NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Title	A Panel-Based Chart Review Study to Examine the Effects of Axitinib Dose Reduction and Interruption for Adverse Event Management among Patients Receiving First-Line Axitinib in Combination with Immune-Oncology Drugs for the Treatment of Advanced Renal Cell Carcinoma
Protocol number	A4061097
Protocol version identifier	Version 1.0
Date of last version of protocol	19 October 2020
Active substance	Not applicable
Medicinal product	Axitinib (INLYTA®)
Research question and objectives	To assess how dose reductions or treatment interruptions related to axitinib can be implemented to manage and resolve adverse events occurring among patients with advanced renal cell carcinoma treated with first-line axitinib in combination with avelumab or pembrolizumab
Country(-ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
AG	Analysis Group, Inc.
AIDS	Acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cerebrovascular disease
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-oncology
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MSKCC	Memorial Sloan Kettering Cancer Center
NCI	National Cancer Institute
NIS	Non-interventional study
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
RCC	Renal cell carcinoma
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
VEGF	Vascular endothelial growth factor

3. RESPONSIBLE PARTIES

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4. AMENDMENTS AND UPDATES

NONE.

5. MILESTONES

Milestone	Planned Date
Start of data collection	30 November 2020
End of data collection	31 January 2021
Final study report	31 July 2021

6. 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.[1-3] RCC comprises 2-3% of all adult malignancies with an estimated 63,000 incident cases and 14,000 deaths from RCC annually in the United States (US).[4] The exact cause of RCC is not well understood, but inherited and acquired mutations in oncogenes, such as von Hippel-Lindau, fumarate hydratase, and folliculin genes, may cause kidney cells to become cancerous. Obesity, hypertension, smoking, occupational exposure to toxic compounds such as cadmium and asbestos, and male gender are potential risk factors for triggering the genetic mutations,[1,2] but many gene changes are random idiopathic events. Due to the lack of early symptoms and clinical indications of disease, up to 30% of patients with RCC are diagnosed with advanced or metastatic disease.[5] Prognosis is poor among advanced RCC patients, with 5-year survival rates of approximately 8%.[6] The burden of advanced RCC is projected to grow with the aging population and increasing prevalence of risk factors for RCC, such as obesity and hypertension.[2,3]

During the last decade, targeted therapies, which are agents that target the vascular endothelial growth factor (VEGF), the VEGF receptor, or the mammalian target of rapamycin, became standard of care for patients with advanced RCC.[7] Since 2005, several targeted therapies have been approved for the treatment of advanced RCC in the US, including axitinib (Inlyta®), sunitinib (Sutent®), bevacizumab (Avastin®), sorafenib (Nexavar®), pazopanib (Votrient®), cabozantinib (Cabometyx®, Cometriq®), everolimus (Afinitor®), and temsirolimus (Torisel®).[7,8] Targeted therapies have been associated with improved progression-free survival and overall survival, favorable side effect profiles, and improved health-related quality of life.[9-15]

Yet, recent advancements in immuno-oncology (IO) therapeutic agents have changed the treatment paradigm for advanced RCC. 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,[16,17] and have demonstrated antitumor activity and durable responses in patients with advanced RCC.[18,19] Specifically, the KEYNOTE-426 trial demonstrated that treatment-naïve advanced RCC patients who were treated with axitinib in combination with pembrolizumab had significantly longer overall survival, progression-free survival, and objective response rate compared to sunitinib,[20] leading to US Food and Drug Administration (FDA) approval of axitinib in combination with pembrolizumab for first-line advanced RCC treatment in April 2019. In addition, the JAVELIN Renal 101 trial showed significantly longer progression-free survival among advanced RCC patients who received avelumab plus axitinib than with sunitinib in first-line,[21] leading to FDA approval of axitinib in combination with avelumab for first-line advanced RCC treatment in May 2019.

While axitinib has generally demonstrated a favorable tolerability profile in real-world studies,[22,23] there is currently limited information on the real-world adverse event (AE) profile of axitinib in combination with IO therapies. In addition, the effect of dose reductions and treatment interruptions used to manage and resolve AEs occurring among patients with advanced RCC who use axitinib in combination with IOs is not well understood. Given this gap in the literature, AG will conduct a physician panel-based chart review to describe how dose reductions or treatment interruptions related to axitinib (in combination with IO therapy including avelumab or pembrolizumab) can be implemented to potentially manage and resolve AEs occurring among patients with advanced RCC. In this way, the study could help demonstrate that AEs associated with axitinib may be mitigated without excess use of healthcare resource use or additional treatment burden to patients beyond modifications related to axitinib.

7. RESEARCH QUESTION AND OBJECTIVES

The specific objectives of the study are as follows:

1. Describe incident AEs experienced among patients with advanced RCC who received first-line axitinib in combination with IO therapies.

    - Type and seriousness of AEs (ie, diarrhea, fatigue, hypertension, nausea, palmar-plantar erythrodysesthesia [hand-foot syndrome]).

- Proportion of patients who experienced repeated AEs.

- Time from treatment initiation to AE onset, overall and by type and seriousness of AEs.

2. Among patients with advanced RCC who developed incident AEs while receiving first-line axitinib in combination with IO therapies, characterize and describe management strategies for AEs, stratified by type and seriousness of AEs.

    - Proportion of patients who used each of the following management strategies:

        - No action for axitinib and IO therapy;

        - No action for axitinib, but treatment modification for IO therapy (ie, treatment interruption, treatment discontinuation);

        - Axitinib dose reduction, but no action for IO therapy;

        - Axitinib treatment interruption, but no action for IO therapy;

        - Axitinib treatment discontinuation, but no action for IO therapy;

        - Axitinib dose reduction, and treatment modification for IO therapy;

        - Axitinib treatment interruption, and treatment modification for IO therapy;

        - Axitinib treatment discontinuation, and treatment modification for IO therapy.

    - Average axitinib dose reduction (absolute and percentage change), where applicable.

    - Duration of treatment interruption, where applicable.

3. Assess the frequency of and time to AE resolution (from AE onset and initiation of management strategy, separately) among patients with advanced RCC who developed incident AEs while receiving first-line axitinib in combination with IO therapies according to different management strategies implemented, stratified further by type and seriousness of AEs, as allowed by sample size.

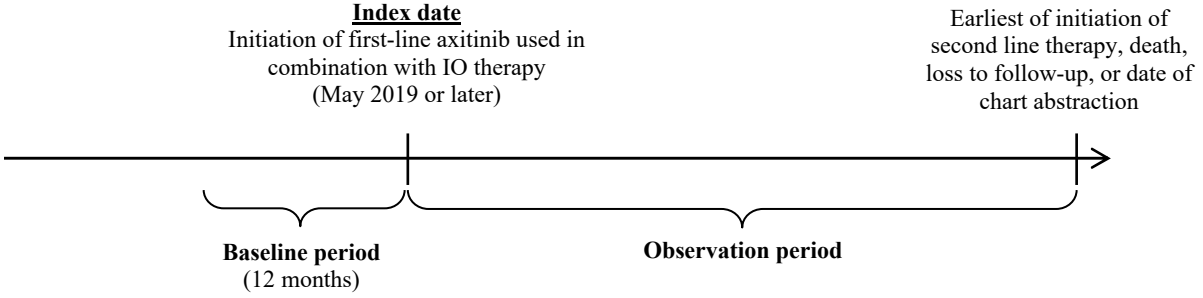
The above objectives will also be conducted for repeated AEs of the same type.

8. RESEARCH METHODS

8.1. Study Design

A retrospective physician panel-based chart review study in the US will be conducted. The index date will be defined as the initiation of first-line axitinib (used in combination with IO therapy) on or after May 2019, which marks FDA approval of axitinib in combination with avelumab for first-line advanced RCC treatment. The baseline period will be defined as the 12-month period prior to the index date. The observation period will be defined as the time from index date to the earliest of initiation of a second line therapy, death, loss to follow-up, or date of chart abstraction. During the observation period, onset, management, and resolution of AEs will be assessed. The study design scheme is depicted in Figure 1.

Figure 1. Study Design Scheme



8.2. Setting

8.2.1. Inclusion Criteria

Physicians meeting the following criteria will be invited to participate in the chart review study:

- Specialty in oncology.
- Access to complete medical records for at least one patient with advanced RCC who meets the patient eligibility criteria.

Eligible oncologists will be asked to select up to three patients meeting the following criteria for inclusion in the chart review study:

- Confirmed diagnosis with advanced RCC.
- Treated with first-line axitinib/IO combination therapy at or after diagnosis.
- Experienced at least one AE (ie, diarrhea, fatigue, nausea, hypertension, and palmar-plantar erythrodysesthesia [hand-foot syndrome]) while treated with axitinib/IO combination therapy.

- Age 18 years or older at the time of advanced RCC diagnosis.
- Initiated axitinib/IO combination therapy at least 3 months prior to the start date of medical chart abstraction to ensure sufficient follow-up time.

In the event that an oncologist has more than three eligible patients, the electronic case report form (eCRF) will have an underlying program that requires the oncologist to select patient charts based on a randomized sequence of letters. Specifically, the program will produce a random letter and request the oncologist to pull the first eligible patient chart with the last name that corresponds to the random letter. If there are no eligible patients whose last name begins with the first letter in the sequence, then the next letter in the order of the sequence will be shown. The random process will repeat for each new patient chart to be completed by the oncologist, until chart abstraction is completed for three eligible patients or until the physician has identified all eligible patients.

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

8.3. Variables

The following variables will be collected in an eCRF.

8.3.1. Physician Characteristics

The following variables will be collected once for each physician participating in the study:

- Geographic region (ie, Northeast, Midwest, South, West, Other).
- Practice setting (ie, academic-based, community-based).
- Practice size (ie, solo [1 physician], small [2-10 physicians], medium [11-50 physicians], large [≥51 physicians]).
- Years in practice since completion of oncology training (ie, <1 year, 1-5 years, 6-10 years, 11-20 years, >20 years).
- Total number of unique advanced RCC patients seen per year.
- Percentage of advanced RCC patients prescribed first-line axitinib in combination with IO therapies in the past year.

8.3.2. Baseline Patient Characteristics

The following variables, to the extent they are available, will be assessed during the baseline period or on the index date:

Demographics

- Month and year of birth (to calculate age at time points of interest).
- Sex (ie, male, female).
- Weight.
- Height.
- Race/ethnicity (ie, American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or other Pacific Islander, White, Other).
- Insurance type (ie, employer, private/non-group, Medicaid, Medicare, military, uninsured, other).

Clinical characteristics

- Date of advanced RCC diagnosis.
- Date of first-line axitinib/IO combination therapy initiation.
- IO agent used in combination with axitinib treatment.
- Initial dose of axitinib.
- Histological type (ie, non-clear cell, clear cell).
- Sarcomatoid differentiation.
- Nephrectomy status.
- Number of metastatic sites and site locations.
- TNM stage according to American Joint Committee on Cancer (AJCC) staging system.
    - Nodal status.
- Fuhrman grade.
- Largest tumor size.
- Necrosis status of the primary tumor (ie, macroscopic, microscopic).
- Microvascular invasion.

- Comorbidities used to derive the NCI Comorbidity Index:
  - Acquired immunodeficiency syndrome (AIDS);
  - Acute myocardial infarction;
  - Cerebrovascular disease (CVD);
  - Chronic obstructive pulmonary disease (COPD);
  - Congestive heart failure (CHF);
  - Dementia;
  - Diabetes;
  - Diabetes with complications;
  - History of myocardial infarction;
  - Mild liver disease;
  - Moderate/severe liver disease;
  - Paralysis (hemiplegia or paraplegia);
  - Peptic ulcer disease;
  - Peripheral vascular disease;
  - Renal disease;
  - Rheumatologic disease.
- Eastern Cooperative Oncology Group (ECOG) performance status.
- Variables to calculate prognostic risk score (ie, Memorial Sloan Kettering Cancer Center [MSKCC] risk or International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] risk).
  - Time from RCC diagnosis to initiation of first-line treatment;
  - Karnofsky performance status;
  - Serum hemoglobin level;
  - Correct calcium level;

- Neutrophil count;
- Platelet count.

8.3.3. Characterization of AEs

The following variables, to the extent they are available, will be assessed during the observation period:

- Type of AE, as defined by Common Terminology Criteria for Adverse Events (CTCAE):
  - Diarrhea, characterized by an increase in frequency and/or loose or watery bowel movements;
  - Fatigue, characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities;
  - Nausea, characterized by a queasy sensation and/or the urge to vomit;
  - Hypertension (new and worsening), characterized by a pathological increase in blood pressure;
  - Palmar-plantar erythrodysesthesia (hand-foot syndrome), characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.
- Serious AE.
  - As specified by the FDA, an AE is considered serious when the patient outcome is: death, life-threatening, hospitalization (either initial admission or prolongation of hospitalization), disability or permanent damage, or congenital anomaly/birth defect.
- Date(s) of AE onset.
- Date(s) of AE resolution.

8.3.4. Management Strategies for AEs

The following variables, to the extent they are available, will be assessed during the observation period:

- Type of management strategy:
  - No action for axitinib and IO therapy;

- No action for axitinib, but treatment modification for IO therapy (ie, treatment interruption, treatment discontinuation);
- Axitinib dose reduction, but no action for IO therapy;
- Axitinib treatment interruption, but no action for IO therapy;
- Axitinib treatment discontinuation, but no action for IO therapy;
- Axitinib dose reduction, and treatment modification for IO therapy;
- Axitinib treatment interruption, and treatment modification for IO therapy;
- Axitinib treatment discontinuation, and treatment modification for IO therapy.

- Treatment modification for axitinib:
  - Date(s) of dose reduction;
    - Modified dosage of axitinib;
  - Date(s) when treatment was halted and reinitiated;
  - Date(s) treatment was discontinued.
- Treatment modification for IO therapy:
  - Date(s) when treatment was halted and reinitiated;
  - Date(s) treatment was discontinued.

8.4. Data Sources

AG will contract with a physician panel vendor, Medefield America Limited LLC, to conduct an oncologist panel-based medical chart review in the US. Medefield has access to a large panel of physicians in a wide range of geographic locations. Oncologists will be recruited based on their medical specialty and selected for the study based on the eligible criteria. Each oncologist will complete eCRFs for up to three patients, with each chart review taking approximately 30 minutes to complete. The study will be double-blinded (physicians will be blinded to study sponsor and study sponsor will be blinded on physicians recruited to participate).

Oncologists will abstract data from medical charts of eligible patients using an online eCRF, which AG and the physician panel vendor will jointly develop specifically for this study. Medefield will set up a web-based portal with consistency checks, quality control, and validation processes built into the eCRF to ensure data quality. To capture all relevant information necessary for the study objectives, the eCRF may include both structured

(eg, multiple choice, select all options that apply) and unstructured fields (eg, open-ended responses).

8.4.1. Pilot Test

Prior to launch of data collection, a pilot test will be conducted with up to three oncologists, who will be abstracting data from patient charts. The purpose of the pilot test is to ensure that the questions in the eCRF are clear and interpreted correctly by the oncologists. Oncologists participating in the pilot test will have the ability to comment on the questions they do not fully understand and to provide suggestions on improving the questions. The pilot test will also help ensure that key data elements are contained in patient charts, such that key data elements of this study could be obtained in a reliable manner through the patient chart abstraction.

Upon completion of the pilot test, AG will clean and analyze the data in order to evaluate their adequacy and quality for addressing the study objectives. Further discussions with Pfizer will take place to discuss these findings and potential updates to the eCRF. Changes to the eligibility criteria as well as alternative analytical approaches that are more suitable for the available data may also be considered. Based on this assessment, the study protocol and the eCRF may be updated as needed.

8.5. Study Size

Approximately 200 oncologists may be recruited by the physician panel vendor to abstract medical charts. AG anticipates to obtain data from the medical charts of 400-600 patients with advanced RCC. No formal sample size computation was performed as all statistical analyses are descriptive in nature and no hypotheses are being tested.

8.6. Data Management

This study will collect de-identified data. No patient identifiable information including names or medical record number will be collected in the eCRF. For variables that may contain potentially identifiable information such as number of years in practice, ranges or categories will be used rather than collecting specific values. Furthermore, physicians extracting the data will not retain a decoding key so that the data cannot be linked back to an individual. Lastly, the identity of physicians participating in this study will not be known to AG, Medefield, or Pfizer.

De-identified data collected from the physicians by the physician panel vendor will be transferred to AG over a secured and encrypted network for analysis, and stored in secure servers accessible only by designated personnel working on the project within AG. The minimum retention time will meet the strictest standard applicable for the study, as dictated by the applicable guidelines or applicable laws or regulations.

8.7. Data Analysis

8.7.1. Analysis of Physician and Patient Characteristics

Baseline patient demographic and clinical characteristics will be summarized overall and by type of IO therapy given in combination with axitinib. In addition, physician characteristics will be described. Continuous variables will be summarized with mean (± standard deviation [SD]) and median (interquartile range [IQR]) values, while categorical variables will be summarized with frequency distributions.

8.7.2. Analysis of AEs

Type and seriousness of AEs will be tabulated and described using frequency and proportions, separately by type of therapy (ie, type of IO therapy given in combination with axitinib). In addition, the proportion of patients who experienced repeated AEs of the same type will be summarized overall and by type of AE. For each type and seriousness of AE, time from index date to onset of AEs will be summarized using means (± SD) and medians (IQR). Furthermore, the time between the first AE and the first repeated AE of the same type will be calculated.

8.7.3. Description of Management Strategies for AEs

Among patients with advanced RCC who developed AEs while receiving axitinib/IO combination therapy, descriptive analyses will be conducted to characterize management strategies used for AEs including repeated AEs of the same type, overall and by type and seriousness of the AEs. Frequencies and proportions will be used to describe the various management strategies related to axitinib and other therapies (eg, IO agents). The proportion of patients using multiple management strategies will also be described. Among patients whose AEs were managed with axitinib dose reduction, the average dose reduction will be described using the absolute and percentage change. Duration of treatment interruption will be summarized using means (± SD) and medians (IQR).

8.7.4. Analysis of Resolution of AEs

The proportion of patients achieving resolution of AEs will be described, overall and by type and seriousness of the AEs. The time to resolution from AE onset and from initiation of management strategy will be calculated for all AEs experienced including repeated AEs. The time to resolution of AE (from the onset of AE and from the initiation of management strategies) will be separately estimated using Kaplan-Meier analysis; median time to event will be reported. Analyses will be conducted separately by type of management strategy.

8.8. Quality Control

Data quality processes will occur at multiple times during the study.

Data collection consistency checks: During the data collection phase, the eCRF will include automatic consistency checks such as date validation rules and checks to prevent entry of values outside of an expected range.

Documentation and diagnostics applied to computer code development: The primary programmer at AG will be responsible for creating and documenting all project-specific code, including comments as to why changes are made over the course of the project. In addition to evaluating diagnostic output independently, the programmer will evaluate this output with the entire project team before results tables are generated.

Independent code review: A second programmer will be assigned to a project for the purpose of performing code review. The code review programmer will work with the primary programmer to confirm that code is written with correct syntax and generates results as specified in the analysis plan. Issues identified by the code reviewer will be documented and resolved.

Validation of study results: AG will validate the results tables to confirm that results are consistent across analysis tables and that the results make sense from a "real-world" perspective. Specifically, the AG team will closely review and audit all results tables for accuracy. Moreover, AG will check to make sure that all results are aligned with expectations and findings from the literature.

Peer review of final deliverables: In addition to the AG study team reviewing all final reports before delivery, an internal, peer reviewer will also be assigned to evaluate final products. This peer reviewer will examine the final results and reports to ensure concordance among all final documents as well as to evaluate content for consistency.

8.9. Limitations of the Research Methods

Several limitations should be considered when interpreting findings from this study.

- There is potential for measurement error in data collection, and the use of a standardized, pilot-tested eCRF with data validation checks will address this to some extent. Overall, the quality of data is limited by how well information was recorded in the patients' medical charts.

- To protect physician and patient anonymity, the collected data cannot be audited against medical records and queries on the accuracy of data entries cannot be conducted. Erroneous data entries can be detected by checking inconsistent responses, but may result in the inability to use certain data points.

- There may be missing information if data have not been recorded in a systematic manner by physicians over time; collecting information on physician characteristics can help understand if missingness is related to physician practice. In addition, AEs never reported to a physician (ie, if they were self-resolved without seeking care), or events not recorded or misclassified in the medical charts, will not be captured. As such, the proportion of management strategies for AEs would only apply to AEs that require healthcare intervention.

- The study is subject to self-reporting bias, including social desirability bias. To minimize the potential for this bias, study materials will emphasize that participation in the survey is anonymous.

- This study is subject to potential selection bias as physicians who elect to participate may differ from those who decline to participate. Demographic and practice characteristics will be presented to describe the sample of physicians enrolled in this study and may be compared to national reports describing similar physician characteristics (eg, Kantar healthcare reports) to provide insight into the generalizability of results.

Despite these limitations, retrospective chart review studies using a panel-based approach are less resource-intensive than prospective cohort studies, allowing for the creation of detailed datasets with information on patient characteristics tailored to specific research questions. Using a physician panel provides direct insight into patient medical history and clinical course, and allows the possibility of supplementing data with physician knowledge when information is not well recorded in patient charts.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

This is a retrospective medical records review study where data collected will be strictly de-identified and will not be traceable back to individual subjects. No subject identifiers will be requested in this study in order to protect subject interests. In addition, the study is double-blinded (physicians will be blinded to study sponsor and study sponsor will be blinded on physicians recruited to participate). Therefore, it will not be possible to identify the patient or physician from the data used for this study.

Only de-identified 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),[24] the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines,[25] and with the ethical principles laid down in the Declaration of Helsinki.

9.1. Patient Information and Consent

The study will be conducted entirely using retrospective medical records. Informed consent is not expected to be required in this study as the data collected does not contain personal identifiers.

9.2. Patient Withdrawal

Not applicable.

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

AG will submit all required materials, including the protocol and the CRF to a central Institutional Review Board (IRB), and make any requested changes to obtain final IRB approval prior to commencement of data collection.

9.4. Ethical Conduct of the Study

This 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 Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is not classified as a PASS because no new safety information will be found due to also the small sample size, as specified on page 15, compared to the overall number of patients treated in the USA (approximately 28,000) with axitinib monotherapy or in combination with IOs.

This study requires physicians participating in the study to review patient-level medical charts, which include 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. Physicians who review medical charts are obligated to report AEs with explicit attribution to any Pfizer drug(s) 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.

Reporting of safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety will be the responsibility of individual physicians, and the requirements are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be 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 medical charts 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.

Following the completion of data collection, Medefield will provide AG with a data export. Within 24 hours of receiving the data export, AG will prepare a line listing of all serious and non-serious AEs associated with Pfizer products as reported by physicians in the eCRF to be forwarded to Pfizer. Since data collected in the study will be strictly de-identified and will not be traceable back to individual subjects or participating physicians, not all demographic fields will be available. However, at least one physician identifier (eg, qualifications) and at least one patient identifier (eg, gender, age) will be provided as a part of the line listing, thus allowing it to be considered valid in accordance with pharmacovigilance legislation. Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” will be documented in month/year (mm/yyyy) format.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Assuming Pfizer protocol approval by October 2020, the final study report will be completed and is estimated to be available in July 2021.

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.

12. REFERENCES

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13. LIST OF FIGURES

Figure 1. Study Design Scheme 9

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.