NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A real world retrospective database study of patients diagnosed with metastatic and/or advanced renal cell carcinoma and treated with sunitinib and/or axitinib in a specialist United Kingdom oncology centre
Protocol number	X9001180
Protocol version identifier	Version 1.2
Date of last version of protocol	22 November 2018 (Draft 1.0)
Active substance	Axitinib (Anatomical Therapeutic Chemical Code [ATC]: L01XE17) Sunitinib (ATC: L01XE04)
Medicinal product	Axitinib (ATC: L01XE17) Sunitinib (ATC: L01XE04)
Research question and objectives	Research Questions: To understand the clinical outcomes of patients treated with sunitinib in first line and axitinib in second line in a real world setting as therapies for metastatic and/or advanced renal cell carcinoma (mRCC). Primary Objective: 1. What is the progression free survival (PFS) of patients treated in first line with sunitinib, and stratified by Memorial Sloan-Kettering Cancer Center/International Metastatic Renal Cell Carcinoma Database Consortium (MSKCC/IMDC) risk category (favourable, intermediate, poor)? 2. What is the progression free survival (PFS) of patients treated in second line with axitinib, and stratified by MSKCC/IMDC risk category (favourable, intermediate, poor)? <u>Secondary Objectives:</u> First Line: 1. What is the overall survival (OS) of all patients in first line with sunitinib, and stratified by MSKCC risk (favourable, intermediate, poor)? 2. What is the duration of therapy with sunitinib in first line (using time to treatment discontinuation [TTD]) for all patients and stratified by MSKCC

	risk (favourable, intermediate, poor). 3. Objective response rate (ORR). 4. Duration of objective response (complete response [CR] or partial response [PR]). 5. Examine factors that predict TTD, eg, risk stratification, or individual/grouped parameters that comprise the prognostic classification systems. a. Less than one year from time of diagnosis. b. Karnovsky performance status less than 80%. c. Haemoglobin less than the lower limit of normal (eg, less than 12 g/dl). d. Serum calcium greater than the upper limit of normal (eg, 10 mg/dl or: 2.5 mmol/l). e. Neutrophil greater than the upper limit of normal (eg, greater than 7.0 $x10^9$ dl). f. Platelets greater than the upper limit of normal (eg, greater than 400 000). g. Lactate dehydrogenase greater than 1.5 times the upper limit of normal. h. Fuhrmann grade of tumour. i. Tumour subtype eg, clear cell versus. non-clear cell. 6. Safety and tolerability data reporting for first line sunitinib. Second line: 1. What is the OS of all patients in second line with axitinib, and stratified by MSKCC risk (favourable, intermediate, poor)? 2. What is the duration of therapy with axitinib in second line (using TTD) for all patients and stratified by MSKCC risk (favourable, intermediate, poor). 3. ORR. 4. Duration of objective response (CR or PR).

	5. Examine factors that predict duration of TTD, eg, risk stratification, or individual/grouped parameters that comprise the prognostic classification systems. a. Less than one year from time of diagnosis. b. Karnovsky performance status less than 80%. c. Haemoglobin less than the lower limit of normal (eg, less than 12 g/dl). d. Serum calcium greater than the upper limit of normal (eg, 10 mg/dl or: 2.5 mmol/l). e. Neutrophil greater than the upper limit of normal (eg, greater than 7.0 $x10^9$ dl). f. Platelets greater than the upper limit of normal (eg, greater than 400 000). g. Lactate dehydrogenase greater than 1.5 times the upper limit of normal. h. Fuhrmann grade of tumour. i. Tumour subtype eg, clear cell vs. non-clear cell. 6. Safety and tolerability reporting for second line axitinib. The objectives listed below will also be assessed as exploratory analyses for various patient subgroups of interest, and will be conducted if sufficient numbers of patients are available: 1. Axitinib PFS and OS, as a second line therapy following sunitinib, pazopanib, or following other Tyrosine kinase inhibitors (eg, sorafenib). 2. Axitinib PFS and OS as a third line therapy. 3. Axitinib (and, if applicable, sunitinib) PFS and OS post-immunotherapy (IO), taking into consideration 2^{nd} and 3^{rd} therapy lines, following all IO therapy options, eg, atezolizumab/bevacizumab, nivolumab/ipilumimab, nivolumab, interleukin-2. 4. For the post-sunitinib axitinib cohort: What was the duration of sunitinib therapy before patients

	transitioned to axitinib? 5. For the post-pazopanib axitinib cohort: What was the duration of pazopanib therapy before patients transitioned to axitinib? 6. Is the duration of therapy on first line sunitinib and/or pazopanib related to duration of therapy for second line axitinib?
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse Event Monitoring
aRCC	Advanced renal cell carcinoma
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
CIOMS	the Council for International Organizations of Medical Sciences
CIs	confidence intervals
CR	Complete response
CRF	Case Report Form
CSA	Clinical Study Agreement
DCT	Data Collection Tool
DOR	Duration of response
DRR	Durable Response Rate
ECOG	The Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HR	Hazard Ratio
IEA	International Epidemiological Association

