by the mechanism of action used in second line after disease the progression will be evaluated.

5.2 SAFETY OBJECTIVES

The safety of Sunitinib will be evaluated by describing the incidence of the serious and non-serious adverse events of highest grade explicitly attributed to Sunitinib in the patient's medical history, as well as the grade of the associated adverse event if it or they lead to treatment discontinuation at some point due to toxicity.

5.3 OTHER OBJECTIVES

The evolution of the neutrophil/leukocyte ratio throughout treatment will be analysed: at 4-6 weeks, 3 months, 6 months, 9 months, 12 months and then every 6 months in the available laboratory data close to these dates.

Several studies suggest that a high neutrophil/leukocyte ratio (NLR) is associated with a poorer disease prognosis. The analysis of the evolution of these two haematological parameters for subsequent exploratory analyses is established as an additional objective.

5.4 COVARIATES

All the covariates have been collected on the paper CRF designed for this study as specified in the study protocol.

Variable	Role	Operational definition
ECOG	Epidemiological datum (covariate)	Risk groups
Patient age at time of diagnosis	Epidemiological datum (covariate)	Age
TNM tumour stage (T describes the size of the tumour and the spread of the cancer to nearby tissue; N (nodes) describes the spread of cancer to nearby lymph nodes and M stands for metastases)	Epidemiological datum (covariate)	Tumour staging
Tumour histology	Epidemiological datum (covariate)	Pathological Anatomy
Fuhrman tumour grade	Epidemiological datum (covariate)	Pathological Anatomy
KPS	Epidemiological datum (covariate)	Risk groups
Previous nephrectomy	Epidemiological datum (covariate)	Surgery
Cardiac, renal, endocrine, autoimmune and hepatic comorbidities.	Epidemiological datum (covariate)	Disease data
Classification of the prognostic risk group	Epidemiological datum (covariate)	Risk groups
Patient baseline status	Epidemiological datum (covariate)	Risk groups
Time elapsed from the nephrectomy to the start of systemic treatment	Epidemiological datum (covariate)	Risk groups
Haemoglobin	Epidemiological datum (covariate)	Risk groups
Corrected calcium	Epidemiological datum (covariate)	Risk groups
LDH levels	Epidemiological datum (covariate)	Risk groups
Lymphocytes	Epidemiological datum (covariate)	Risk groups
Platelets	Epidemiological datum (covariate)	Risk groups
Baseline Neutrophil/Lymphocyte rate and at 6 weeks of treatment, 3 months, 6 months, 9 months, 12 months and then every 6 months.	Epidemiological datum (covariate)	Risk groups

Variable	Role	Operational definition
Number of metastases	Disease data (covariate)	Disease data
Number of organs with metastases	Disease data (covariate)	Disease data
Time on treatment before reaching CR	Secondary objective	Disease data
Duration of CR	Secondary objective	Disease data
Reason why CR ends: progression, tumour stabilisation or intolerable toxicity	Disease data (covariate)	Disease data
Dosage and regimens of Sunitinib	Treatment data (covariate)/Secondary objective	Treatment data
Temporary treatment interruptions	Treatment data (covariate)	Treatment data
Definitive interruption of treatment after reaching CR	Treatment data (covariate)	Treatment data
Active patient participation in the decision to interrupt the treatment definitively once CR is obtained	Patient empowerment (covariate)/Secondary objective	
Time on treatment with Sunitinib once CR is reached	Treatment data (covariate)	Treatment data
Local treatment techniques of residual lesions	Secondary objective	Treatment data
PA (pathological anatomy) of the metastasectomy: histology and degree of necrosis	Disease data (covariate)	Disease data
Highest grade of adverse events related to the treatment with Sunitinib	Secondary objective	Treatment data
Serious adverse events (SAEs) during treatment with Sunitinib	Secondary objective	Treatment data
Pharmacological group of second-line treatment after disease progression after a period of time in CR (TKI, mTOR, Immunotherapy)	Secondary objective	Treatment data
Causes of death	Disease data (covariate)	Disease data

6 HANDLING OF MISSING DATA

No replacement criterion for missing values will be used, except for dates, as appropriate.

- If the year is unknown, the date will not be imputed and will it be treated as a missing value.
- If the day and month are unknown, it will be imputed as July 1.
- If the day is unknown, the value of 15 will be assigned.

7 STATISTICAL ANALYSIS AND METHODOLOGY

7.1 STATISTICAL METHODS

The investigator will collect the data from the patients enrolled in an electronic Case

Report Form specially designed for this study.

