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Study Information

Title	The Effect of Vascular Endothelial Growth Factor Receptor (VEGFR) Tyrosine Kinase Inhibitors (TKI) on Clinical Outcomes among Patients with Metastatic Renal Cell Carcinoma (mRCC) Who Received First-Line Sunitinib in the International mRCC Database Consortium (IMDC) based on Prognostic Risk Score
Protocol number	A6181229
Protocol version identifier	01
Date of last version of protocol	11 December 2018
Research question and objectives	The study aims to assess clinical outcomes in mRCC patients treated with sunitinib as first-line in real world clinical practices, stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk groups.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AGI	Analysis Group, Inc.
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
Hb	hemoglobin
HR	hazard ratio
IRB	Institutional Review Board
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LSLV	last subject last visit
NCCN	National Comprehensive Cancer Network
OS	overall survival
PFS	progression free survival
RCC	Renal cell carcinoma
SD	standard deviation
TTD	time to treatment discontinuation

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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PPD , MD	Senior Investigator; PPD PPD Associate Professor, PPD	PPD	PPD PPD PPD
PPD PPD MPH, ScD	Co-investigator; Chief Epidemiologist	Analysis Group, Inc.	PPD PPD PPD
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4. MILESTONES

Milestone	Planned date
Start of data collection	July 2018
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).*	September 2018
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 2019

5. RATIONALE AND BACKGROUND

Renal cell carcinoma (RCC) is the most common kidney cancer, accounting for about 90% of all kidney cancers.[1-3] It accounts for 2-3% of all adult malignancies with an estimated 63,000 incident cases and 14,000 deaths per annum in the United States.[4] Approximately 25-30% of patients with RCC are diagnosed with metastatic disease due to the lack of early symptoms and clinical indications of disease.[5] Prognosis is poor among metastatic renal cell carcinoma (mRCC) patients, with 5-year survival rates of 5-10%.[6] As the population ages and risk factors for RCC become more prevalent, the burden of mRCC is expected to grow.[1-3]

Among patients with relapse or stage IV and surgically unresectable RCC, the National Comprehensive Cancer Network (NCCN) recommends sunitinib and pazopanib as category 1, preferred first-line targeted therapy treatments.[7] More recently, NCCN expanded its first-line RCC treatment recommendations to include cabozantinib after the Food and Drug Administration (FDA) approved cabozantinib for first-line treatment of mRCC in December 2017 based on the CABOSUN (NCT01835158) trial results. The CABOSUN trial was a randomized, open-label phase II multicenter study in 157 patients with intermediate and poor-risk previously untreated clear cell mRCC.[8] Intermediate and poor risk were classified based on IMDC prognostic risk groups (favorable, intermediate and poor). Patients received cabozantanib (n=79) 60 mg orally daily or sunitinib (n=78) 50 mg orally daily (4 weeks on treatment followed by 2 weeks off) until disease progression or unacceptable toxicity.[8] Estimated median progression-free survival (PFS) for patients taking cabozantanib was 8.2 months (95% confidence interval [CI]: 6.2, 8.8) compared with 5.6 months (95% CI: 3.4, 8.1) for patients taking sunitinib (hazard ratio for progression or death = 0.66; 95% CI: 0.46, 0.95; p=0.012).[8] Based on these results, the NCCN guidelines recommended cabozantinib for first-line RCC treatment in poor- and intermediate-risk groups.

Findings from the CABOSUN trial showed that patients (IMDC intermediate and poor risk) taking sunitinib had a PFS of 5.6 months. This was lower than the results from a phase III trial that examined sunitinib versus interferon alfa in untreated clear cell mRCC patients where the PFS was 11.0 months in the sunitinib group vs. 5.0 months in the interferon alfa group.[9] A recent retrospective analysis of the phase III trial demonstrated that, of the 373 patients treated with sunitinib, there were 36% favorable, 55% intermediate, and 9% poor based on the IMDC prognostic risk group. In addition, the median PFS for patients treated with sunitinib was 14.1 months (95% CI: 13.4, 17.1), 10.7 months (95% CI: 10.5, 12.5), and 2.4 months (95% CI: 1.1, 4.7) for favorable, intermediate, and poor risk groups, respectively. When intermediate and poor IMDC risk groups were combined, the median PFS was 10.6 months (95% CI: 8.1, 10.9).[10] CheckMate 214 was another phase III trial that compared nivolumab plus ipilimumab (nivo+ipi) with sunitinib for previously untreated clear cell mRCC. The results from this trial showed that among patients in the intermediate and poor IMDC risk groups, the median PFS was 11.6 months (95% CI: 8.7, 15.5) in the nivo+ipi vs. 8.4 months (95% CI: 7.0, 10.8) in the sunitinib. Of the 426 patients in the intermediate and poor risk groups, 334 (79%) and 91 (21%) patients were identified as intermediate and poor risk, respectively.[11] Based on the differences in PFS between these studies, patient IMDC prognostic risk group may play a role in the effect of first-line treatment on clinical outcomes.

In addition to differences between IMDC prognostic risk groups, heterogeneity may exist within a risk group as well. Specifically, patients with IMDC intermediate risk group (defined as having 1 or 2 IMDC risk factors) may have different clinical outcomes depending on the number of risk factors. A retrospective analysis of six clinical trials examining sunitinib treatment for mRCC reported that among patients in the intermediate risk group, time interval less than 1 year from RCC diagnosis to targeted therapy was the most common risk factor as observed in 36% of patients with 1 risk factor alone or in combination with low serum hemoglobin as observed in 25% of patients with 2 risk factors. The study also found that patients with 1 risk factor had longer OS (25.6 vs. 16.3 months) and PFS (9.8 vs. 8.6 months), and greater ORR (39.5% vs. 31.8%) when compared to those with 2 risk factors.[12] These results are comparable to those from the retrospective analysis of sunitinib vs. interferon alfa phase III trial, where the median OS in patients with 1 risk factor was 28.2 months vs. 16.3 months in those with 2 risk factors. ORR was 33.3% (95% CI: 25.9, 41.5) in patients with 1 risk factor and 31.7% (95% CI: 20.3, 45.0) in those with 2 risk factors. Median PFS in intermediate risk group patients with 1 or 2 risk factors was 10.7 months.[10]

Given the high interest to examine the effect of lines of treatments on clinical outcomes by IMDC prognostic risk group, Analysis Group, Inc. (AGI) will conduct a study to further understand the clinical outcomes in mRCC patients treated with sunitinib as first-line stratified by IMDC prognostic risk groups in real-world clinical practices using the IMDC database. This will provide contemporary benchmarks for outcomes and survival among mRCC treated with first-line sunitinib in the real world. Additionally, the clinical heterogeneity within the IMDC intermediate risk group and impact of individual IMDC prognostic risk factors will be explored.

6. RESEARCH QUESTION AND OBJECTIVES

The study aims to address the following:

1. To describe patient demographic and clinical characteristics among all mRCC patients treated with sunitinib in first-line, stratified by IMDC prognostic risk score (ie, favorable, intermediate, and poor).

2. To characterize the following clinical outcomes in patients treated with sunitinib in first-line, stratified by IMDC prognostic risk groups and Karnofsky Performance Status (KPS).

   - OS;

   - Time to treatment discontinuation (TTD);

   - Reasons for treatment discontinuation;

   - Physician-assessed best response (objective response rate [ORR], progressive disease, stable disease).

3. To conduct a subgroup analysis assessing demographic and clinical characteristics and the following clinical outcomes among mRCC patients in the intermediate IMDC prognostic risk group, stratified by patients having only 1 IMDC risk factor versus 2 IMDC risk factors.

   - OS;

   - TTD;

   - Physician-assessed best response (ORR, progressive disease, stable disease).

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. A cohort of mRCC patients who initiated sunitinib as first-line therapy will be evaluated.

The index date will be defined as the date of initiation of first-line 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
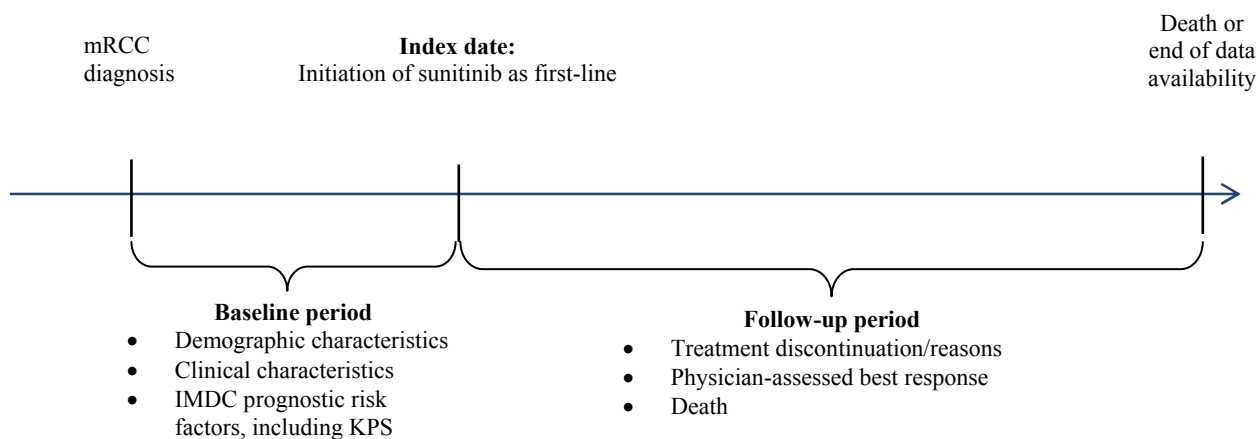
7.2. Setting

7.2.1. Inclusion Criteria

1. Patients will be selected based on the eligibility criteria listed below. Participation in 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;

- Initiated treatment post mRCC diagnosis and received sunitinib as first-line therapy;

- Age 18 years or over at the time of mRCC diagnosis;

- Actively treated at an IMDC clinical center.

7.2.2. Exclusion Criteria

- Initiated first-line sunitinib treatment before 2010;

- Had non-clear cell mRCC.

7.3. Variables

Primary exposure

- Sunitinib as first-line therapy.

Outcomes

- OS, defined as the time between index date and death.

- TTD, defined as the time between index date and discontinuation of therapy due to any reason including progression, death, or toxicity.

- Reasons for treatment discontinuation, categorized as progression, death, toxicity, or other.

- Physician-assessed best response, defined as ORR (sum of partial response and complete response), progressive disease, and stable disease.

Covariates (assessed during the baseline period or at index date).

- Gender.

- Age at time of mRCC diagnosis.

- Race.

- Date of RCC diagnosis.

- Date of mRCC diagnosis.

- Prior nephrectomy.

- Date of nephrectomy (if applicable).

- Pathology.

  - 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).

- IMDC prognostic risk factors.

  - Time from diagnosis to treatment initiation.

  - Karnofsky performance status at index date.

  - Serum hemoglobin at index date.

- Serum corrected calcium at index date.

- Neutrophil count (absolute count) at index date.

- Platelet count at index date.

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 35 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.

AGI will collaborate with Dr. PPD from the 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, which is updated frequently (ie, quarterly or continuously). Data cleaning and consolidation of the data occur twice a year.

For this proposed study, a "limited" dataset of first-line sunitinib patients will be provided. The "limited" dataset will be anonymized and will not contain any personal data. All first-line sunitinib patients are included in the "limited" dataset, but only a select number of variables necessary to fulfill the study objectives will be included. CCI

7.5. Study Size

The IMDC database has approximately 7,000 mRCC patients who received sunitinib at any line of treatment. About 2,000-3,000 patients received first-line sunitinib. Power calculation was not performed as the main objectives were descriptive.

7.6. Data Management

AGI 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 AGI over a secured network to ensure that the latest available data are used in the analysis. Data provided to AGI will be anonymized and will not contain any personal data. After obtaining the data, AGI 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 the Study Cohort

The study population of interest in the current study are patients treated with first-line sunitinib. Each patient's eligibility for study will be verified against the eligibility criteria.

Description of patient demographic and clinical characteristics among patients in the study cohort, stratified by IMDC prognostic risk group

Baseline demographic and clinical characteristics prior to the index date will be described using the mean (standard deviation [SD]) and median values for continuous variables and frequency distributions for categorical variables. Demographic and clinical characteristics will also be summarized, stratified by IMDC prognostic risk groups (ie, favorable, intermediate, and poor). Comparisons will be performed using chi-square tests or Fisher's exact test, as appropriate, for categorical variables and Wilcoxon-Mann-Whitney non-parametric tests for continuous variables. CCI

Characterization of clinical outcomes of mRCC patients treated with first-line sunitinib

The following clinical outcomes will be stratified by IMDC prognostic risk groups (ie, favorable, intermediate, and poor) and KPS (eg, 0-40%, 50-70%, and 80-100%).

- OS and TTD will be analyzed using Kaplan-Meier estimator.

- Reasons for first-line sunitinib therapy discontinuation will be described using relative frequencies.

- Physician-assessed best tumor response (ie, objective response rate, stable disease, and progressive disease) to first-line sunitinib will be described using relative frequencies.

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Indirect qualitative evaluation of the real-world clinical outcomes of mRCC patients treated with first-line sunitinib with that of phase II and III clinical trials

An indirect qualitative, side-by-side evaluation of clinical outcomes will be conducted between the following groups:

- Previously untreated sunitinib patients with intermediate or poor IMDC risk score from the real-world IMDC database *vs* previously untreated sunitinib patients with intermediate or poor IMDC risk score from the 1) CABOSUN trial, 2) CheckMate 214, and 3) sunitinib vs. IFN-α trial.

Subgroup analysis describing demographic and clinical characteristics and characterizing clinical outcomes among patients in the IMDC intermediate risk group, stratified by patients having only 1 vs 2 risk factors

- Among patients identified as having intermediate IMDC risk score (defined as having 1 or 2 IMDC risk factors), a subgroup analysis will assess baseline demographic and clinical characteristics, distribution of individual IMDC risk factors, and clinical outcomes (ie, OS, TTD, and ORR), stratified by patients having only 1 risk factor vs. 2 risk factors. Demographic and clinical characteristics and clinical outcomes (ie, OS, TTD, and ORR) will be analyzed using the same methodology applied in the full study cohort. Absolute and relative frequency of each IMDC factor within the intermediate risk group will be reported.

7.8. Limitations of the Research Methods

With an analysis of non-randomized treatment groups, unmeasured confounders and reporting bias could account for any observed associations. In addition, there may be potential biases in the retrospective study design (eg, selection bias, recall bias, and non-random missing data).

In addition, 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 accordance 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. All correspondence with the IRB/IEC should be retained in the Investigator File.

8.4. 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), 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-GSOP-RF06 *Safety Reporting Language: Secondary Data Collection Study - Does Not Include Protocol-Required Human Review of Unstructured Data*

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In these data sources, 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) are not available* and AEs are not reportable as individual AE reports.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)*" and any relevant Your Reporting Responsibilities supplemental training. This training 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.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

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.

11. REFERENCES

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12. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

13. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

14. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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