Study information

Title	Clinical Effectiveness of Second-Line Sunitinib Following Immune-oncologic (IO) therapy in Patients with Metastatic Renal Cell Carcinoma in the International Metastatic Renal Cell Carcinoma Database (IMDC)
Protocol number	A6181233
Protocol version identifier	01
Date of last version of protocol	21 October 2019
Research question and objectives	The study aims to assess clinical outcomes in mRCC patients treated with sunitinib in second-line following immune-oncologic (IO) therapy in real world clinical practices.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
2L	Second-line
AE	Adverse event
CCI	[redacted]
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
Hb	Hemoglobin
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-oncology
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KPS	Karnofsky performance status
LLN	Lower limit of normal
LSLV	Last subject last visit
mRCC	Metastatic renal cell carcinoma
mTOR	Mammalian target of rapamycin
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RCC	Renal cell carcinoma
SD	Standard deviation
TKI	Tyrosine kinase inhibitors
TTD	Time to treatment discontinuation
ULN	Upper limit of normal
US	United States
VEGFR	Vascular endothelial growth factor receptor

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , MD, MPH, FRCPC	Principal Investigator; PPD	PPD	
PPD MPH, ScD	Co-investigator; PPD		
PPD PharmD, MSc	Co-investigator; PPD		

3. AMENDMENTS AND UPDATES

None.

4. MILESTONES

Milestone	Planned date
Start of data collection	October 2019
End of data collection *For studies with primary data collection, enter the planned date for last subject last visit (LSLV). For studies with secondary data collection, enter the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).*	November 2019
Final study report *Enter the planned date for approval of final study report. For NI PASS protocols, the final study report must be submitted within 12 months of the end of data collection.*	January 2020

5. RATIONALE AND BACKGROUND

An estimated 400,000 new cases of kidney cancer, of which renal cell carcinoma (RCC) accounts for approximately 90%, are diagnosed worldwide every year.[1] RCC comprises 2-3% of all adult malignancies, with approximately 63,000 incident cases and 14,000 deaths from RCC each year in the United States (US).[2] Due to the lack of early symptoms and clinical indications of disease, around 20% of patients present with the most advanced stage of the cancer, metastatic RCC (mRCC), at time of diagnosis.[3,4] Prognosis is poor among mRCC patients, with 5-year survival rates of 5-10%.[5] The burden of mRCC is projected to grow with the aging population and increasing prevalence of risk factors for RCC, such as obesity and hypertension.[6-8]

During the last decade, targeted therapies, which are agents that target the vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), or the mammalian target of rapamycin (mTOR), became standard of care for patients with mRCC.[9] Since 2005, several targeted therapies have been approved for the treatment of mRCC in the US, including bevacizumab (Avastin®), sunitinib (Sutent®), sorafenib (Nexavar®), pazopanib (Votrient®), axitinib (Inlyta®), cabozantinib (Cabometyx®, Cometriq®), everolimus (Afinitor®), and temsirolimus (Torisel®).[9,10] Targeted therapies have been associated with improved progression-free survival (PFS) and overall survival (OS), favorable side effect profiles, and improved health-related quality of life.[11-17]

Yet, recent advancements in immuno-oncology (IO) therapeutic agents have changed the treatment paradigm for mRCC. IO therapies work by blocking immune checkpoints (eg, programmed death-1 [PD-1]/PD-ligand 1 [PD-L1]) and restoring tumor-specific T-cell-mediated immune responses,[18,19] and have demonstrated antitumor activity and durable responses in both pre-treated and treatment naïve mRCC.[20,21] Specifically, among mRCC patients with intermediate or poor prognostic risk, the IO combination therapy of nivolumab (Opdivo®) plus ipilimumab (Yervoy®) showed higher OS and objective response rate than sunitinib.[21] Two recent phase 3 trials reported that patients treated with 1L IO therapies in combination with VEGFR-tyrosine kinase inhibitors (TKI) also had improved PFS and/or OS outcomes compared to patients treated with 1L sunitinib.[22,23] However, despite promising early results of 1L IO therapy, some patients develop progressive disease requiring subsequent systemic therapy.[19]

Clinical decisions on optimal treatment sequences for patients with mRCC who discontinue IO therapy have been challenging for practitioners, since treatment guidelines and regulatory policies are not yet available. Further, real-world evidence on the effectiveness of treatment sequences for patients with mRCC who discontinue IO therapy is limited. Several studies have suggested antitumor activity of targeted therapy after PD-1/PD-L1 inhibition.[24-28] One retrospective study examined targeted therapies following IO therapy and found that both VEGFR-TKI and mTOR inhibitor demonstrated antitumor activity following PD-1/PD-L1 blockade.[24] A recent retrospective study showed that among clear cell mRCC patients treated with second-line (2L) VEGFR-TKI after 1L IO therapy, 2L antitumor activity and tolerance was comparable to that in 1L TKI based on historical data.[28] Another retrospective analysis found that clinical activity of subsequent VEGFR-TKI therapy after IO therapy was affected by the 1L combination therapy.[26] That is, among mRCC patients treated with 2L VEGFR-TKI, patients treated with IO only in 1L showed numerically higher ORR compared to patients treated with IO in combination with anti-VEGFR. However, these studies have only included mRCC patients enrolled in clinical trials, and thus lack generalizability to real-world clinical settings.

Given this gap in the literature, we will use real-world clinical data from the International Metastatic RCC Database Consortium (IMDC) database to evaluate clinical outcomes among patients with mRCC treated with IO therapies in 1L followed by sunitinib in 2L.

6. RESEARCH QUESTION AND OBJECTIVES

The study aims to assess the clinical effectiveness of 2L sunitinib following IO therapy in 1L (ie, IO monotherapy, IO + VEGFR, or nivolumab + ipilimumab), among patients with mRCC. The specific objectives are as follows:

- To describe patient demographic and clinical characteristics among patients with mRCC treated with IO in 1L followed by sunitinib in 2L.

- To characterize the following clinical outcomes in patients with mRCC treated with IO in 1L followed by sunitinib in 2L, overall and stratified by IMDC prognostic risk groups, pending on sample size:
  - OS;
  - Time to treatment discontinuation (TTD);
  - Reasons for treatment discontinuation;
  - Physician-assessed best response.
- To describe treatment patterns among patients with mRCC treated with IO in 1L followed by sunitinib in 2L (eg, duration of IO therapy, duration of sunitinib therapy, time from IO therapy discontinuation to initiation of sunitinib therapy).

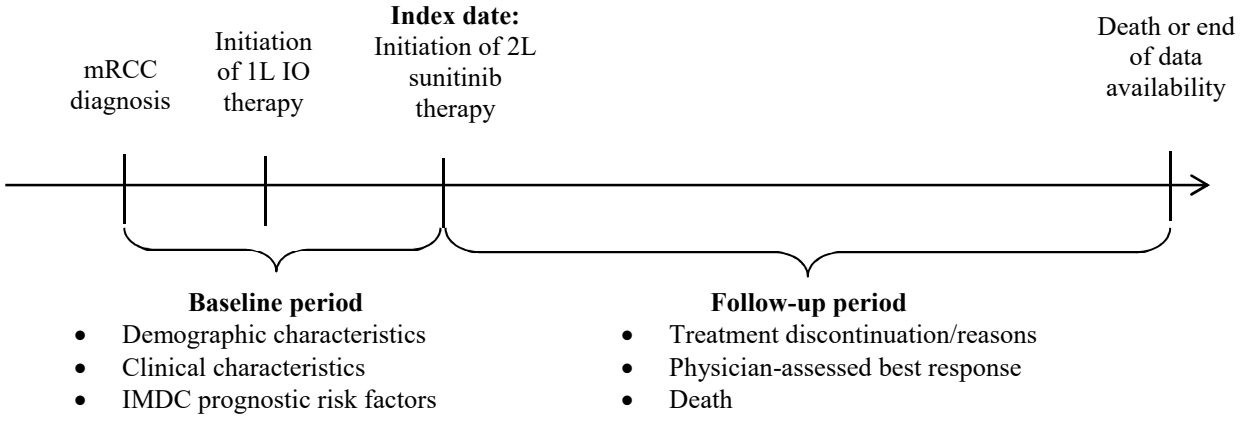
7. RESEARCH METHODS

7.1. Study Design

This is a retrospective, longitudinal cohort study that involves the analysis of retrospective data collected through the IMDC database for selected academic clinical sites participating in this study (detail on clinical sites is provided in Section 7.4). A cohort of patients treated with sunitinib as the 2L therapy after treatment with IO agents as 1L therapy will be assessed.

The *index date* will be defined as the date of initiation of 2L sunitinib therapy. The *baseline period* will be defined as the time from mRCC diagnosis to the index date. The *follow-up period* will be defined as the time from the index date to the earliest of death or end of data availability. Figure 1 depicts the study design scheme.

Figure 1. Study Design Scheme



7.2. Setting

7.2.1. Inclusion Criteria

Patients will be selected based on the eligibility criteria listed below. Participation in an interventional trial for mRCC disease is allowed. Subjects will be selected irrespective of their survival status.

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

- Diagnosed with mRCC;
- Received IO therapy as 1L therapy;
- Received sunitinib as 2L therapy;
- Age 18 years or over at the time of mRCC diagnosis;
- Actively treated at an IMDC clinical center (to avoid incomplete data).

7.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

7.3. Variables

Primary exposure

- Sunitinib as 2L therapy following IO as 1L therapy.

Outcomes

- OS, defined as the time between initiation of 2L sunitinib therapy and death.
- TTD, defined as the time between initiation of 2L sunitinib therapy and discontinuation of therapy for any reason including progression, death, and toxicity.
    - TTD for 1L IO (ie, time between initiation of 1L IO and discontinuation of therapy for any reason).
- Time to initiation of 2L sunitinib from discontinuation of 1L IO.
- Reasons for treatment discontinuation in 1L IO and 2L due to:
    - Disease progression;
    - Toxicity;

  - Death;
  - Other reasons.
- Physician-assessed best response in 2L while being treated with sunitinib, defined as the objective response rate (ORR) (sum of partial response and complete response), progressive disease, and stable disease.

Covariates (assessed during the baseline period or on index date)

- Gender;
- Age at time of 2L sunitinib initiation;
- Race[redacted];
- Date of mRCC diagnosis;
- Prior nephrectomy status;
- [redacted].
- Histology type:
  - Non-clear cell RCC;
  - Clear cell RCC.
- Number of metastatic sites (eg, 1 site or more than 1 site).
- Site of metastases (eg, brain metastasis, bone metastasis).
- IMDC prognostic risk factors:
  - Time from RCC diagnosis to systemic treatment initiation <1 year.
  - Karnofsky performance status (KPS) <80%.
  - Hemoglobin <lower limit of normal (LLN).
  - Serum corrected calcium >upper limit of normal (ULN).
  - Neutrophil count >ULN.
  - Platelet count >ULN.

7.4. Data Sources

Data will be obtained retrospectively from the IMDC clinical sites.

The IMDC cohort is a multi-institutional cohort that collects data globally from international cancer centers in the United States, Canada, Denmark, Greece, South Korea, Australia, New Zealand, Japan, Singapore, Italy, and Belgium. Demographic, clinical, laboratory, and outcome data on patients with mRCC are collected retrospectively from medical charts using uniform database templates and standardized definitions to ensure data are collected consistently. Medical records include longitudinal information on patient demographic and disease characteristics, oncology-specific workups and evaluations, treatment types and duration, concurrent diagnoses as documented in physician notes, and treatment discontinuation/halt decisions.

CCI will collaborate with Dr. PPD from the University of Calgary PPD who will serve as the principal investigator for this study and who is also the Chair of the IMDC, to obtain data from clinical centers. The clinical centers send data to the IMDC database, and data cleaning and consolidation of the data occur twice a year.

For this proposed study, a "limited" dataset of patients treated with 1L IO therapy and 2L sunitinib therapy will be provided only. The "limited" dataset will be anonymized and will not contain any personal data. All 1L IO and 2L sunitinib patients are included in the "limited" dataset, but only a select number of variables necessary to fulfill the study objectives will be included.

7.5. Study Size

The IMDC database has 73 patients who received 1L IO and 2L sunitinib. Power calculations were not performed as the objectives were descriptive.

7.6. Data Management

CCI will work with the IMDC data manager and Dr. PPD to understand all available data elements from the IMDC database.

Once study site contracts have been completed, the most recent data will be transferred to CCI over a secured network to ensure that the latest available data are used in the analysis. Data provided to CCI will be anonymized and will not contain any personal data. After obtaining the data, CCI will assess the quality of the data downloaded and work with data managers from each center to rectify any potential data entry errors and discrepancies.

7.7. Data Analysis

Identification of study cohort

The study population of interest in this study are patients with mRCC treated with 2L sunitinib therapy following 1L IO therapy whereby the earliest date of 2L sunitinib initiation was April 15, 2014. Each patient's eligibility for this study will be verified against the eligibility criteria.

Description of demographic and clinical characteristics among patients with mRCC treated with 2L sunitinib therapy following 1L IO therapy

Baseline demographic and clinical characteristics prior to or on the index date will be described using the mean (standard deviation [SD]) and median (interquartile range [IQR]) values for continuous variables and frequency distributions for categorical variables.

Characterization of clinical outcomes among patients with mRCC treated with 2L sunitinib therapy following 1L IO therapy

The clinical outcomes will be analyzed as follows:

- OS and TTD will be analyzed using Kaplan-Meier estimator;
- Reasons for 1L IO and 2L sunitinib therapy discontinuation will be described using relative frequencies;
- Physician-assessed best tumor response (ie, ORR, stable disease, and progressive disease) to 2L sunitinib therapy will be described using relative frequencies.

Stratification by IMDC prognostic risk groups (ie, favorable, intermediate, and poor) may be performed pending on sample size. One interim analysis will be performed to examine sufficiency of sample size and duration of follow-up.

Description of real-world treatment patterns among patients with mRCC treated with 2L sunitinib therapy following 1L IO therapy

The following treatment patterns will be described:

- Median (IQR) and mean (SD) time from mRCC diagnosis to initiation of 1L IO therapy.
- Median (IQR) and mean (SD) time from initiation of 1L IO therapy to discontinuation of IO therapy.
- Median (IQR) and mean (SD) time from discontinuation of 1L IO therapy to initiation of 2L sunitinib therapy.
- Median (IQR) and mean (SD) time from initiation of 2L sunitinib to discontinuation of sunitinib.

7.8. Limitations of the Research Methods

Assessments of disease progression and tumor response in real-world settings may be based on heterogeneous criteria and assessment schedules. In contrast to clinical trials with protocol-specified definitions of clinical events, assessments of progression and clinical response in retrospective studies of clinical practice may not be made consistently across subjects and across physician practices.

7.9. Other Aspects

Not Applicable.

8. PROTECTION OF HUMAN SUBJECTS

This is a retrospective medical records review study where data collected will be strictly anonymous and will not be traceable back to individual subjects by the sponsor. No subject identifiers will be requested in this study to protect subject interests. Only anonymized aggregated data will be presented in the final study report.

Compliance with Pfizer and regulatory standards provides assurance that the rights, safety, and well-being of subjects participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in line with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

8.1. Patient Information and Consent

The study will be conducted entirely using retrospective medical records and no subject identifiers will be requested in this study. Informed consent is not expected to be required in this study as the data collected does not contain personal identifiers.

8.2. Patient Withdrawal

Not Applicable.

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

It is the responsibility of the investigator to have prospective approval from the IRB/IEC for the IMDC database study. All correspondence with the IRB/IEC should be retained in the Investigator File (ie, documentations of IRB approval) and will be provided as requested.

8.4. Ethical Conduct of the Study

The study will be conducted in line 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), European Medicines Agency (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.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

CT24-WI-GL02-RF02A *Safety Reporting Language Secondary Data Collection Study Structured Data Analysis.*

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

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.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.