The patient number assigned provide is a correlative number with no identification value.

All information will be stored in a database designed for the study that will be a true reflection of the case report form. Once the project is finished, the data will be transferred to SAS for the final validation and the statistical analysis.

A Data Management Plan (DMP) will be drawn up, and once it has been approved by the person in charge of the study, Queries will be programmed in the database.

7.2 STATISTICAL ANALYSIS

7.2.1. Included and evaluable population

The descriptive statistics of patients who meet all the inclusion criteria and none of the exclusion criteria will be presented.

In the subpopulation of non-evaluable patients, their frequency distribution will be presented, depending on the reasons for non-eligibility:

- Patients who are not 18 years of age or older and who have been treated for metastatic renal carcinoma with Sunitinib as first-line (prior cytokine treatment is admitted) between 2007 and October 30, 2018.
- Patients aged 18 years or older who have been treated for a metastatic renal carcinoma with Sunitinib as second line.
- Patients aged 18 years or older who have been treated for a metastatic renal carcinoma with Sunitinib as first line (prior cytokine treatment is admitted) between 2007 and October 30, 2018 and who have not obtained, as best response to treatment, total disease remission in the opinion of the treating physician from the clinical, radiological and/or macroscopic standpoint.
- Patients whose duration of CR has not been confirmed with at least 2 consecutive imaging tests, with no limit on the duration of this response.
- Patients treated with another drug other than Sunitinib.
- Patients without radiology reports that substantiate the CR.
- Patients without a record of the dose and regimen of Sunitinib.
- Patients who achieved complete remission after October 30, 2018.

7.2.2. Descriptive analysis

The mean value, standard deviation, median, minimum, maximum, interquartile range (RIQ) and 95% confidence interval (CI 95%) of the following variables will be provided:

- Age of the patients at the start of treatment.
- Pre-treatment necrosis percentage

- Laboratory data at the start of treatment:
    - Haemoglobin
    - Leukocytes
    - Corrected calcium
    - LDH levels
    - Lymphocytes
    - Platelets
    - Neutrophil/Lymphocyte rate
- Time elapsed from the nephrectomy to the start of systemic treatment
- Time on treatment until CR is reached
- Duration of CR
- Time on treatment after CR is reached

The frequency distribution of patients will be presented according to:

- ECOG:
    - 0
    - 1
    - 2
    - 3
    - 4
- KPS (Karnosfsky Performance Status):
    - 0%
    - 10%
    - 20%
    - 30%
    - 40%
    - 50%
    - 60%
    - 70%
    - 80%
    - 90%
    - 100%
- Motzer prognostic criteria:
    - Favourable (0 factors)
    - Intermediate (1-2 factors)
    - Poor (3 or more factors)
- Heng prognostic criteria:
    - Favourable (0 factors)
    - Intermediate (1-2 factors)
    - Poor (3 or more factors)
- Comorbidities:

  - Cerebrovascular disease
  - Liver disorders
  - Renal failure
  - Autoimmune disease
  - Chronic dermatological disease
  - Obesity
  - Bowel disease

- Metastasis site:
  - Lung
  - Liver
  - Brain
  - Pancreas
  - Nodes
  - Other

- Fuhrman grade:
  - I
  - II
  - III
  - IV

- TNM tumour stage
- Histological type:
  - Clear cell
  - Chromophobe
  - Sarcomatoid, percentage
    - <20%
    - 20-30%
    - 31-50%
    - 51-75%
    - >75%
  - Papillary type 1
  - Papillary type 2
  - Mixed
  - Not performed

- Previous nephrectomy:
  - Yes
  - No

- Complications during surgery;
  - Yes
  - No

- Initial dose and treatment regimen:

  - Sunitinib 50 mg 4/2 regimen
  - Sunitinib 50 mg 2/1 regimen
  - Sunitinib 37.5 mg 4/2 regimen
  - Sunitinib 37.5 mg 2/1 regimen
  - Sunitinib 25 mg 4/2 regimen
  - Sunitinib 25 mg 2/1 regimen

- Type of treatment received:
  - Sunitinib monotherapy
  - Sunitinib + subsequent local treatment
  - Local treatment techniques for residual lesions:
    - Traditional surgery
    - Radiotherapy
    - SBRT

7.2.3. Follow-up analysis

The evolution of the following variables will be presented for each one of the predefined times for data collection:

- **Neutrophil/leukocyte rate** throughout treatment:
  - Baseline
  - At 6 weeks
  - At 3 months
  - At 6 months
  - At 9 months
  - At 12 months
  - Subsequently, every 6 months in the available analyses close to these dates.