Abbreviation	Definition
IEC	Independent Ethics Committee
IFN-α	Interferon-alpha
IL-2	Interleukin-2
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-oncology
IRAS	Integrated Research Application System
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	The International Society for Pharmacoeconomics and Outcomes Research
mRCC	Metastatic renal cell carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Center
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Non Interventional Study
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease
PDGF	platelet derived growth factor
PFS	Progression free survival
PR	Partial response

Abbreviation	Definition
RCC	Renal cell carcinoma
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real world data
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TNM	TNM Classification of Malignant Tumours
TTD	Time to treatment discontinuation
UK	United Kingdom
VEGF	Vascular endothelial growth factor
VHL	Von Hippel Lindau

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 August 2019
End of data collection	15 August 2019
Final study report	31 October 2019

7. RATIONALE AND BACKGROUND

Metastatic renal cell carcinoma (mRCC) is a global health problem, resulting in the deaths of more than 14,000 patients every year. Over the past 20 years, there has been a shift from cytokine based therapy towards agents targeting vascular endothelial growth factor (VEGF) receptors, due to the conference of longer progression free survival and overall survival rates with these agents.

Pfizer have two VEGF targeted medicines to treat mRCC: sunitinib and axitinib, and these are used in first and second line respectively. It is important that we have a clear understanding of the real world use and efficacy of our medicines.

The Christie Hospital has been building a detailed database of information regarding patients with mRCC, and now has over 3000 patients' details included.

The information that has been collated includes:

1. Memorial Sloan-Kettering Cancer Center (MSKCC) Criteria (see annex 3.1).[1]
2. Heng Criteria (see annex 3.2).[2]
3. The Eastern Cooperative Oncology Group (ECOG) performance status (see annex 3.3).[3]
4. PFS.
5. OS.
6. Lines of therapy.
7. Fuhrmann grade (see annex 3.4).[4]
8. TNM Classification of Malignant Tumours (TNM) stage (see annex 3.5).[5]

9. Best response.

10. Stable disease *vs* partial response.

11. Metastasis diagnosis.

12. Histology.

13. Duration of therapy.

14. Therapy discontinuation due to toxicity/progression.

Although more than 4,000 patients die due to kidney cancer in the UK every year,[6] in the past 20 years there has been considerable progress in survival outcomes achieved through the delivery of systemic therapy for metastatic and advanced renal cell carcinoma (mRCC and aRCC).[7] For many years, cytokine therapies including, interferon alpha (IFN-α) and interleukin-2 (IL-2), were the preferred first-line treatments; however, they have been replaced by therapies with longer PFS and OS.[8]

Understanding the abnormal signal transduction pathways in mRCC has enabled the identification and development of molecular targets. For example, loss of the von Hippel Lindau (VHL) tumour suppressor gene leads to upregulated transcription of platelet derived growth factor (PDGF) and VEGF, both of which are major factors in mRCC tumorigenesis (Najjar and Rini, 2012).[9] As a result of this, there has been a large shift from cytokine based therapy towards agents targeting VEGF pathways, and in particular tyrosine kinase inhibitors (TKIs).

The Food and Drug Authorization (FDA), European Medicines Agency (EMA) and the National Institute for Health and Care Excellence (NICE) have approved several TKIs over the years, the first being sorafenib and sunitinib, and later pazopanib, axitinib, cabozantinib and lenvatinib.[10] It is important that first-line therapies are strategically chosen to devoid the need for sequential therapy lines. In order for HCPs to select the optimal first-line TKI, head-to-head RCT comparison studies are undertaken.[11]

This study presents an opportunity to investigate TKI therapies used for the treatment of renal cell carcinoma, using a high quality real world evidence database, which was developed and has been maintained at the Christie Hospital, Manchester.

8. RESEARCH QUESTION AND OBJECTIVES

Research Questions:

To understand the clinical outcomes of patients treated with sunitinib in first line and axitinib in second line in a real world setting as therapies for mRCC and/or aRCC.

Primary Objective:

1. What is the PFS of patients treated in first line with sunitinib, and stratified by MSKCC/IMDC risk category (favourable, intermediate, poor)?

2. What is the PFS of patients treated in second line with axitinib, and stratified by MSKCC/IMDC risk category (favourable, intermediate, poor)?

Secondary Objectives:

First Line:

1. What is the OS of all patients in first line with sunitinib, and stratified by MSKCC risk (favourable, intermediate, poor)?

2. What is the duration of therapy with sunitinib in first line (using time TTD) for all patients and stratified by MSKCC risk (favourable, intermediate, poor).

3. ORR.

4. Duration of ORR (CR or PR).

5. Examine factors that predict duration of therapy on sunitinib (TTD), eg, risk stratification, or individual/grouped parameters that comprise the prognostic classification systems.

    a. Less than one year from time of diagnosis.

    b. Karnovsky performance status less than 80%.

    c. Haemoglobin less than the lower limit of normal (eg, less than 12 g/dl).

    d. Serum calcium great than the upper limit of normal (eg, 10 mg/dl or: 2.5 mmol/l).

    e. Neutrophil greater than the upper limit of normal (eg, greater than 7.0 $x10^9$ dl).

    f. Platelets greater than the upper limit of normal (eg, greater than 400 000).

    g. Lactate dehydrogenase greater than 1.5 times the upper limit of normal.

    h. Fuhrmann grade of tumour.

    i. Tumour subtype eg, clear cell vs. non-clear cell.

6. Safety and tolerability data reporting for first line sunitinib.

Second line:

1. What is the OS of all patients in second line with axitinib, and stratified by MSKCC risk (favourable, intermediate, poor)?

2. What is the duration of therapy with axitinib in second line (using TTD) for all patients and stratified by MSKCC risk (favourable, intermediate, poor).

3. ORR.

4. Duration of ORR (CR or PR).

5. Examine factors that predict duration of therapy on axitinib (TTD), eg, risk stratification, or individual/grouped parameters that comprise the prognostic classification systems.

    a. Less than one year from time of diagnosis.

    b. Karnovsky performance status less than 80%.

    c. Haemoglobin less than the lower limit of normal (eg, less than 12 g/dl).

    d. Serum calcium great than the upper limit of normal (eg, 10 mg/dl or: 2.5 mmol/l).

    e. Neutrophil greater than the upper limit of normal (eg, greater than 7.0 $x10^9$ dl).

    f. Platelets greater than the upper limit of normal (eg, greater than 400 000).

    g. Lactate dehydrogenase greater than 1.5 times the upper limit of normal.

    h. Fuhrmann grade of tumour.

    i. Tumour subtype eg, clear cell vs. non-clear cell.

6. Safety and tolerability reporting for second line axitinib.

The objectives listed below will also be assessed as exploratory analyses for various patient subgroups of interest, and will be conducted if sufficient numbers of patients are available:

1. Axitinib PFS and OS, as a second line therapy following sunitinib, pazopanib, or following other TKIs (eg, sorafenib).

2. Axitinib PFS and OS as a third line therapy.

3. Axitinib (and, if applicable, sunitinib) PFS and OS post-immunotherapy (IO), taking into consideration 2nd and 3rd therapy lines, following all IO therapy options, eg, atezolizumab/bevacizumab, nivolumab/ipilumimab, nivolumab, interleukin-2.

4. For the post-sunitinib axitinib cohort: What was the duration of sunitinib therapy before patients transitioned to axitinib?

5. For the post-pazopanib axitinib cohort: What was the duration of pazopanib therapy before patients transitioned to axitinib?

6. Is the duration of therapy on first line sunitinib and/or pazopanib related to duration of therapy for second line axitinib?

9. RESEARCH METHODS

This will be a retrospective real world data (RWD) non-interventional study examining aspects of first and second line therapy for renal cell carcinoma.

9.1. Study Design

A retrospective RWD non-interventional study examining aspects of first and second line therapy for renal cell carcinoma, using the Christie National Health Service (NHS) database, from its inception until the end of June 2017.

9.2. Setting

All data will be sourced retrospectively from participant medical records of care received at The Christie NHS Foundation Trust.

NHS staff members with permitted access to medical records have searched the electronic medical record database and paper medical records to identify participants. This data collection was conducted independently of this study, at an earlier time point. This is a clinical database, used in the routine care of patients.

