NONINTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-world treatment patterns and outcomes of patients with advanced renal cell carcinoma (aRCC) treated with first-line (1L) axitinib + pembrolizumab therapy
Protocol number	A4061101
Protocol version identifier	V2.0
Date	10 June 2024
EU Post Authorization Study (PAS) register number	EUPAS1000000104
Active substance	Axitinib and pembrolizumab PF-01367866
Medicinal product	Axitinib (Inlyta)
Research question and objectives	**Research question:** What are the real-world treatment patterns, outcomes, and characteristics of patients with aRCC who are treated with 1L axitinib + pembrolizumab therapy? **Primary objectives** 1. To describe patient-level treatment patterns and sequences of therapy after initiation of 1L axitinib + pembrolizumab therapy among patients with aRCC, including: a. Rationale for treatment initiation and discontinuation b. Dose modifications c. Duration of treatment d. Time to next treatment e. Frequency of therapy modifications/discontinuations **Secondary objectives** 1. To describe the demographic and clinical characteristics among patients with aRCC treated with 1L axitinib + pembrolizumab therapy 2. To assess physicians' perceptions of treatment management approaches for aRCC via administration of a provider survey, including: a. Factors influencing the selection of initial therapy for aRCC b. Treatment management approaches

	Exploratory objectives 1. To describe real-world clinical outcomes among study patients with aRCC treated with 1L axitinib + pembrolizumab therapy, including: a. Real-world overall response rate b. Real-world progression-free survival c. Real-world overall survival
Country of Study	United States of America
Author	[redacted]

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L, 2L, 5L	first-line, second-line, fifth-line (therapy)
AE	adverse event
AEM	adverse event monitoring
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
aRCC	advanced renal cell carcinoma
axi + pembro	axitinib and pembrolizumab
BMI	body mass index
CBC	complete blood count
CCI	Charlson Comorbidity Index
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CSA	clinical study agreement
CTCAE	Common Terminology Criteria for Adverse Events
DCT	data collection tool
DOD	Department of Defense
DOR	duration of response
DOT	duration of therapy
EC	Ethics committee
eCRF	electronic case report form
EHR	electronic health record
EMR	electronic medical record
ER	emergency room
FDA	United States Food and Drug Administration
GPO	group purchasing organization
GPP	Good Pharmacoepidemiology Practice
HCP	healthcare professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
I-O	immunotherapy
IMDC	International Metastatic Renal-Cell Carcinoma Database Consortium
IQR	interquartile range
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
KM	Kaplan-Meier
KPS	Karnofsky performance status

Abbreviation	Definition
LOT	line of therapy
NCI	National Cancer Institute
NIS	non-interventional study
OPEN	Oncology Provider Extended Network
ORR	overall response rate
OS	overall survival
PASS	Post-Authorization Safety Study
PD	progressive disease
PD-1	programmed cell death – 1 protein
PFS	progression-free survival
PH	proportional hazards
PHI	protected health information
PR	partial response
PS	performance status
QA	quality assessment
QC	quality control
RCC	renal cell carcinoma
RW	real-world
RWD	real-world data
rwDOR	real-world duration of response
rwDOT	real-world duration of therapy
rwORR	real-world overall response rate
rwOS	real-world overall survival
rwPFS	real-world progression free survival
rwTFI	real-world treatment-free interval
rwTTNT	real-world time to next treatment
rwTTR	real-world time to treatment response
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TFI	treatment-free interval
TKI	tyrosine kinase inhibitor
TT	targeted therapy
TTR	time to initial response
VEGFR	vascular endothelial growth factor receptor
UAT	user acceptance testing
US	United States
YRR	Your Reporting Responsibility

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Research Team Members

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Title

Real-world treatment patterns and outcomes of patients with advanced renal cell carcinoma (aRCC) treated with first-line (1L) axitinib + pembrolizumab therapy

Version 2

Lead author: [redacted]

Rationale and background

Combination therapy using axitinib plus pembrolizumab (axi+pembro) is a standard of care in the first-line treatment of patients with advanced renal cell carcinoma (aRCC). Axitinib (Inlyta®), a Pfizer product, was first approved by the US Food and Drug Administration (FDA) in January 2012, and subsequent FDA approval of 1L axi+pembro for aRCC in 2019 was based on results of the KEYNOTE-426 phase 3 trial, which showed benefit in both overall survival and median progression-free survival. In an extended follow-up of the trial, potential treatment-related adverse events led to one-fifth (20%) of patients discontinuing axitinib treatment and nearly two-thirds (62%) requiring treatment interruption. A better understanding of treatment patterns, therapy management, and outcomes of patients with aRCC treated with 1L axi+pembro in the real-world setting may inform strategies to optimize treatment duration and potentially improve clinical outcomes.

Research question and objectives

Research Question: What are the real-world treatment patterns, outcomes, and characteristics of study patients with clear cell aRCC who are treated with 1L axitinib + pembrolizumab therapy?

Primary objectives:

1. To describe patient-level treatment patterns and sequences of therapy after initiation of 1L axitinib + pembrolizumab therapy among patients with clear cell aRCC, including:
    a. Rationale for treatment initiation and discontinuation
    b. Dose modifications
    c. Duration of treatment
    d. Time to next treatment
    e. Frequency of therapy modifications/discontinuations

Secondary objectives:

1. To describe the demographic and clinical characteristics among study patients with clear cell aRCC treated with 1L axitinib + pembrolizumab therapy

2. To assess physicians' perceptions of treatment management approaches for aRCC via administration of a provider survey, including:
    a. Factors influencing the selection of initial therapy for aRCC
    b. Treatment management approaches

Exploratory objectives:

1. To describe real-world clinical outcomes among study patients with clear cell aRCC treated with 1L axitinib + pembrolizumab therapy, including:
    a. Real-world overall response rate
    b. Real-world progression-free survival
    c. Real-world overall survival

Study design

This is a cohort study that includes a cross-sectional physician survey and a retrospective, multi-site, oncology community-based, medical chart abstraction of patients with clear cell aRCC treated with 1L axitinib + pembrolizumab therapy. Cardinal Health will recruit physicians to participate in the study through a proprietary network of community oncologists. Primary data will be collected from participating physicians, who will be asked to complete a one-time survey on treatment management approaches for aRCC. Participating physicians will then be asked to complete electronic case report (eCRF) forms for patients meeting the study selection criteria based on their existing medical records. All patient-level data are secondary data that will be collected retrospectively from existing medical records originally collected as part of routine care by participating providers.

Population

Providers from Cardinal Health Oncology Provider Extended Network (OPEN) in the United States (US) will be eligible to participate in the study if they have treated at least 5 aRCC patients in the past year, are able to participate in research monitored/approved by a centralized independent institutional review board (IRB), and agree to participate in data quality assurance (QA)/quality control (QC) procedures. For the retrospective chart abstraction, patients meeting the eligibility criteria will be identified by oncologists in OPEN. These patients will be adults diagnosed with aRCC who initiated axitinib + pembrolizumab as 1L treatment and have at least six months of follow-up data after initiation of index therapy.

Variables

Exposure: Receipt of axitinib + pembrolizumab as 1L therapy

Primary outcomes: Treatment patterns (duration of treatment, rationale for treatment discontinuation, treatments received beyond 1L axi+pembro); treatment management (dose holds, dose modifications, etc.)

Secondary outcomes: Demographic and clinical characteristics; physicians' perceptions of treatment management approaches for aRCC

Exploratory outcomes: Real-world overall response rate, real-world progression-free survival, real-world overall survival

Key covariates: Physician characteristics (practice location, practice size/setting, years in practice, medical specialty), age at diagnosis, International Metastatic RCC Database Consortium (IMDC) risk score, Eastern Cooperative Oncology Group Performance Status

Data sources

Primary data on physicians' treatment management approaches will be collected via a one-time physician survey. Retrospective patient data will be abstracted and entered into an electronic case report form by patients' treating physicians or another physician in that patient's treating practice within the oncology network. The source documents are the patient chart/medical record data housed within the electronic health records (EHRs) and accessed by the participating providers.

Study size

This study aims to collect information from at least 30 providers and data abstracted from the medical charts of N=300 total patients with clear cell aRCC who received 1L axitinib + pembrolizumab therapy.

Data analysis

This is a descriptive analysis of physician survey data a patient-level data, and no formal hypotheses are specified a priori. Counts and frequencies will be used to describe dichotomous and categorical variables and measures of central tendency (mean, median) and spread (minimum, maximum, standard deviation [SD], interquartile range [IQR], as appropriate) for continuous variables. The Kaplan-Meier method will be used for time-to-event estimates, accounting for right-censoring. All statistical analyses will be conducted using Statistical Analysis Software (SAS v. 9.4).

Milestones

Milestone	Planned date
Completion of feasibility assessment	19 October 2022
Start of data collection	30 July 2024
End of data collection	26 August 2024
Registration in the HMA-EMA Catalogues of RWD studies register	18 July 2024
Final study report	31 January 2025

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	10 June 2024	Substantial	Section 9.1 Study Design Section 9.7 Data Analysis	Protocol revised to indicate that study is one-way blinded. The Sponsor (Pfizer) will be blinded to the identity of participating physicians but physicians will not be blinded to the identity of the Sponsor.	Study team decision to alter study design.
2.0	10 June 2024	Administrative	Abstract Section 6. Milestones	Protocol milestones updated to reflect study delays.	Changes to study design have resulted in study delays.

6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	19 October 2022
Start of data collection	30 July 2024
End of data collection	26 August 2024
Completion of data QC/validation	9 September 2024
Completion of data analysis	19 November 2024
Registration in the HMA-EMA Catalogues of RWD studies register	18 July 2024
Final study report	31 January 2025

7. RATIONALE AND BACKGROUND

In the United States (US), an estimated 81,800 people are diagnosed with and 14,890 die from kidney cancer each year, the vast majority of which are renal cell carcinoma (RCC) (Siegel, Miller, Wagle, & Jemal, 2023). RCC, which originates in the renal cortex, is more common in males than females and is most frequently diagnosed between age 60 to 70 years (Bahadoram et al., 2022). While mortality is high, overall survival for renal cancer has improved in recent years with 5-year survival rates at 93% for localized disease, 74% for regional disease, and 17% for distant disease (Surveillance Research Program, 2023). It is estimated that up to 30% of RCC cases are metastatic at time of diagnosis and among those with early-stage RCC, 20 to 50% will progress to metastatic stage IV (Padala et al., 2020).

Historically negligible response rates have been reported for the treatment of advanced or metastatic RCC (aRCC) with chemotherapy or hormone therapy. The treatment landscape for aRCC has shifted due to recent advancements in targeted therapies (TTs), including immunotherapies (I-Os) and tyrosine kinase inhibitors (TKIs). Most aRCCs are highly vascularized and overexpress multiple growth factors, which led to the development of the TKI targeted agents against vascular endothelial growth factor receptor (VEGFR). For more than a decade beginning with sunitinib (2006), pazopanib (2009), and then axitinib (2011), single agent TKIs were the standard of care (SOC) treatment approach for aRCC. In 2018, the FDA approved the combination of nivolumab and ipilimumab, both I-O drugs, for treatment of aRCC based on results from the CheckMate-214 trial, which demonstrated significant improvements in overall survival (OS) and objective response rate (ORR) compared to sunitinib alone (Motzer et al., 2018). Nevertheless, many patients continued to have progressive disease, therefore further studies explored the efficacy of VEGFR inhibitors (e.g., axitinib) combined with immune checkpoint inhibitors.

In April 2019, the programmed cell death 1 protein (PD-1) checkpoint inhibitor pembrolizumab, a type of I-O therapy, in combination with axitinib was the first TKI+I-O combination approved by the FDA for first-line (1L) treatment of aRCC patients. The

approval was based on findings from the phase III KEYNOTE-426 trial that found a 23.6% higher ORR and a significantly longer median progression-free survival (PFS; 15.1 months vs. 11.1 months) in the axitinib + pembrolizumab combination arm compared with the sunitinib monotherapy arm (Rini et al., 2019). Axitinib + pembrolizumab is approved as 1L treatment regardless of patient risk score.

While axitinib + pembrolizumab combination therapy has been shown to improve clinical outcomes for aRCC compared to sunitinib, several studies have also identified treatment-related adverse events. In the extended follow-up to the Phase 3 KEYNOTE 426 trial, which demonstrated sustained clinical benefit for axitinib + pembrolizumab compared to single agent sunitinib in both OS and PFS, treatment-related adverse events led to approximately one fifth of the patients discontinuing axitinib + pembrolizumab and almost two-thirds having treatment interruptions (Powles et al., 2020). More recently, a real-world (RW) electronic health record (EHR) based study found that among patients with aRCC who initiated axitinib + pembrolizumab as 1L treatment, approximately 83% of the study population experienced therapy management (e.g., dose hold, dose change or discontinuation) with toxicity of therapy as the most cited reason for each type of therapy management (Zakharia et al., 2022).

To date, few RW studies of treatment patterns and outcomes for patients with aRCC treated with 1L axitinib + pembrolizumab have been published. Limited information is also available on the clinical characteristics (e.g., tumor features) in a RW setting, including on clear cell RCC, the most common RCC subtype accounting for approximately 75% of RCC diagnoses (Padala et al., 2020). It is expected that this study, while similar to the study by Zakharia et al. (2022), will be able to contribute to the overall understanding of the RW treatment and safety landscape for patients with aRCC on 1L axitinib + pembrolizumab. This study aims to describe physician treatment management strategies in general, as well as on a patient-specific level, occurrence and management of potential adverse events, and detailed clinical characteristics not previously examined. These RW data and RW evidence can be used to inform treatment strategies for 1L axitinib + pembrolizumab and, ultimately, improve outcomes among patients with aRCC.

This noninterventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Question

What are the real-world treatment patterns, outcomes, and characteristics of patients with clear cell aRCC who are treated with 1L axitinib + pembrolizumab therapy?

8.2. Study objectives

This study seeks to meet the following objectives among patients with confirmed clear cell advanced or metastatic RCC who were treated with 1L axitinib + pembrolizumab therapy:

8.2.1. Primary objectives

1. To describe patient-level treatment patterns and sequences of therapy after initiation of 1L axitinib + pembrolizumab therapy among patients with clear cell aRCC, including:
    a. Rationale for treatment initiation and discontinuation
    b. Dose modifications
    c. Duration of treatment
    d. Time to next treatment
    e. Frequency of therapy modifications/discontinuations

8.2.2. Secondary objectives

1. To describe the demographic and clinical characteristics among patients with clear cell aRCC 1L axitinib + pembrolizumab therapy
2. To assess physicians' perceptions of treatment management approaches for aRCC via administration of a provider survey, including:
    a. Factors influencing the selection of axitinib + pembrolizumab as 1L therapy for aRCC
    b. Treatment management approaches

8.2.3. Exploratory objectives

1. To describe real-world clinical outcomes among patients with clear cell aRCC treated with 1L axitinib + pembrolizumab therapy, including:
    a. Real-world overall response rate
    b. Real-world progression-free survival
    c. Real-world overall survival

9. RESEARCH METHODS

9.1. Study Design

This is a non-interventional, observational cohort study based on a cross-sectional physician survey as well as a retrospective medical chart review. Cardinal Health will recruit oncologists within the Cardinal Health Oncology Provider Extended Network (OPEN) in the United States (US) to participate in the study. A study invitation will be emailed to potential participants within OPEN that includes physician and patient eligibility criteria for the study. A link will also be included in the study invitation that physicians will use to access and

complete an AE training (see **Section 11**), after which physicians will be directed to the study electronic case report form (eCRF). For the study eCRF, physicians will first complete a one-time physician survey that includes questions about physician/practice characteristics, questions to confirm physician eligibility, survey questions about treatment management approaches for aRCC (see below, Primary data collection-Physician Survey), and a link to review the study consulting agreement. Eligible physicians will then complete patient-level chart abstraction (see below, Secondary Data Collection – Patient-Level Chart Abstraction).

Primary Data Collection – Physician Survey

Primary data will be collected from participating physicians, who will first be asked to complete a one-time survey on treatment management approaches for aRCC. Providers will be asked to indicate factors influencing aRCC treatment selection and to describe relevant additional data-related needs. Providers who report AEs as the rationale for dose modifications or treatment discontinuations will be prompted to answer follow-up questions on details regarding AE management. The survey will be completed once per provider prior to the patient-level, retrospective, chart-based data collection.

Secondary Data Collection – Patient-Level Chart Abstraction

Participating physicians will then be asked to identify patients that meet the inclusion criteria of this study per documented information in their electronic medical records (EMRs), including notes, reports, scans, and other chart documentation. After the providers respond to questions regarding the eligibility of each patient chart in an electronic case report form (eCRF), de-identified, patient-level data for this study will then be abstracted from eligible patient EMRs into the eCRF. All patient-level data are secondary data that will be collected retrospectively from existing medical records originally collected as part of routine care by participating providers.

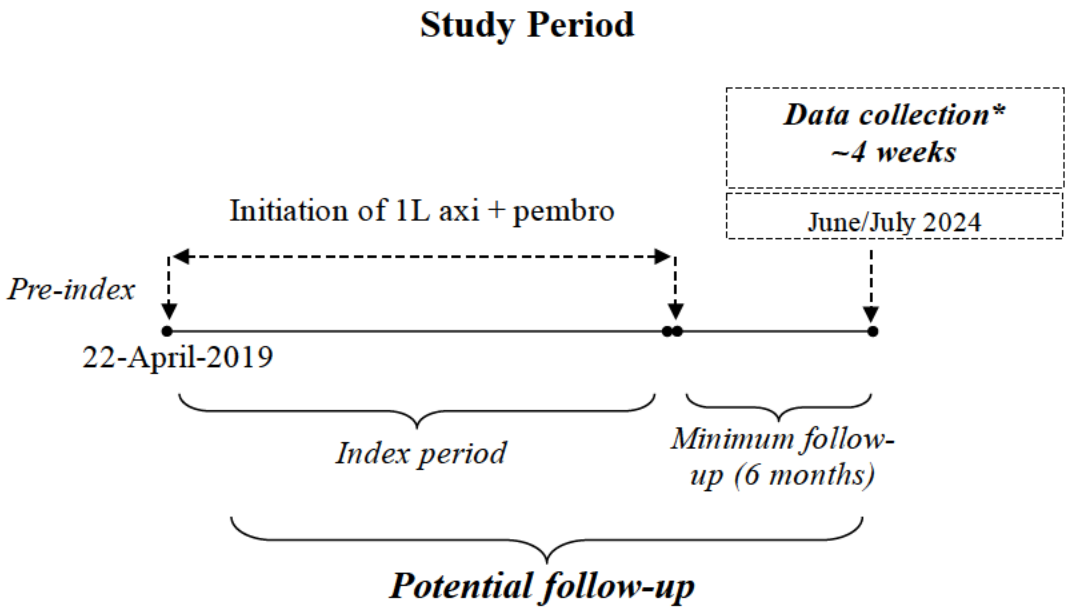
The eCRF will be used to capture de-identified information about demographic and baseline clinical characteristics, therapy modifications/discontinuations, treatment patterns, and clinical outcomes of patients with clear cell aRCC who received 1L axitinib + pembrolizumab therapy. Data points to be captured include baseline clinical characteristics (eg, diagnosis dates, stage, risk scores, performance status, and comorbidities), treatment patterns (e.g., regimens received, date(s) of treatment initiation/discontinuation, reason for treatment initiation/discontinuation, dose modifications), including therapy modifications (e.g., cause, date of onset, management, and severity if applicable). Additional outcome-related variables to be collected include tumor response, progression, and date of death (if applicable). Exploratory clinical outcomes of interest that will be calculated include real-world overall response rate, progression-free survival, and overall survival. The study index date is the date of 1L axitinib + pembrolizumab therapy initiation (i.e., date patient was started actively receiving both drugs). The index date must occur between 22 April 2019 and 6 months before the start of data collection. These data will be abstracted from the patients' EMRs into the eCRF relation to the time points as shown in Figure 1.

Providers will complete the eCRF one time per patient, and the total follow-up time per patient will vary based on the date that the provider completes the eCRF. However, all

patients will be required to have been followed for a minimum of 6 months, unless deceased, following initiation of 1L axitinib + pembrolizumab therapy. The sample size target for the retrospective chart-based study is N=300 patients. The Sponsor will be blinded to the identity of the participating physicians. In the case of an audit, participating physician IDs may be shared with the study Sponsor.

All assessments described in this protocol are collected as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this noninterventional study is being conducted.

Figure 1. Study period



* Estimated dates based on projected completion of project milestones prior to eCRF release to physicians.

Notes: Follow-up may be less than 6 months if the patient died within 6 months of initiating 1L axitinib + pembrolizumab.

9.2. Setting

Patients meeting the eligibility criteria will be identified by oncologists from the Cardinal Health Oncology Provider Extended Network (OPEN) in the US who are the patients' treating providers or work in the patient's treating practice. OPEN is a community of over 7,000 group purchasing organization (GPO) agnostic oncologists, hematologists, and urologists from across the US, with varying levels of time in practice, from practices both within and outside of group purchasing organizations. The database represents approximately 39% of physicians providing oncology subspecialty patient care (based on an estimated 18,000 providers). Providers are contracted with directly after attendance at Cardinal Health Oncology Summits (internal research conducted with 70-100 providers 7-10 times per year) or if they or their practice use Cardinal Health point of care claims remittance management

software. As such, physician participation in the proposed research is under an agreement between the physician and Cardinal Health. Providers practice predominantly in community practices (>75%), ranging in size from solo practitioners to physicians practicing in hospital systems; all are able to participate in research monitored by a central Institutional Review Board (IRB). In the last 5 years more than 1,500 unique providers in OPEN have completed over 30,000 individual eCRFs. Because OPEN is a provider-level (as opposed to site-based) network, Cardinal Health can obtain large, representative samples of patients and collect detailed clinical data from the clinicians treating the patients of interest. No protected health information (PHI) beyond dates of diagnosis, treatments, and outcomes will be collected.

After IRB approval of the research protocol, the physician survey and eCRF will be pre-tested with 4 providers. Data collected as part of the pre-test will not be used in the final analytic dataset. After testing and revisions (if necessary), providers from OPEN will be contacted and asked to participate in the research. Providers who participated in the prior related feasibility survey and who reported having treated potentially eligible patients will be invited to participate in this study. These providers volunteered to participate in the feasibility survey after receiving invitations to participate that were sent out to a subset (approximately 800) of Cardinal Health's OPEN providers. Additional physicians from the OPEN may also be recruited to achieve the targeted patient numbers. Recruited providers who volunteer to participate in this study will confirm their own eligibility for the provider survey as well as identify patients meeting the study selection criteria through a series of screener questions. Additionally, these physicians will provide an estimate of their total eligible patient population.

Data collection will be conducted over the course of 4 weeks.

Primary Data Collection

For primary data collection on treatment management approaches, participating physicians will be asked to complete a one-time survey on factors influencing aRCC treatment selection, their approach to therapy management, and relevant additional data-related needs. The survey will be completed once per provider as part of the patient-level, retrospective, chart-based data collection. A waiver of obtaining physician consent will be sought for the study given the minimal risk imposed by the data elements to be collected.

Secondary Data Collection

For secondary data collection, providers will submit a maximum of 10 eCRFs each (the maximum number of eCRFs per provider may be increased, if necessary, to achieve target patient numbers following pre-approval from Pfizer). Physicians will be asked to identify all eligible patients, report the total number of eligible patients, and chronologically select consecutive eligible patients, starting with the earliest eligible. The source documents are the patient chart/medical record data housed within the EHRs and accessed by the participating providers. Providers will be compensated through honoraria payment for each completed and validated eCRF. A waiver of obtaining patient consent will be sought for the study.

The study population includes adults diagnosed with aRCC who received combination 1L axitinib + pembrolizumab therapy with at least 6 months of follow up data available after initiation of index therapy. Patients who died during the 6-month follow-up period would remain eligible for inclusion.

9.2.1. Patient --WI-Inclusion Criteria - Secondary Data Collection

Patients must meet all the following inclusion criteria to be eligible for inclusion in the patient-level chart abstraction study:

1. Patients with a confirmed diagnosis of clear cell aRCC (stage IV)
2. Patients who initiated 1L axitinib + pembrolizumab therapy for clear cell aRCC on or after 22 April 2019 and at least 6 months prior to initiation of data collection
3. Patients ≥18 years of age at time of initiation of 1L axitinib + pembrolizumab therapy for clear cell aRCC
4. A minimum of 6 months follow-up since initiation with 1L axitinib + pembrolizumab therapy for clear cell aRCC*
   *Patients who died during this interval would still be eligible.

9.2.2. Patient Exclusion Criteria - Secondary Data Collection

Patients meeting any of the following criteria will not be included in the patient-level chart abstraction study:

1. Patients who received axitinib or pembrolizumab for aRCC as part of a clinical trial
2. Patients who had any additional active malignancy in the 3 years prior to initiation of 1L therapy for aRCC
3. Patients who received systemic therapy prior to 1L axitinib + pembrolizumab therapy, including immunotherapy or TKI therapy*
   *Note: Patients who received systemic therapy in an adjuvant setting are not eligible for this study.

9.2.3. Provider qualifications for participation in the physician survey study and abstraction of patient-level chart data are:

- Treated a minimum of five aRCC patients in the past year
- Able to participate in research monitored/approved by a centralized independent institutional review board (IRB)
- Agreement to participate in data quality assurance (QA)/quality control (QC) procedures

9.3. Variables

Primary Data Collection – Physician Survey

The following de-identified provider-level variables/data elements will be collected from physician surveys. Variable names/topics and roles will not show up as part of provider surveys. Table 1 represents data elements of interest that may be captured as part of the final data collection tool (DCT). Table 2 represents additional data elements that will be captured if providers select AEs as the rationale for dose modification or treatment discontinuation. Survey questions, response options, and display logic will be finalized during the development of the eCRF.

Table 1. Physician survey variables – characteristics and treatment management approaches for secondary objective

Variable	Operational definition	Role	Data Source
Physician practice type/size	- Solo practitioner - Small private community practice (2-5 physicians) - Small private community practice (2-5 physicians) owned by a hospital - Medium-sized private community practice (6-10 physicians) - Medium-sized private community practice (6-10 physicians) owned by a hospital - Large private community practice (>10 physicians) - Large private community practice (>10 physicians) owned by a hospital - Community practice owned by an academic center - Academic medical center - Affiliated teaching hospital - VA/military hospital/Department of Defense (DOD) - Other	Baseline characteristic	Physician reported
US region of practice	- Northeast (CT, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT) - Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI) - South (AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV) - West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)	Baseline characteristic	Physician reported

Table 1. Physician survey variables – characteristics and treatment management approaches for secondary objective

Variable	Operational definition	Role	Data Source
Setting of practice	- Urban - Suburban - Rural	Baseline characteristic	Physician reported
Years in practice	Open-ended numeric; 1-99	Baseline characteristic	Physician reported
Medical specialty	- Medical Oncology - Urology - Other	Baseline characteristic	Physician reported
Estimated patient caseload with aRCC and those treated with 1L axitinib + pembrolizumab therapy in the past year	Open-ended numeric; 1-250	Baseline characteristic	Physician reported
Treatment selection	Please rank the top 3 factors that influence your choice of using axitinib + pembrolizumab for 1L treatment of aRCC: - Overall survival - Progression free survival - Complete response - Overall response rate - Safety profile - Quality of life - Number of contraindications - Trial follow-up time - Treatment free interval - Practice reimbursement - Patient out-of-pocket cost - Patient preference - Patient compliance	Outcome	Physician reported
Dose modification or treatment discontinuation	Please select factor(s), other than completion of scheduled treatment duration or death, that influence dose modifications and/or treatment discontinuations for axitinib + pembrolizumab for 1L	Outcome	Physician reported

Table 1. Physician survey variables – characteristics and treatment management approaches for secondary objective

Variable	Operational definition	Role	Data Source
	treatment of aRCC [multiple select]: • Disease progression • Patient request to stop treatment • Adverse events • Financial factors • Other		

Table 2. Follow-up questions for providers who list AEs as rationale for dose modifications or treatment discontinuation (Physician Survey)

Variable	Operational Definition	Role	Data Source
AE management tools	What tools are available at your practice for AE management? • Published guidelines (e.g., IO Essentials Care Step Pathway; ASCO Guidelines for Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy) • Laboratory testing (e.g., liver enzyme tests, CBC, renal function [e.g., creatinine], stool culture) • Multispecialty consultation (e.g., consult with nephrology) • Other [please specify]	Outcome	Physician reported
Most concerning AEs	Based on the known safety profile of the regimen, what are the top 5	Outcome	Physician reported

Table 2. Follow-up questions for providers who list AEs as rationale for dose modifications or treatment discontinuation (Physician Survey)

Variable	Operational Definition	Role	Data Source
	most concerning AEs you encounter during your practice? • Diarrhea • Fatigue/asthenia • Hypertension • Hepatotoxicity • Hypothyroidism • Decreased appetite • Palmar-plantar erythrodysesthesia • Nausea • Stomatitis/mucosal inflammation • Dysphonia • Rash • Cough • Constipation		
AE Etiology	What tool(s) do you use to distinguish AE etiology for patients treated with 1L axitinib + pembrolizumab (e.g., AE is axitinib-related vs. immune-related)[multiple select]? • Interruption of axitinib treatment • Laboratory tests • Resolution of AE with corticosteroids • Other [please specify]		Physician reported
AE-related treatment changes by severity	For the following AEs (separately by grade), which treatment changes (if any) would you typically make? Grades: 1-2 or 3-4 AEs: • Diarrhea		Physician reported

Table 2. Follow-up questions for providers who list AEs as rationale for dose modifications or treatment discontinuation (Physician Survey)

Variable	Operational Definition	Role	Data Source
	• Fatigue/asthenia • Hypertension • Hepatotoxicity • Hypothyroidism • Decreased appetite • Palmar-plantar erythrodysesthesia • Nausea • Stomatitis/mucosal inflammation • Dysphonia • Rash • Cough • Constipation Treatment Change Options: • Continuation (no change) • Dose reduction of axitinib • Treatment interruption of axitinib • Treatment interruption of pembrolizumab • Treatment interruption of both axitinib + pembrolizumab • Discontinuation of axitinib • Discontinuation of pembrolizumab • Discontinuation of both axitinib + pembrolizumab		
Factors informing treatment change vs. discontinuation decisions	If a patient experiences an AE of moderate severity while being treated for aRCC with axitinib + pembrolizumab, what factor(s) are the most influential in your decision to modify 1L axitinib + pembrolizumab therapy (e.g., axitinib dose modification, treatment interruption versus		Physician reported

Table 2. Follow-up questions for providers who list AEs as rationale for dose modifications or treatment discontinuation (Physician Survey)

Variable	Operational Definition	Role	Data Source
	discontinue therapy) (multiple select) 1. Patient performance status 2. Patient comorbidities 3. Patient compliance 4. Patient preference 5. Availability of suitable subsequent line of therapy (LOT) 6. Type of AE 7. Probability the AE will fully resolve 8. First-time AE vs. recurrent AE 9. Disease response prior to AE 10. Other [please specify]		

Secondary Data Collection Variables – Chart Abstraction

The following de-identified patient-level variables/data elements will be collected from patient medical records via the eCRF by their treating providers or another physician in the patient's treating practice. Variable names/topics and roles will not show up as part of chart abstraction. Table 3-Table 7 represent data elements of interest that may be captured as part of the final DCT and Table 8 includes the definition of endpoints/outcomes calculated from the collected data. Survey questions, response options, and display logic will be finalized during the development of the eCRF. Note that the data elements included in Table 6 will only be captured if providers report AEs as the rationale for dose modification or treatment discontinuation.

Table 3. Patient demographic characteristics for secondary objective

Variable	Operational definition	Role	Data Source
Year of birth	Patient's four-digit year of birth	Baseline characteristic	Patient medical records
Sex	Patient's sex assigned at birth: - Male - Female	Baseline characteristic	Patient medical records

Table 3. Patient demographic characteristics for secondary objective

Variable	Operational definition	Role	Data Source
Ethnicity	Patient's ethnicity: - Hispanic or Latino - Not Hispanic or Latino - Unknown	Baseline characteristic	Patient medical records
Race	Patient's race, with option to select multiple races: - American Indian or Alaska Native - Asian - Black or African-American - Native Hawaiian or Other Pacific Islander - White - Unknown	Baseline characteristic	Patient medical records
Region	Patient's region of residence: - Northeast (CT, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT) - Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI) - South (AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV) - West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)	Baseline characteristic	Patient medical records
Insurance	Patient's most recent primary insurance: - Medicare - Medicaid - Commercial - Military - Self-pay - Unknown - Other	Baseline characteristic	Patient medical records
Height	Patient's height	Baseline characteristic	Patient medical records
Weight	Patient's weight	Baseline characteristic	Patient medical records

Table 3. Patient demographic characteristics for secondary objective

Variable	Operational definition	Role	Data Source
Body mass index (BMI)	Physician-reported BMI	Baseline characteristic	Patient medical records or calculated using height and weight

Table 4. Patient clinical characteristics for secondary objective

Variable	Operational definition	Role	Data Source
Date of initial RCC diagnosis	Physician-reported date of patient's initial RCC diagnosis	Baseline characteristic	Patient medical records
Date of advanced or metastatic RCC diagnosis	Physician-reported date of patient's aRCC diagnosis	Baseline characteristic	Patient medical records
Stage at initial diagnosis	Patient's stage based on the AJCC TNM staging system at initial diagnosis of RCC • Stage I • Stage II • Stage III • Stage IV	Baseline characteristic	Patient medical records
Grade of tumor differentiation at or prior to initiation of 1L axitinib + pembrolizumab therapy	Grade 1- well differentiated Grade 2- moderately differentiated Grade 3- poor differentiated Grade 4- undifferentiated	Baseline characteristic	Patient medical records
Sarcomatoid Features	• Presence of sarcomatoid features (yes/no)	Baseline characteristic	Patient medical records
Number and location of metastatic sites	Number and sites of metastases at initiation of 1L axitinib + pembrolizumab therapy for aRCC • Number of metastases (open-ended numeric) • All sites where metastatic disease was detected	Baseline characteristic	Patient medical records

Table 4. Patient clinical characteristics for secondary objective

Variable	Operational definition	Role	Data Source
	including: adrenal gland, bone, brain, local lymph node(s), regional/distal lymph node(s), skin/soft tissue, gastrointestinal system, genitourinary system, ovary, gynecologic system (excluding ovary), liver, lung, pleura/pericardial/peritoneal cavity, other (multiple select)		
International Metastatic RCC Database Consortium (IMDC) risk score	Patients' most recent IMDC risk score at or prior to initiation of 1L axitinib + pembrolizumab therapy: - Favorable risk - Intermediate risk - Poor risk - Unknown	Baseline characteristic	Patient medical records
Eastern Cooperative Oncology Group performance status (ECOG-PS)	Patient's most recent known ECOG-PS at or in the 90 days prior to the initiation of 1L axitinib + pembrolizumab therapy and at or in the 90 days prior to initiation of 2L therapy as applicable: - 0 – Fully active; no restriction - 1 – Restricted in strenuous physical activities; fully ambulatory and able to carry out light work. - 2 – Capable of all self-care but unable to carry out any work activities; up and about >50 percent of waking hours. - 3 – Capable of only limited self-care; confined to bed or chair >50 percent of waking hours. - 4 – Completely disabled; could not carry out any self-care; totally confined to bed or chair. - Unknown	Baseline characteristic	Patient medical records

Table 4. Patient clinical characteristics for secondary objective

Variable	Operational definition	Role	Data Source
Karnofsky Performance Status (KPS)	If ECOG-PS is unknown, patient's most recent known KPS at or in the 90 days prior to the initiation of 1L axitinib + pembrolizumab therapy and at or in the 90 days prior to the initiation of 2L therapy as applicable: - 100 – Normal; no complaints; no evidence of disease - 90 – Able to carry on normal activity; minor signs or symptoms of disease - 80 – Normal activity with effort; some sign or symptoms of disease - 70 – Cares for self; unable to carry on normal activity or do active work - 60 – Requires occasional assistance - 50 – Requires considerable assistance - 40 – Disabled, requires special assistance - 30 – Severely disabled - 20 – Very sick, requires active supportive treatment - 10 – Moribund - Unknown	Baseline characteristic	Patient medical records
Comorbid conditions	Comorbidities/chronic conditions present at the initiation of 1L axitinib + pembrolizumab therapy, with option to select multiple conditions, including: • Acquired immunodeficiency syndrome (AIDS)/Human immunodeficiency virus (HIV) • Hepatitis B • Hepatitis C	Baseline characteristic	Patient medical records

Table 4. Patient clinical characteristics for secondary objective

Variable	Operational definition	Role	Data Source
	• Cerebrovascular disease • Chronic obstructive pulmonary disease (COPD) • Coronary artery disease • Congestive heart failure • Dementia • Diabetes with or without complications • Liver disease – mild, moderate or severe • Myocardial infarction – history • Myocardial infarction - acute • Paralysis – hemiplegia or paraplegia • Peptic ulcer disease • Peripheral vascular disease • Renal disease (specify if chronic kidney disease [CKD] and if so, CKD stage) • Rheumatologic disease • Other [please specify] • None of the above		
NCI Comorbidity Index score	National Cancer Institute (NCI) version of the Charlson Comorbidity Index (CCI) as calculated with patient's most recent available comorbidities data in the 90 days prior to or on the 1L index date	Baseline characteristic	Patient medical records
History of prior treatments (surgery, radiation, etc)	Type of treatment for RCC patient received prior to initiation of 1L axitinib + pembrolizumab therapy including surgery, radiation, none	Baseline characteristic	Patient medical records
Surgery for RCC received	Type(s) and date(s) of surgical resection patient received among those who received surgery for RCC prior to initiation of 1L	Baseline characteristic	Patient medical records

Table 4. Patient clinical characteristics for secondary objective

Variable	Operational definition	Role	Data Source
	axitinib + pembrolizumab therapy including radical nephrectomy, partial nephrectomy, cytoreductive surgery, or tumor ablation (radiofrequency/cryo)		

Table 5. Treatment pattern-related variables for primary objective

Variable	Operational definition	Role	Data Source
Treatment regimen or drugs received for aRCC after 1L axitinib + pembrolizumab therapy	Treatment(s) received following index (1L) treatment regimen (when applicable, up to 5 LOT) until data cut-off/end of follow-up. Subsequent treatments captured may include approved systemic treatments for aRCC.	Outcome	Patient medical records
Radiation therapy during 1L axitinib + pembrolizumab therapy	Receipt of radiation therapy during 1L axitinib + pembrolizumab therapy (yes/no/unknown). If yes, specify date of first dose and site(s) of radiation therapy (primary renal mass, bone, lung, liver, lymph nodes, brain, other metastatic site)	Outcome	Patient medical records
Date(s) of treatment initiation and discontinuation	Dates of treatment initiation and discontinuation (when applicable) for index 1L axitinib + pembrolizumab treatment*, and subsequent treatment(s) (up to 5 LOT, when applicable) received. The initiation date of axitinib + pembrolizumab therapy will be the index date for this study.	Outcome	Patient medical records

Table 5. Treatment pattern-related variables for primary objective

Variable	Operational definition	Role	Data Source
	*Allow for differing dates of discontinuation for axitinib and pembrolizumab.		
Rationale for treatment discontinuation	Reason(s) for discontinuing index/subsequent treatment (up to 5 LOT): • Scheduled duration of treatment complete • Disease progression • Patient request to stop treatment • Financial factors • AEs • Death • Other *Allow for separate answers for axitinib and pembrolizumab	Outcome	Physician reported
Rationale for **NOT** initiating a LOT post-1L axitinib + pembrolizumab	Reason for **not** treating patient with a subsequent LOT after discontinuation of 1L axitinib + pembrolizumab therapy, including: • Death • Patient choice • Financial factors • Poor drug availability • Other [please specify]		Physician reported
Rationale for treatment selection	Reason for selection of index and subsequent treatments including but not limited to disease progression, metastasis, other	Outcome	Physician reported
Initial dose/schedule of 1L therapy	Dosage and frequency/schedule of administration of 1L axitinib +	Outcome	Patient medical records

Table 5. Treatment pattern-related variables for primary objective

Variable	Operational definition	Role	Data Source
	pembrolizumab therapy at initiation.		
Dose modifications for axitinib during 1L therapy	Type and number of dose modifications for axitinib during 1L treatment including dose delayed/interrupted, dose increased, or dose reduced (multiple select; up to 5 dose modifications).	Outcome	Patient medical records
Dose interruptions for pembrolizumab during 1L therapy	Number of dose interruptions/delays for pembrolizumab during 1L treatment	Outcome	Patient medical records
Rationale for dose modification during 1L therapy	Rationale for each dose modification for 1L axitinib and/or pembrolizumab (i.e., dose delayed/interrupted, dose increased, or dose reduced) including*: - Aggressive disease - Cost benefit to patient - Patient performance status - Patient comorbidities - To improve patient compliance - To improve patient tolerance - To increase efficacy/patient response - To follow recommended dosing guidelines - To titrate before eventual discontinuation - AE(s) - To return to original dose after resolution of AE - Other	Outcome	Physician reported

Table 5. Treatment pattern-related variables for primary objective

Variable	Operational definition	Role	Data Source
	*Allow for separate answers for axitinib and pembrolizumab		
Date of dose modification during 1L axitinib + pembrolizumab therapy	The date of each dose modification of each type of modification (i.e., dose delayed/interrupted, dose increased, or dose reduced)* *Allow for different dates for axitinib and pembrolizumab	Outcome	Patient medical records
Length of treatment interruption	For reported dose delays/interruptions, length of treatment interruption (days)	Outcome	Patient medical records
Dose/schedule at the end of 1L axitinib + pembrolizumab therapy	Patients' dose and frequency/schedule at the end of 1L axitinib + pembrolizumab therapy, or most recent dose if patient is still on therapy* *Allow for separate answers for axitinib and pembrolizumab	Outcome	Patient medical records
Date of death	Date following the index date on which patient was determined to have deceased	Outcome	Patient medical records
Cause of death	Patients cause of death • Disease progression, toxicity related to treatment, Covid-19 related, unknown/not available, other	Outcome	Patient medical records
Date of last follow-up visit	The most recent date the abstracting physician has information on the patient, which can include date of clinician visit, lab or radiology visit, phone call, and/or electronic communication	Outcome	Patient medical records

Table 5. Treatment pattern-related variables for primary objective

Variable	Operational definition	Role	Data Source
Disposition at data cut-off/end of follow-up	Patient disposition at data cut-off/end of follow-up, which can include alive and in remission not receiving active treatment for aRCC, alive with measurable disease but not receiving active treatment for aRCC, alive and receiving active treatment for aRCC, alive and receiving best supportive care only, deceased, unknown/lost to follow-up, other	Outcome	Patient medical records

Table 6. Follow-up questions for providers who report AEs as rationale for dose modification or treatment discontinuation (Chart Abstraction)

Variable	Operational definition	Role	Data Source
AE type	For each reported AE-associated therapy modification or discontinuation previously reported, the associated AE that occurred during 1L index axitinib + pembrolizumab therapy, including: • Diarrhea • Hypertension • Fatigue • Decreased appetite • Nausea • Dysphonia • Palmar-plantar • Erythrodysesthesia (hand-foot) syndrome • Weight decreased • Vomiting • Asthenia • Constipation • Other	Outcome	Patient medical records

Table 6. Follow-up questions for providers who report AEs as rationale for dose modification or treatment discontinuation (Chart Abstraction)

Variable	Operational definition	Role	Data Source
Date of AE occurrence	For each AE-associated therapy modification or discontinuation previously reported, the date the associated AE(s) occurred	Outcome	Patient medical records
Highest grade of AE	The highest grade (Grade 1, 2, 3, 4, 5, unknown) of each AE type reported to have caused a therapy modification or discontinuation based on common terminology criteria for adverse events (CTCAE)	Outcome	Patient medical records
Cause of AE	Cause of each AE reported to have resulted in a therapy modification or discontinuation during 1L axitinib + pembrolizumab therapy, if available • All-cause, treatment-related* * If treatment-related, follow-up question on whether AE was axitinib-related, pembrolizumab-related, or unknown.	Outcome	Patient medical records
Treatment/care of each AE	Type of treatment/care received for each AE occurrence reported to have resulted in a therapy modification or discontinuation during 1L index axitinib + pembrolizumab therapy including: - Hospitalization, Emergency Room (ER) admission, steroid use, supportive care only (e.g., management using anti-emetics, anti-diarrheals, anti-hypertensives, or topical treatments), no treatment, other, unknown	Outcome	Patient medical records
Type of supportive care received for AE	Among those who received supportive care for AEs resulting in therapy modifications or discontinuation during 1L index axitinib + pembrolizumab therapy, the type of care received including anti-emetics, anti-diarrheals, anti-hypertensives, corticosteroids, or topical treatments	Outcome	Patient medical records

Table 6. Follow-up questions for providers who report AEs as rationale for dose modification or treatment discontinuation (Chart Abstraction)

Variable	Operational definition	Role	Data Source
AE resolution	Whether the AE during 1L index axitinib + pembrolizumab therapy that resulted in a therapy modification resolved or improved (yes/no) and date of resolution/improvement	Outcome	Patient medical records
AEs with explicit attribution to a Pfizer product during study period	Fields to capture date and verbatim record of adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider [by the healthcare professional (HCP) who ORIGINALLY wrote the note/piece of unstructured data in the medical chart of the patient's reviewed data] linking drug administration to the AE. These data are collected to comply with CT24-WI-GL02-RF02B Version 5.0.	Compliance with CT24-WI-GL02-RF02B Version 5.0 Safety Reporting Language Secondary Data Collection Study Includes Protocol Required Human Review of Unstructured Data.	Patient medical records

Table 7. