



## NON-INTERVENTIONAL (NI) STUDY PROTOCOL

### Study information

<b>Title</b>	Clinical Effectiveness of First-Line immuno-oncology (IO) Combination Treatment and Subsequent Lines of Therapy in Patients with Metastatic Renal Cell Carcinoma (mRCC) in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)
<b>Protocol number</b>	A4061100
<b>Protocol version identifier</b>	V1.0
<b>Date</b>	11 May 2022
<b>Research question and objectives</b>	The study aims to evaluate the real-world impact of the first-line immuno-oncologic (IO) combination treatment and subsequent lines of therapy on clinical outcomes and survival in mRCC patients.
<b>Author</b>	<p>PPD [REDACTED], MD, MPH, FRCPC PPD [REDACTED]</p> <p>PPD [REDACTED] [REDACTED] [REDACTED] Email: PPD [REDACTED]</p> <p>PPD [REDACTED] ScD, MPH PPD [REDACTED] [REDACTED] Email: PPD [REDACTED]</p> <p>PPD [REDACTED], PhD, RAC PPD [REDACTED] [REDACTED] Email: PPD [REDACTED]</p> <p>PPD [REDACTED], MSc</p>

	<p>PPD [REDACTED] [REDACTED] Email: PPD [REDACTED]</p> <p>PPD [REDACTED], PhD PPD [REDACTED] [REDACTED] Email: PPD [REDACTED]</p>
--	---

## 1. TABLE OF CONTENTS

1. TABLE OF CONTENTS.....	3
2. LIST OF ABBREVIATIONS.....	5
3. RESPONSIBLE PARTIES.....	7
4. MILESTONES .....	8
5. RATIONALE AND BACKGROUND.....	8
6. RESEARCH QUESTION AND OBJECTIVES .....	9
7. RESEARCH METHODS.....	10
7.1. Study design .....	10
7.2. Setting.....	11
7.2.1. Inclusion criteria .....	11
7.2.2. Exclusion criteria .....	11
7.3. Variables .....	11
7.4. Data sources.....	12
7.5. Study size .....	13
7.6. Data management.....	13
7.7. Data analysis.....	14
7.8. Quality control.....	16
7.9. Limitations of the research methods.....	16
7.10. Other aspects.....	16
8. PROTECTION OF HUMAN SUBJECTS.....	16
8.1. Patient information.....	16
8.2. Patient consent.....	17
8.3. Institutional review board (IRB)/Independent ethics committee (IEC).....	17
8.4. Ethical conduct of the study.....	17
9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS.....	17
10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS.....	18
11. REFERENCES .....	19
12. LIST OF TABLES.....	20
13. LIST OF FIGURES.....	20
ANNEX 1. LIST OF STAND ALONE DOCUMENTS.....	21

ANNEX 3. ADDITIONAL INFORMATION.....21

14. APPENDIX: SELECT LIST OF VARIABLES IN THE IMDC DATABASE.....21

## 2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
2L	Second-line
3L	Third-line
AE	Adverse event
AG	Analysis Group
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
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IPCW	Inverse probability of censoring weight
IPTW	Inverse probability of treatment weight
IO	Immuno-oncology
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LOT	Line of therapy
mRCC	Metastatic renal cell carcinoma
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PS	Propensity Score
RCC	Renal cell carcinoma
rwORR	Real-world objective response rate
SD	Standard deviation
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
US	United States
VEGF	Vascular endothelial growth factor

### 3. RESPONSIBLE PARTIES

#### Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD [REDACTED], MD, MPH, FRCPC	PPD [REDACTED]	PPD [REDACTED]	PPD [REDACTED]
PPD [REDACTED], MPH, ScD	PPD [REDACTED]	PPD [REDACTED]	PPD [REDACTED]
PPD [REDACTED] PhD, RAC	PPD [REDACTED]	PPD [REDACTED]	PPD [REDACTED]
PPD [REDACTED] MSc	PPD [REDACTED]	PPD [REDACTED]	PPD [REDACTED]
PPD [REDACTED] PhD	PPD [REDACTED]	PPD [REDACTED]	PPD [REDACTED]

#### 4. MILESTONES

Milestone	Planned date
Development of study protocol	March 2022
Protocol approval	May 2022
Data transfer	May 2022
Preparation of analytical files	June 2022
Selection of study sample	June 2022
Delivery of preliminary results 1. Part 1: Descriptive analyses Part 2 [optional]: Comparative analyses	1. June-July 2022 2. TBD
Delivery of final results	September 2022
Delivery of draft study report	November 2022

#### 5. RATIONALE AND BACKGROUND

Each year, an estimated 400,000 new cases of kidney cancer, of which renal cell carcinoma (RCC) accounts for approximately 90%, are diagnosed worldwide.<sup>1</sup> Due to a lack of early symptoms or clinical indications of disease, approximately 20% of patients present with metastatic RCC (mRCC) at time of diagnosis.<sup>2,3</sup> During the last decade, targeted therapies became standard of care for patients with mRCC. Targeted therapy has been associated with improved clinical efficacy, including progression-free survival (PFS) and overall survival (OS), favorable side effect profiles, and improved health-related quality of life.<sup>4-10</sup>

In recent years, IO therapeutic agents changed the treatment paradigm for mRCC by blocking immune checkpoints (e.g., programmed cell death protein-1 [PD-1]/PD-ligand 1 [PD-L1]) and restoring tumor-specific T-cell-mediated immune responses.<sup>11,12</sup> IO therapeutic agents demonstrated antitumor activity and durable responses in both pre-treated and treatment naïve mRCC.<sup>13,14</sup> Ipilimumab + nivolumab, approved in 2018, and IO/vascular endothelial growth factor (VEGF) inhibitor combinations, are now standard of care first-line (1L) treatment options for mRCC in patients who have intermediate/poor IMDC risk scores.<sup>15,16</sup> Pembrolizumab + axitinib and avelumab + axitinib were both approved as 1L treatment for mRCC in 2019.<sup>17</sup> Nivolumab + cabozantinib is a 1L combination with a Category 1 preferred designation across all risk groups in clear-cell mRCC, and was recently approved in 2021.<sup>18,19</sup> This new era of targeted treatment options requires an understanding of prognostic factors that may be used to inform clinical trial data and risk specific treatments.<sup>18</sup> Given that patients may

utilize combination therapies, there remains a need for the development of optimal treatment sequences for the management of AEs that comes with the combination treatments. Specifically, treatment sequencing may assist with toxicity concerns.<sup>20</sup>

Recent findings presented at the American Society of Clinical Oncology supports future research that may answer these concerns. For example, Ernst et al. found a significant differences in OS across IMDC risk groups in patients who received ipilimumab + nivolumab, combinations of IO with VEGF, and VEGF targeted therapy in 1L. Notably, patients treated with VEGF targeted therapy had worse overall outcomes compared to other treatment groups.<sup>21</sup> A separate study assessing predictors of objective response to 1L IO therapies found that improved IMDC prognostic risk was associated with response.<sup>22</sup> Finally, preliminary results from Navani et al. demonstrated the activity of cabozantinib as a second-line (2L) therapy following either ipilimumab + nivolumab, combinations of IO with VEGF, or other 1L therapies as having clinically meaningful activity, suggesting that investigation of sequence is warranted to assist with patient counseling.<sup>23</sup>

The order of treatment sequences may have an overall clinical benefit on response rate and OS. However, selecting optimal treatment sequences for patients with mRCC remains a challenge for practitioners because treatment guidelines and regulatory policies are not yet available. Real-world evidence on the effectiveness of treatment sequences in patients with mRCC treated with 1L IO combination therapy is limited. Thus, real-world evaluation of the impact of the 1L IO combination treatment and subsequent treatments on clinical outcomes and OS is warranted. The aim of the study is to understand the impact of treatment sequences on overall clinical outcomes using the IMDC database.

## 6. RESEARCH QUESTION AND OBJECTIVES

This study will be designed and executed in two parts:

### *Part 1: Descriptive analyses*

Among patients with mRCC treated with IO combination in 1L:

1. To describe demographic and clinical characteristics
2. To describe mRCC treatment in each line (e.g., 1L, 2L, and third-line (3L)) including treatment flow diagram (ie., Sankey diagram)
3. To characterize patients (eg., age, clinical characteristics, IMDC risk score, etc.) with mRCC receiving *clinically meaningful treatment sequences* selected based on clinical inputs. Such as:
  - Ipilimumab + nivolumab (1L) → sunitinib (2L) → *Any* (eg., cabozantinib, axitinib, or pazopanib) (3L)
  - Axitinib-based regimens (1L) → *Any* (e.g., cabozantinib, axitinib, or pazopanib)

4. To describe the real-world treatment outcomes
  - OS
  - Physician-assessed best response (real-world overall response rate – complete response/partial response) for each line of therapy (LOT)
  - Time to treatment discontinuation (TTD) for each LOT
  - Time to next treatment (TTNT)

*Part 2 [optional]: Comparative analyses*

1. To compare OS between 2 select treatment sequences of interest, overall and by IMDC risk score
  - The 2 treatment sequences for comparison will be selected based on the review of Stage 1 findings

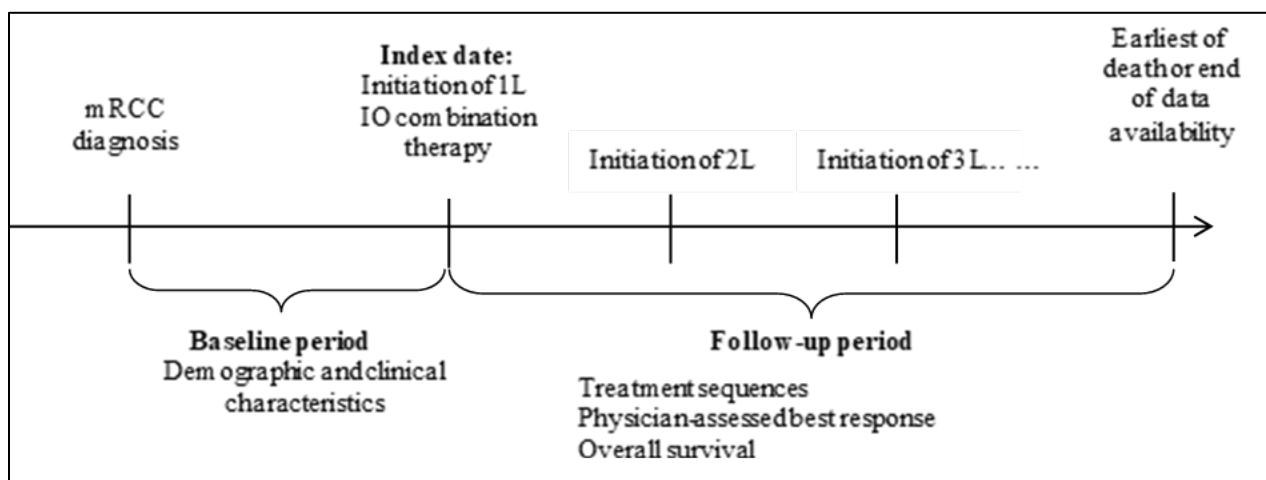
## 7. RESEARCH METHODS

### 7.1. Study design

This is a retrospective, longitudinal cohort study that involves the analysis of data collected through the IMDC database from selected academic clinical sites participating in this study. The study population consists of mRCC patients treated with 1L IO combination therapy and subsequently received additional lines of treatment.

The *index date* will be defined as the date of initiation of 1L IO combination 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.

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

1. Diagnosed with mRCC
2. Age 18 years or over at the time of mRCC diagnosis
3. Received IO combination treatment in 1L such as receiving ipilimumab + nivolumab or an axitinib-based regimen (i.e., axitinib + pembrolizumab or axitinib + avelumab) as 1L
4. Received subsequent treatments following 1L (e.g., 2L, 3L)
5. 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

- 1L IO combination therapy

### Outcomes

- OS, defined as the time between initiation of 1L IO combination therapy to death
- Physician-assessed best response
  - Overall best response rate (complete or partial)
  - Stable disease
  - Progressive disease
- TTD, defined as the time from treatment initiation to discontinuation of each therapy due to any reason including progression, death, or toxicity
- TTNT, defined as time from the initiation of 1L treatment to initiation of subsequent therapy or death

### Covariates

*Patient characteristics* (assessed during the baseline period or on index date, unless otherwise specified)

- Demographics
  - Gender
  - Age at time of 1L initiation
  - Race
  - Region indicator (i.e., US vs. ex-US)

- Clinical characteristics
  - Date of mRCC diagnosis
  - Prior nephrectomy status
  - Date of nephrectomy (if applicable)
  - Tumor characteristics
    - Histology type (i.e., clear cell vs. non-clear cell RCC)
    - Number of metastatic sites (e.g., 1 site or more than 1 site)
    - Site of metastases (e.g., brain, bone, lung)
  - IMDC risk score (assessed on index date and at initiation of each LOT)

#### *Treatment pattern information*

- Number of LOTs received
- Treatment agents received at each LOT
- Duration of each LOT
- Time from discontinuation of previous LOT to initiation of subsequent LOT
- Reasons for discontinuation for each LOT

#### **7.4. Data sources**

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.

Analysis Group (AG) 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, and data cleaning and consolidation of the data occur twice a year.

Table 1 below presents sample sizes for varying treatment sequences in the IMDC database provided by Pfizer.

**Table 1. Sample sizes of select 1L mRCC IO combination treatment in the IMDC database as of November 2021**

1L mRCC IO combination treatment	Number of patients
Ipilimumab + nivolumab	780
Axitinib-based regimen	244
• Axitinib + pembrolizumab	181

1L mRCC IO combination treatment	Number of patients
• Axitinib + avelumab	63

## 7.5. Study size

Sample size calculations were performed to determine the required study size for detecting differences in OS between patients treated with axitinib-based IO regimens and comparator IO combination regimens (e.g., ipilimumab + nivolumab). In a randomized phase 3 trial comparing axitinib + pembrolizumab to sunitinib among patients with previously untreated mRCC, the estimated percentage of patients who were alive at 1 year was 89.9% in the pembrolizumab + axitinib group<sup>24</sup>, while a multi-center retrospective study reported a 75% 1-year OS rate among mRCC patients treated with ipilimumab + nivolumab in 1L.<sup>25</sup> Provided with these estimates and assuming a 2-year follow-up time on average, sample sizes required to detect a difference in OS with two-sided significance level 0.05 and 80% power are presented in Table 2 below. Assuming similar levels of efficacy as observed in literature (i.e., 90% 1-year OS in the axitinib-based group and 75% in the comparator group), a sample size of 67 patients per group (134 in total) is needed. More conservatively, a sample size of 174 per group (348 in total) is needed to detect a difference of 85% vs. 75% in OS. Given the preliminary patient counts shown in Table 1, the current study should be sufficiently powered.

**Table 2. Sample size calculations based on the log-rank test**

1-year OS in the axitinib-based group	1-year OS in the comparator group (e.g., ipilimumab + nivolumab)	Hazard ratio	Sample size per group	Total sample size
0.90	0.75	0.37	67	134
0.90	0.78	0.42	98	196
0.90	0.80	0.47	135	270
0.90	0.83	0.57	254	508
0.85	0.70	0.46	84	168
0.85	0.72	0.49	108	216
0.85	0.75	0.56	174	348
0.85	0.78	0.65	335	670

## 7.6. Data management

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

Data will be transferred to AG over a secured network to ensure that the latest available data are used in the analysis. Data provided to AG will be anonymized and will not contain any personal data. After obtaining the data, AG will assess the quality of the data downloaded

and work with IMDC data manager to rectify any potential data entry errors and discrepancies.

## 7.7. Data analysis

### Part 1: Descriptive analyses

#### Description of demographic and clinical characteristics

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]), minimum and maximum for continuous variables and frequencies and proportions for categorical variables. The descriptive analysis of patient characteristics will be conducted overall as well as for patients receiving select treatment sequences, for example:

- Nivolumab + ipilimumab (1L) → sunitinib (2L) → Any (e.g., cabozantinib, axitinib, or pazopanib) (3L)
- Axitinib-based regimens (1L) → Any (e.g., cabozantinib, sunitinib or pazopanib)

#### Description of mRCC treatment in each line (e.g., 1L, 2L, 3L... etc.)

A treatment flow diagram (e.g., Sankey diagram) will be produced to describe mRCC treatment in each line. Specific treatment agents used in each line will be described with frequencies and proportions. Duration of each LOT and time from discontinuation of the previous LOT to initiation of the subsequent LOT will be described using mean (SD) and median (IQR). Reasons for treatment discontinuation will be described using frequencies and proportions.

#### Characterization of real-world treatment outcomes

Physician-assessed best tumor response (i.e., real world objective response rate [rwORR] (i.e., complete/partial response), stable disease, and progressive disease) to each LOT will be described using frequencies and proportions. OS, TTD, and TTNT will be analyzed using the Kaplan-Meier estimator. All analyses will be stratified by IMDC risk scores.

#### Comparison of patient characteristics between two select treatment sequences

Descriptive comparisons of patient characteristics of select treatment sequences of interest to Pfizer in Part 1 will be conducted to inform whether Part 2 analysis should be performed. Specifically, discrepancies between patients' baseline characteristics and treatment patterns will be summarized using standardized differences. Part 2 will be considered if major differences in key prognostic factors between the two groups are not observed, or the existing differences are deemed likely to be balanced after weighting procedures (described in the following paragraph). Further discussion with Pfizer and clinical expert will take place before embarking on Part 2 analysis.

### Part 2 (optional): Comparative analysis

In comparing OS between two treatment sequences, biases could arise from imbalanced baseline characteristics and/or artificial censoring at initiation of further lines of therapies post-IO. A weighted Cox regression model will be employed in order to minimize

confounding and induced selection bias. The weights will be calculated as the product of inverse probability of treatment weight (IPTW) and inverse probability of censoring weight (IPCW). IPTW will be used to adjust for baseline imbalances between patients who underwent the two treatment sequences, while IPCW will be used to correct selection bias induced by artificial censoring (e.g., censoring patients at initiation of further lines of therapies post-IO). The IPTW/IPCW weighting achieves confounding control by creating a pseudo population in which all observed potential confounders are balanced between the two comparator groups.

To implement the IPTW approach, weights will be created through propensity score (PS) modeling, where the PS is defined as the probability of receiving certain treatment sequence given an observed set of baseline covariates. Specifically, each patient's weight will be calculated as the inverse of the conditional probability of receiving their observed treatment sequence, given their baseline characteristics. Initial inverse-probability weights will be calculated as  $1/PS$  for the group received treatment sequence A and  $1/(1-PS)$  for the group received treatment sequence B. To enhance precision in the effect estimates, each patient's weight will be stabilized by the marginal probability of being in their respective treatment sequence group. The stabilized weights will thus be calculated as  $[Pr(\text{receiving treatment sequence A})]/PS$  for the treatment sequence A group and  $[1 - Pr(\text{receiving treatment sequence A})]/(1-PS)$  for the treatment sequence B group.

IPCW will be implemented to account for potential informative censoring at initiation of further lines of therapies post-IO. In this approach, subjects who remained uncensored are weighted according to their similarity to those who were censored. To compute the weights, a logistic regression model will be used to estimate the probability of remaining uncensored at each event time given the observed past. The weights would follow the formula below:

$$w_{ij} = \frac{\prod_{k=0}^j P(C(k)_i = 0 | C(k-1)_i = 0, X_i)}{\prod_{k=0}^j P(C(k)_i = 0 | C(k-1)_i = 0, X_i, L(k)_i)}$$

For a non-censored subject, the numerator calculates the probability of remaining uncensored up to the j-th time point conditional on baseline covariates  $X_i$ .  $C(k)_i$  is a binary indicator where  $C(k)_i=1$  represents being censored at the k-th time point and 0 not censored. The denominator of his/her weight at the j-th time point is the predicted probability of remaining uncensored up to the j-th time point conditional on both time-varying covariates  $L(k)_i$  (e.g. IMDC risk score), and time-invariant covariates  $X_i$  (e.g., age, gender).

Zero weight will be assigned to censored subjects from their respective censoring time onwards. The final inverse probability weights will be calculated as the product of the IPTW and IPCW (IPTW×IPCW). After weighting, the distribution of baseline characteristics will be evaluated between patients who underwent the two treatment sequences to ensure comparability, and standardized differences will be estimated with values >10% indicating an imbalance.

A weighted Cox regression model will then be fitted which includes an indicator variable of treatment sequence group. If there exist variables that are inadequately balanced after weighting, they will be included as regression model covariates to build a doubly robust model. Analysis stratified by the IMDC prognostic risk groups (i.e., favorable, intermediate, and poor) may be performed pending on sample sizes.

### **7.8. Quality control**

AG will assess the quality of the data downloaded and work with IMDC data manager to rectify any potential data entry errors and discrepancies.

### **7.9. Limitations of the research methods**

The current study is not without limitations, specifically:

- Assessments of disease progression and tumor response in real-world settings may be based on heterogeneous criteria and assessment schedules.
- Assessments of progression and clinical response in retrospective studies of clinical practice may not be made consistently across subjects and across physician practices.
- Dose information may be lacking which may provide differential treatment effects.
- Medical charts may contain incomplete or missing data.
- Treatment sequences may be limited by differences in reimbursement policies across countries. For instance, in some countries, only two lines of treatment are allowed of axitinib + pembrolizumab is prescribed first.

### **7.10. Other aspects**

Not Applicable

## **8. PROTECTION OF HUMAN SUBJECTS**

This is a retrospective database analysis 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**

This study involves data that exist in anonymized structured format and contain no patient personal information.

## **8.2. Patient consent**

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

## **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 (i.e., 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 GPP issued by the 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**

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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

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

- “*Your Reporting Responsibilities (YRR) Training for Vendors*”.

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.

“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**

The final study report will be completed by AG and is estimated to be available in November 2022.

In the event of any prohibition or restriction imposed (e.g., 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

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2018;68(6):394-424.
2. Fisher R, Gore M, Larkin J. Current and future systemic treatments for renal cell carcinoma. Elsevier; 2013:38-45.
3. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *New England Journal of Medicine*. 2017;376(4):354-366.
4. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *New England Journal of Medicine*. 2007;356(2):125-134.
5. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *New England Journal of Medicine*. 2007;356(22):2271-2281.
6. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *The Lancet*. 2008;372(9637):449-456.
7. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *Journal of clinical oncology*. 2009;27(22):3584.
8. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *New England Journal of Medicine*. 2007;356(2):115-124.
9. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *The Lancet*. 2007;370(9605):2103-2111.
10. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *Journal of clinical oncology*. 2010;
11. Alsharedi M, Katz H. Check point inhibitors a new era in renal cell carcinoma treatment. *Medical Oncology*. 2018;35(6):1-5.
12. Rodriguez-Vida A, Hutson TE, Bellmunt J, Strijbos MH. New treatment options for metastatic renal cell carcinoma. *ESMO open*. 2017;2(2):e000185.
13. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *New England Journal of Medicine*. 2018;
14. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *New England Journal of Medicine*. 2015;373(19):1803-1813.
15. Gan CL, Dudani S, Wells JC, et al. Outcomes of first-line (1L) immuno-oncology (IO) combination therapies in metastatic renal cell carcinoma (mRCC): Results from the

International mRCC Database Consortium (IMDC). American Society of Clinical Oncology; 2021.

16. Sheng IY, Ornstein MC. Ipilimumab and nivolumab as first-line treatment of patients with renal cell carcinoma: the evidence to date. *Cancer Management and Research*. 2020;12:4871.
17. Powles T, Albiges L, Bex A, et al. ESMO clinical practice guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. *Annals of Oncology*. 2021;32(12):1511-1519.
18. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. [www.nccn.org/professionals/physician\\_gls/PDF/occulpdf](http://www.nccn.org/professionals/physician_gls/PDF/occulpdf). 2008;
19. US Food and Drug Administration. FDA approves nivolumab plus cabozantinib for advanced renal cell carcinoma. 2021.
20. George DJ, Lee C-H, Heng D. New approaches to first-line treatment of advanced renal cell carcinoma. *Therapeutic Advances in Medical Oncology*. 2021;13:17588359211034708.
21. Ernst MS, Navani V, Wells JC, et al. Characterizing IMDC prognostic groups in contemporary first-line combination therapies for metastatic renal cell carcinoma (mRCC). American Society of Clinical Oncology; 2022.
22. Navani V, Ernst MS, Wells C, et al. Predictors of objective response to first-line immuno-oncology combination therapies in metastatic renal cell carcinoma: Results from the international metastatic renal cell database consortium (IMDC). American Society of Clinical Oncology; 2022.
23. Navani V, Wells C, Boyne DJ, et al. CABOSEQ: The efficacy of cabozantinib post up-front immuno-oncology combinations in patients with advanced renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). American Society of Clinical Oncology; 2022.
24. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine*. 2019;380(12):1116-1127.
25. Tanaka T, Hatakeyama S, Numakura K, et al. Efficacy and safety of first - line nivolumab plus ipilimumab in patients with metastatic renal cell carcinoma: A multicenter retrospective study. *International Journal of Urology*. 2020;27(12):1095-1100.

## 12. LIST OF TABLES

*All tables referenced in the protocol should be listed.*

## 13. LIST OF FIGURES

*All figures referenced in the protocol should be listed.*

## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

*Annex 1 should be used to list stand-alone documents not included in the protocol, e.g., contact details of responsible parties and all investigators if applicable.*

If there is no document to be listed, delete the table and write “None”.

Number	Document reference number	Date	Title

## ANNEX 3. ADDITIONAL INFORMATION

### 14. APPENDIX: SELECT LIST OF VARIABLES IN THE IMDC DATABASE

<b>Demographics/Date</b>	Male DOB DDx Dmet DTKI DxTKITimeYrs DxAge Nephrectomy Dnephrectomy
<b>Tumor Characteristics</b>	T N LN status determinde M Size Necrosis MVI Fuhrman Grade Nonclearcell ccRCC papRCC chrRCC unclassifiedRCC collecDuct XpTranslocation Sarcomatoid
<b>First Line Therapy and First Line Risk Factors</b>	FirstSecondLine SUSOAGAVAZTEPAEV

	Hb HbLLN Hblow CorrCa CaHigh LDH LDHULN Neutrophil_0Weeks Lymphocyte_0Weeks  Neutrophil_6Weeks  Lymphocyte_6Weeks  Neutrophil_12Weeks  Lymphocyte_12Weeks Plt Na KPS  KPS (end 1TKI)
<b>Met Sites at First Line Therapy</b>	gt1met KidneyMet(multifocality,bilateral,met)  OtherMetSite(i.e. soft tissue, adrenal gland)  LymphNodes DxNodes DxDxNodes LN Site LND LungMets Brainmet Livermet Bonemet
<b>Renal Function</b>	Cr Baseline CAD Cr Baseline Weight kg Height cm Race Black=1
<b>Best Response to First Line</b>	Best Response  Max Change

	cleaned BR cleaned MaxChange
<b>First Line Dose</b>	Dose Reduce Date of DR Toxicity Leading to DR Final dose level Why Stopped Rx (T/P/D/O) Toxicity leading to Rx stopping (if T) 1IO TBP 1IO 1st Progression
<b>Follow Up Calculations</b>	Dstop/lastfu DStopcnsr Ddeathlastfu Ddeathcnsr Survivalmon PFSmon Survival-PFS
<b>Second Line Therapies and Second Line Risk Factors</b>	Drug2 SUSOAGAVTEEVIFILPACACT drug2_response drug2_Start drug2_Stop/last f/u drug2_Stopcnsr 2Hb 2Hb LLN 2Corrected Ca 2Ca High = 1 2LDH 2ULNLDH 2KPS 2KPS End 2Platelet 2Neutrophil 2Lympho 2Serum sodium 2Serum Creatinine 2Weight (kg) Sites of Metastases at 2nd line 2gt1met 2Brain Mets
<b>Second Line Doses</b>	2Dose Reduce

	2Date of DR 2Toxicity Leading to DR 2Final dose level 2Why Stopped Rx (T/P/D/O) 2Toxicity leading to Rx stopping (if T) 2IO TBP 2IO 1st Progression
<b>Third Line Therapies and Third Line Risk Factors</b>	Drug3 SUSOAGAVTEEVIFILPACACTrial 3BestResponse drug3_Start drug3_Stop/last f/u drug3_Stopcnsr 3Hb 3Hb LLN 3Corrected Ca 3Ca High = 1 3LDH 3ULNLDH 3KPS 3KPS End 3Platelet 3Neutrophil 3Lympho 3Serum sodium 3Serum Creatinine 3Weight (kg) Sites of Metastases at 3nd line 3gt1met
<b>Fourth Line Therapies and Third Line Risk Factors</b>	Drug4 SUSOAGAVTEEVIFILPACACTrial 4BestResponse drug4_Start drug4_Stop/last f/u drug4_Stopcnsr 4Hb 4Hb LLN 4Corrected Ca 4Ca High = 1 4LDH 4ULNLDH 4KPS

	4KPS End 4Platelet 4Neutrophil 4Lympho 4Serum sodium 4Serum Creatinine 4Weight (kg) Sites of Metastases at 4th line 4gt1met
--	---