Patients with a diagnosis of renal cell carcinoma will be eligible for inclusion, and recruitment of patients to the wider data collection study at the NHS trust is/was by consecutive ongoing enrollment. This cohort is therefore felt to be representative of the patient population being studied.

Patients were followed up until they withdrew consent, death occurred or the patient could no longer be contacted by the clinical team. Data collection for the wider study is ongoing.

For this non-interventional study, patients who are have been treated with sunitinib and/or axitinib will be selected, as these are the medicines of interest to the Pfizer Oncology team.

This is a secondary data collection study, as the clinical database already exists, and the clinical academic team who administrate the database have agreed to provide data to the Pfizer team for research purposes.

9.2.1. Inclusion Criteria

1. Over the age of 18 years.

2. Diagnosis of renal cell carcinoma.

3. Treatment with sunitinib and/or axitinib.

4. Timeframe: from database inception date (2002) until the end of June 2017.

Research Ethics Committee (REC) approval has been sought in the UK. The Integrated Research Application System (IRAS) number for this study is: 266899 and the REC number is 19/LÖ/1041. No data will be transferred until this approval has been granted.

9.2.2. Exclusion Criteria

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

1. Under the age of 18 years.

2. Diagnosis other than renal cell carcinoma.

3. No treatment with sunitinib and/or axitinib.

9.3. Variables

Variable	Operational definition
Demographic details	Anonymised, linked details
Diagnosis Date	Date of diagnosis
Diagnosis	Renal cell carcinoma: clear cell, non-clear cell
Prior surgery eg, nephrectomy	Yes/No; add details as necessary
Line of therapy	1st line, 2nd line, 3rd line
Start date	Start date of therapy
Drug treatment	Drug name
MSKCC Risk Grade	Numeric value, subcategorise if possible: favourable/intermediate/poor risk. Include individual parameters that comprise this grading system where possible
IMDC/Heng Risk Grade	Numeric value, subcategorise if possible: favourable/intermediate/poor risk. Include individual parameters that comprise this grading system where possible
ECOG performance status at outset	Numeric value with related functional level attributed to this
TNM Stage	3 part cancer staging system; provide details where possible
Histology; Fuhrmann grade	Histopathological diagnosis and grading system
Metastasis diagnosis, if applicable	Site and extent of metastatic disease
Response to treatment	PFS, OS, TTD, Best overall response (BOR)
Date of discontinuation	Date of discontinuation of drug treatment
Therapy discontinuation	Reason for discontinuation

Data cut offs	Overall survival, loss to follow-up, withdrawal from study Data cut-off date for OS and PFS is June 2017
Adverse event reporting	It is expected that this data will have been reported through normal mechanisms, and will not have been recorded in the clinical database

9.4. Data Sources

This study is a secondary data collection of information held on a clinical database within the Christie Hospital in Manchester, which is specific to renal cell carcinoma. This database was administered and managed by a nominated staff member during the period of interest (until June 2017). The internal source validity of this information will be performed by another team member at the Christie Hospital, who has expertise in medical oncology, but who has had no prior role related to data entry to this resource. A sample of the entries (10%) in the database will be checked prior to transfer to Pfizer Ltd.

9.5. Study Size

The clinical database, in its entirety, comprises approximately 3000 patients. The observed incidence of RCC in the UK is around 21 per 100,000, and this is expected to rise to 32 per 100,000 by 2035.[12] The rarity of the disease makes it challenging to locate cases.

A specific power calculation was not performed, as this is a descriptive analysis. The expected number of patients eligible for this study is approximately 678 patients who received sunitinib, and 163 who received axitinib (based on information from the Christie NHS Foundation Trust).

9.6. Data Management

Participants will be pseudo- anonymised by the assignment of a unique patient identification number to each record.

Data will be transferred using a secure data transfer to Pfizer, which satisfies the Pfizer secure data transfer requirements, and allows an audit trail. There will be a data validation step to ensure all data have been transferred successfully.

Any missing or illegible data on any patient will result in Pfizer contacting the physician with the anonymized-linked identifier and submitting the form for validation of the missing data against the patient's medical chart. However, certain information may not be available in charts, in which case it will be described as unknown/ missing.

All work will be subject to quality control and documentation procedures to make certain the report is accurate and thorough, and the analyses can be reproduced.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

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

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

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

The source documents are the hospital or the physician's chart, in this case, as an electronic health record. In these cases, data collected on the CRF/DCTs must match this record.

9.6.2. Record Retention

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

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

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

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

9.7. Data Analysis

The Statistical Analysis Plan (SAP) for this study will be outlined in this section, not in a separate document. Consequently any major modifications to the analysis plan will be reflected in a NI protocol amendment. Statistical Analysis Software (SAS) (Version 9.1, 9.2, 9.3 or 9.4) will be used for all analyses.

Descriptive Analysis

Descriptive statistics will be reported for all variables of interest. Results will be reported in aggregate, and for the subgroups described below provided there are sufficient subjects in each subgroup to create a meaningful summary. The number and percent of patients along with descriptive statistics (mean, standard deviation, median, 25^{th} and 75^{th} percentiles, number of non-missing and number of missing values) will be reported for continuous data. Categorical variables (eg, age groups) – sometimes created from continuous variables – will have the number and percent of patients reported. In case of missing observations, the calculation of percentages will always include the missing category. Counts of missing observations will thus be included in the denominator and presented as a separate category. Patient demographics, selected clinical characteristics, and line of therapy treatment response will be summarised.

Baseline characteristics

All baseline characteristics will be summarised by the treatment groups listed below, where the data are available:

- Gender (male/female);
- Race (Caucasian, Other);
- Age;
  - Continuous variable;
  - Categorised: <65, 65-74, 75-84, and ≥85;
- Weight (kg);
- Height (m);
- BMI (Weight[kg]/Height[m]^2);
- Co-morbidities;
- Risk Stratification: IMDC (Heng) and/or MSKCC;

- Date of metastatic and/or advanced RCC diagnosis (dd/mm/yyyy);
- RCC diagnosis (advanced or metastatic);
- Stage at diagnosis (eg, TNM).

Treatment groups

The proposed analyses will be presented for each of the following treatment groups:

- Sunitinib as a first line therapy;
- Axitinib as a second line therapy eg, post-sunitinib, post-pazopanib etc.

Descriptive analyses will be presented for each of the following treatment groups:

- Axitinib as a third line therapy;
- Axitinib (and, if applicable, sunitinib) post-immunotherapy (IO), taking into consideration 2nd and 3rd therapy lines, following all IO therapy options.
    - eg, atezolizumab/bevacizumab, nivolumab/ipilumimab, nivolumab, interleukin-2.

Primary Endpoint

Progression free survival (PFS)

PFS will be measured from the index date of each treatment line to the date of progression, or date of death due to any cause, or date of initiation of new regimen. Patients who are still alive and have not progressed at the last office visit date without clinical or radiographic evidence of progression will be censored (final study cutoff will be June 2017). PFS will be estimated in months using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at each month interval included. Kaplan-Meier plots for PFS will be presented for the overall population and stratified by MSKCC/IMDC risk category (favourable, intermediate, poor). A log rank test will be performed to compare the stratification groups.

Secondary Endpoints

All secondary endpoints will be analysed as follows:

Overall survival (OS)

OS will be defined as the time between the index date (dependent on treatment line) and the date of death from any cause. Patients who are still alive at the study end date or the last visit date available will be censored (using whichever occurred first). If a death date is known beyond the study end date, then the study end date (June 2017) will be used as the censoring

date. Median OS will be estimated in months using the Kaplan-Meier method with 95% confidence intervals (CIs), and summary tables of the number of events and censored patients at each month interval included. Kaplan-Meier plots will be presented for Overall Survival for the overall population, and stratified by MSKCC/IMDC risk (favourable, intermediate, poor). A log rank test will be performed to compare the stratification groups.

Best overall response (BOR)

In prospective clinical trials, BOR is generally assessed according to the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1.[13] However, the parameters underlying these criteria are less reliably available in retrospective, observational studies. While an attempt will be made to mimic the RECIST guideline, it should be noted that assessments based on information garnered during routine clinical practice could be more subjective than assessments in a controlled clinical trial and decision making about continued therapy could include symptomatic criteria. Additionally, timing of repeat imaging may vary. All evaluation in this observational study will be as best determined by clinicians, either as noted in the patient chart by the radiologist-written scan report or the treating physician's progress notes or as interpreted by the clinician reviewer. The BOR for a line of treatment is the best response across all timepoints during that line of therapy assessed using the following categories: Complete response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

Objective response rate (ORR)

BOR will be summarized as ORR, which is defined as the number of patients having reached a BOR of CR or PR divided by the number of patients (the primary analysis population), including the NE patients.

ORR = Number of patients achieving a response (BOR = PR or CR)/Number of patients (BOR=CR+PR+SD+PD+NE).

Patients who do not have a BOR assessment for a particular line of therapy will be excluded from the summary for that line of therapy. The number of patients with a missing BOR assessment will be summarized.

Duration of response (DOR)

DOR will be calculated for each patient with a BOR of CR or PR as the duration of time from first documented CR/PR, to the earliest date of first progression or recurrent disease, or date of death, or date of initiation of new regimen. Patients who are still alive and did not progress will be censored at the last physician office visit date without clinical or radiographic evidence of progression. DOR will be estimated in months using Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at each month interval included.

Time to treatment discontinuation (TTD)

TTD will be calculated as the duration between the start of a treatment line to the end of the treatment line for patients with discontinuation of treatment for any reason, or censoring if a stop date is not documented (at end of study), if the patient dies, is lost-to follow up, or is still on-therapy. Patients without a discontinuation event will be censored on the study end date or at last office visit date without clinical or radiographic evidence of progression, whichever occurred first. Time to TTD will be analysed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at each month interval included.

Durable response rate (DRR)

DRR will be determined as the proportion of patients with objective response (CR or PR) with a duration of at least 6 months. Duration of response will be calculated as previously defined for DOR.

Time-to-Event Analysis

The Kaplan-Meier method will be used to estimate median OS, PFS and TTD. P values comparing survival curves by stratification groups, will be calculated using log-rank tests. Univariate and multivariable Cox proportional hazards regressions will be used to evaluate explanatory factors and to calculate hazard ratios (HRs) with two-sided 95% CIs for OS, PFS and TTD. Demographic and clinical factors will be included in multivariable Cox regression models based on their clinical relevance and/or the univariate significance level (assessed at the level of $p<0.05$).

In order to account for the impact of baseline patient and disease characteristics outlined in this protocol and the disease characteristics below, unadjusted Cox models and multivariable Cox models adjusting for selected patient demographics and clinical characteristics identified by Pfizer as clinically relevant will be included in the adjusted models. Time-to-event analyses will be assessed in the overall population and by stratifications of interest (MSKCC/IMDC category). The disease characteristics of interest are:

a. Less than one year from time of diagnosis;

b. Karnovsky performance status less than 80%;

c. Haemoglobin less than the lower limit of normal (eg, less than 12 g/dl);

d. Serum calcium greater than the upper limit of normal (eg, 10 mg/dl or: 2.5 mmol/l);

e. Neutrophil greater than the upper limit of normal (eg, greater than 7.0 $x10^9$ dl);

f. Platelets greater than the upper limit of normal (eg, greater than 400 000);

g. Lactate dehydrogenase greater than 1.5 times the upper limit of normal;

h. Fuhrmann grade of tumour;

i. Tumour subtype eg, clear cell vs. non-clear cell.

The SAP outlined in this section may be subject to modifications; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

The data collection tool is an Microsoft Access database. The investigators have entered pseudo-anonymized data directly from patient charts/electronic records into the database, which will have a function to directly export the collected data into an Excel/CSV file. Therefore the data collection tool will also serve as a project database (once exported into Excel).

Review of the patient records was be conducted by a carefully selected team of physicians and/or their assigned staff trained on the study specific protocols and guidelines. Physicians and/or site staff will be instructed to assign a unique identifier for each patient enrolled in the study to facilitate follow-up on data queries and for data validation.

The Data Collection Manager/Team Lead will review pilot data for accuracy and consistency. During full chart review, the Data Collection Manager/Team Lead will perform random checks. During both the pilot and full chart review, the study's Principal Clinical Investigator addresses clinical questions posed by the chart review team. The Data Collection Manager will also initiate normalization of data, quality control all charts, and review of the final data set before submission to the sub-study team.

Finally, the principal investigator and statistical lead will provide a final examination of the data before and during preparation of analyses.

The principal investigator will create the CT24 Study Data Quality Control plan.

9.9. Strengths and Limitations of the Research Methods

This is a large scale retrospective non-interventional RWD study. The strengths of this methodology include:

- A representative impression of the real world use and activity of medicines is obtained;
- Patients who may not be eligible for randomized controlled trials can be included;
- Retrospective nature mitigates bias in regard to treatment selection and outcome monitoring.

Potential limitations of this study design are:

- Compliance issues eg, missed doses, treatment breaks, schedule modifications may not be captured in detail;
- The place of real world studies in the hierarchy of medical evidence levels is not fully understood;
- Retrospective studies can detect associations, but not causality;
- Data are collected on a voluntary basis (convenience sampling) without any requirement in terms of sample design and stratifications;
- There could be errors in data entry that are unaccounted for, and which represent information bias. This cannot be controlled in the analysis.

In the analysis, all steps taken by the study team will be auditable. The protocol has been written very specifically, in order that the research objectives and methods are open and transparent.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer,

Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Research Ethics Committee (REC) approval has been sought in the UK. The Integrated Research Application System (IRAS) number for this study is: 266899 and the REC number is 19/LÖ/1041. No data will be transferred until this approval has been granted.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database.

The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the Non-interventional Study Adverse Event Report Form (see Annex 1) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be developed when data collection and analysis is complete.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

1. Tsui, KE-Hung et al. Prognostic Indicators For Renal Cell Carcinoma: A Multivariate Analysis Of 643 Patients Using The Revised 1997 TNM Staging Criteria. The Journal of Urology 2000, 163 (4) , 1090-5.

2. Daniel Y.C. Heng, Wanling Xie, 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. Journal of Clinical Oncology 2009 27:34, 5794-5799.

3. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

4. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982 Oct;6(7):655-63.

5. L H Sobin (Editor) et al. TNM Classification of Malignant Tumours (7th Edition). Wiley-Blackwell, 2009.

6. Cancer Research UK, accessed here: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer.

7. Khosravi-Shahi, P. 2017. Systemic Therapy for Metastatic Non-Clear Cell Renal Carcinoma. Cancer therapy & Oncology International Journal. 4(2).

8. Takagi, T., Kondo, T., Kennoki, T., Iizuka, J., Kobayashi, H., Hashimoto, Y. and Tanabe, K. 2013. Comparison of Survival Rates in Patients with Metastatic Renal Cell Carcinoma According to Treatment Era Including Cytokine and Targeted Therapy. Japanese Journal of Clinical Oncology. 43(4),pp.439-443.

9. Najjar, Y. and Rini, B. 2012. Novel agents in renal carcinoma: a reality check. Therapeutic Advances in Medical Oncology. 4(4),pp.183-194.

10. Hutson, T. 2011. Targeted Therapies for the Treatment of Metastatic Renal Cell Carcinoma: Clinical Evidence. The Oncologist. 16(Supplement 2),pp.14-22.

11. Zarrabi, K., Fang, C. and Wu, S. 2017. New treatment options for metastatic renal cell carcinoma with prior anti-angiogenesis therapy. Journal of Hematology & Oncology. 10(1).

12. Cancer Research UK, accessible at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer#heading-Zero.

13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer, 2009; 45 (2):228-47.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Non-interventional Study Adverse Event Report Form

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

Pfizer

AER # (*insert when known*)									

PROTOCOL # **SUBJECT #**

Protocol Title:

☐ Initial Report ☐ Follow Up Report			**Country where event occurred:**
Patient Data	Date of Birth ☐ Male ☐ Female	Height ☐ in ☐ cm Weight ☐ lb ☐ kg	

Patient's Race:

☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ American Indian or Alaska Native
☐ White ☐ Unknown ☐ Cannot ask per local regulations , Other (specify)

Patient's Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

If patient has died:	Date of Death	Cause(s) of Death	Determined by Autopsy: Y ☐ N ☐ Unknown ☐ *If yes, what was the autopsy determined cause of Death:*

Patient History ☐ None ☐ Unknown *Provide relevant medical history below Include other illnesses present at time of event and pre-existing medical conditions. If additional space is necessary, use addiitonal copies of this page.*

Illness (specify)	Onset Date	Stop Date	*Check box if Ongoing*	Pertinent Details *Include surgical procedures and dates*
			☐	
			☐	
			☐	
			☐	

Study Drug (Trade and Generic), Formulation, Route, Indication	*Check box if Pfizer Drug*	Dose	Units	Frequency	Start Date	Stop Date	*Check box if Ongoing*
	☐						☐
	☐						☐
	☐						☐
	☐						☐

Concomitant Drugs
☐ None
☐ Unknown
List below concomitant drugs taken within two weeks before the event onset. Exclude all drugs only administered more than two weeks before the event, and any drug used to treat the event or taken after event onset. If additional space is necessary, use additional copies of this page.

Drug Name (Trade and Generic)	Reason for Use	Route	Start Date	Stop Date	*Check box if Ongoing*
					☐
					☐
					☐
					☐

Relevant Tests *List only relevant confirmatory test results for adverse event(s), for example, from blood tests, diagnostic imaging. If additional space is necessary, use additional copies of this page.*

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments

Version 5.0, Effective August 2016 **Page _____ of _____** **Pfizer Confidential**

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

ADVERSE EVENTS *(if more than two, use additional copies of this page)*
Specify diagnosis if known, rather than symptoms or signs

Adverse Event Term	**Adverse Event Term**
Onset Date:	Onset Date:
Is the event serious? ☐ **Yes** ☐ **No** **If yes, identify seriousness criteria below:**	**Is the event serious?** ☐ **Yes** ☐ **No** **If yes, identify seriousness criteria below:**
Seriousness Criteria (Check all that apply): ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event	**Seriousness Criteria (Check all that apply):** ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event
Status at date of report or at death: ☐ Recovered } ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown Date of Recovery:	**Status at date of report or at death:** ☐ Recovered } ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown Date of Recovery:
Is there a reasonable possibility that the event is related to Study Drug? ☐ **Yes** ☐ **No** **If yes, specify Study Drug:**	**Is there a reasonable possibility that the event is related to Study Drug?** ☐ **Yes** ☐ **No** **If yes, specify Study Drug:**
Is there a reasonable possibility that the event is related to Concomitant Drug? ☐ **Yes** ☐ **No** **If yes, specify Concomitant Drug:**	**Is there a reasonable possibility that the event is related to Concomitant Drug?** ☐ **Yes** ☐ **No** **If yes, specify Concomitant Drug:**
Last Action Taken In Response to Event(s); specify drug name:	**Last Action Taken In Response to Event(s); specify drug name:**
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable ☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable ☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:	Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

AER # (*insert when known*)									

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Event Narrative

Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form. If additional space is necessary, use additional copies of this page.

Reporter Comments:

Reporter: - -

First Name | Last Name (*Please* PRINT) | Date: DD-MMM-YYYY

Address: /

Street | City / State | Zip Code | Country

Telephone: Fax: Email:

Investigator's Name: _____ **Investigator/Designee Signature:**

Investigator/Designee Awareness Date: - - DD-MMM-YYYY

Report this form to Pfizer within 24 hours of awareness or immediately in case of death and life-threatening SAEs.

RECORD ALL PERTINENT INFORMATION ON THE FORM. DO NOT ATTACH SOURCE DOCUMENTS.

ANNEX 2. ADDITIONAL INFORMATION

1. MSKCC Criteria.[1]

Patients are stratified according to the presence of five risk factors:

- KPS <80%;
- Time from diagnosis to start of systemic therapy <12 months;
- Haemoglobin < lower limit of laboratory's reference range;
- Lactate dehydrogenase 1.5 × the upper limit of laboratory's reference range;
- Corrected serum calcium >10.0 mg/dl (2.4 mmol/l).

The number of risk factors present is added up and the risk is stratified as follows:

Number of risk factors	Risk group
0	Favourable
1–2	Intermediate
3–5	Poor

2. IMDC (Heng) Criteria.[2]

Patients are stratified according to the presence of six risk factors:

- Karnovsky performance status (PS) <80%;
- Haemoglobin less than lower limit of normal;
- Time from diagnosis to treatment <1 year;
- Corrected calcium above the upper limit of normal;
- Platelets greater than the upper limit of normal;
- Neutrophils greater than the upper limit of normal.

The number of risk factors present is added up and the risk is stratified as follows:

Number of risk factors	Risk group
0	Favourable
1–2	Intermediate
3–6	Poor

3. ECOG performance status.[3]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

4. Fuhrmann grade.[4]

Pathologic material was classified as to pathologic stage, tumor size, cell arrangement, cell type and nuclear grade. Four nuclear grades (1--4) were defined in order of increasing nuclear size, irregularity and nucleolar prominence. Nuclear grade was more effective than each of the other parameters in predicting development of distant metastasis following nephrectomy.

5. TNM stage.[5]

Staging of RCC (UICC TNM classification of malignant tumors, 7th edition, 2009).

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4.0 cm
T1b	Tumor >4.0 cm but ≤7.0 cm
T2	Tumor >7.0 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends to major veins or peri-nephric tissues but not into the ipsi-lateral adrenal gland and not beyond Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades peri-renal and/or renal sinus fat (peri-pelvic) but not beyond Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsi-lateral adrenal gland)
N	Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M	Distant metastases
cM0	Clinically no distant metastasis
cM1	Clinically distant metastasis
pM1	Pathologically proven distant metastasis, eg, needle biopsy

Stage grouping	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1-3 N1 M0
Stage IV	T4 Any M0
	Any Any M1