At all the time points when this analytical variable is gathered, the possible occurrence of significant changes in the neutrophil/lymphocyte rate versus the baseline (at the beginning of treatment) will be analysed. For this purpose, generalised linear mixed-effects models will be used over time as a fixed factor and the patient as a random factor.

- **Dose modifications during treatment with Sunitinib.** The absolute and relative frequencies of the number of patients who have had dose modifications since the start of treatment will be reported. In the subpopulation of patients with dose modifications, the frequency distribution with regard to the number of dose modifications will be presented:
  - 1 modification:
    - Type of modification:
      - ✓ Increase
      - ✓ Reduction
      - ✓ Changes in the rest regimen
    - Reason for the modification:
      - ✓ Toxicity
      - ✓ Other different reasons)
    - New dose prescribed:
      - ✓ Sunitinib 50 mg 4/2 regimen

- ✓ Sunitinib 50 mg 2/1 regimen
- ✓ Sunitinib 37.5 mg 4/2 regimen
- ✓ Sunitinib 37.5 mg 2/1 regimen
- ✓ Sunitinib 25 mg 4/2 regimen
- ✓ Sunitinib 25 mg 2/1 regimen
- ✓ Other treatment regimen

- 2 modifications:
  - Type of modification:
    - ✓ Increase
    - ✓ Reduction
    - ✓ Changes in the rest regimen
  - Reason for the modification:
    - ✓ Toxicity
    - ✓ Other different reasons)
  - New dose prescribed:
    - ✓ Sunitinib 50 mg 4/2 regimen
    - ✓ Sunitinib 50 mg 2/1 regimen
    - ✓ Sunitinib 37.5 mg 4/2 regimen
    - ✓ Sunitinib 37.5 mg 2/1 regimen
    - ✓ Sunitinib 25 mg 4/2 regimen
    - ✓ Sunitinib 25 mg 2/1 regimen
    - ✓ Other treatment regimen

A summary calculation of the dose modifications will be made for the aspects described above.

- **Temporary dose interruption during treatment with Sunitinib.** The absolute and relative frequencies of the number of patients who interrupted the treatment will be reported. In the subpopulation of patients with treatment interruptions, frequency distribution will be presented for:
  - Number of treatment interruptions:
    - 1
    - 2
    - 3
    - 4
  - Reason for interruption:
    - Toxicity
    - CR. In this subgroup of patients:
      - Active participation by the patient in the decision to discontinue the product once CR is reached
      - At the patient's decision
      - At the doctor's decision
    - Other reasons
  - Calculation of total days of treatment interruption

A summary calculation of the dose modifications will be made for the aspects described above. For the calculation of total days of interruption of treatment, descriptive central tendency (mean, median) and dispersion (standard deviation, interquartile range)

statistics will be presented.

- **Post-treatment.** The absolute and relative frequency of the number of patients who discontinue first-line Sunitinib treatment will be reported definitively after the CR. In the subpopulation of patients who remain on second-line treatment, frequency distribution will be presented for:
  - Reason for terminating the treatment:
    - Toxicity
    - Progression
    - Death, reason:
      - Progression
      - Toxicity, in this case:
        - ✓ In the investigator's opinion related to Sunitinib
        - ✓ Not related to Sunitinib
    - Another reason
  - Total number of days of duration of treatment with second-line Sunitinib.
  - Post-second-line Sunitinib pharmacological treatment group after disease progression after a period of CR:
    - TKI
    - mTOR
    - Immunotherapy

7.2.4. Efficacy analysis

Depending on the **primary objective of the study**, the complete responses (CR) observed in Spanish daily clinical practice in patients with advanced carcinoma with a renal cell component that have received first-line treatment with Sunitinib will be described. All demographic and clinical characteristics will be summarised descriptively.

More specifically, the following baseline features of both patient and tumour will be described:

- Demographic characteristics (age at the start of treatment of the metastatic disease).
- Comorbidities: presence of cardiovascular, hepatic, renal, autoimmune, chronic dermatological, obesity and/or intestinal disease.
- Tumour data: number and site of metastases, tumour histology, Fuhrman grade and presence of tumour necrosis.
- Previous nephrectomy in the treatment of metastatic renal cancer and time elapsed from nephrectomy to the start of systemic treatment.
- Classification of the risk group according to Motzer and/or Heng criteria.
- Patient's baseline status, including ECOG grade, presence of anaemia, corrected calcium, LDH levels, neutrophil and platelet levels.

Central tendency measures (mean and median) and dispersion measures (standard deviation and interquartile range) will be used for the quantitative variables. Frequency distributions (absolute and relative) will be presented for categorical data. Bivariate comparisons between baseline characteristics and events of interest of a continuous nature will be made by parametric tests (Student's t test, one-way ANOVA) or their non-parametric equivalents (Mann-Whitney, Kruskal-Wallis) depending on the distribution of the variables. In the case of categorical variables, the Chi-squared test or Fisher's exact

test, as applicable, will be used for the comparison of frequency distribution.

The **secondary outcome measures** pertaining to the follow-up time until the event of interest (complete disease remission, disease progression, change of treatment due to unacceptable toxicity or death from any cause) will be described by estimating survival functions using the Kaplan-Meier method. Specific estimates and 95% confidence intervals will be provided for the median, 25th percentile and 75th percentile of the distributions of each secondary variable. The secondary outcome variables related to follow-up time are:

- Time on treatment with Sunitinib until complete remission of lesions, calculated as the difference between treatment start date and CR confirmation date (2nd CT scan).
- Duration of complete remission (DOR)
- Progression-free survival (PFS) or time from remission to disease progression, change of treatment due to unacceptable toxicity or death. It will be calculated as the time elapsed from the RC confirmation date (2nd CT scan) until the date of progression/death or change of treatment for unacceptable toxicity, as applicable, or else it will be censored on the date of the last patient follow-up.

Taking into account the asymmetry normally observed in the distribution of survival times and that follow-up periods may be uneven (different study entry date), the Kaplan-Meier method will be used to estimate the median time to CR together with its 95% confidence interval. The median will indicate when complete remission of the disease occurred in 50% of patients.

In order to find associations between time to CR and the baseline features of both patient and tumour, a log-rank test will be used for comparison between groups and the determination of the statistical significance of the correlation between each of the baseline variables and the time to complete remission of disease. The following baseline characteristics are considered:

- Demographic characteristics
- Comorbidities
- Tumour data
- Prior nephrectomy in the treatment of metastatic renal cancer
- Classification of the risk group according to Motzer and/or Heng criteria.
- Patient's baseline status, including ECOG grade, presence of anaemia, corrected calcium, LDH levels, neutrophil and platelet levels.

This analysis will establish which baseline characteristics are associated with a shorter complete response time to treatment.

As part of the secondary objectives, the doses and treatment regimens observed in the sample will also be descriptively summarised by means of absolute and relative frequencies. In the case of changes in the treatment dose, the frequency of patients with dose increase, dose reduction and changes in the rest regimen will be specified. Similarly, the most frequent reasons for changes in dosage and/or treatment regimen to RC will be reported.

Frequencies of the type of treatment received will be presented, depending on whether it

is monotherapy or combination with a local treatment for one or several residual lesions. In the group of patients who received local treatment, the frequency distribution of the techniques used (traditional surgery, radiotherapy and SBRT) will be presented, at the time they are applied, as well as histology, degree of tumour necrosis and the surgical complications reported.

In the sub-sample of patients who discontinue systemic treatment after a period of treatment with maintenance of CR, the most frequent reasons for the decision and the frequency of cases in which the patient was consulted in the decision to discontinue treatment will be reported, and the cases in which it was at the patient's or the investigator's request.

The distribution of frequencies of the pharmacological group by mechanism of action used in patients in the second-line treatment after disease progression will be reported.

Once the descriptive statistics have been presented, and provided that the proportional *hazards* assumption or relative risk of the covariates of interest (patient and tumour baseline conditions, dose and treatment regimen and type of treatment received) are fulfilled, a multivariate Cox regression will be performed to investigate the effect of all prognostic factors on CR/PFS. The *hazards ratio* (HR) will be estimated, along with their 95% confidence intervals, as parameters of association between each one of the predictive factors of response and the time to complete remission or disease progression.

This information will make it possible to produce recommendations for the therapeutic strategy to be followed in patients who obtain complete remission of the macroscopic lesions to the treatment with Sunitinib.

For the safety analysis of treatment with Sunitinib, the percentage of patients who have presented serious and non-serious adverse events explicitly attributed to Sunitinib during treatment will be presented by means of descriptive tables. The frequency of adverse events recorded will be reported based on severity, the highest grade and whether it or they led to a dose interruption or modification.

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ANNEX I: ECOG VS KARNOFSKY EQUIVALENCE TABLE

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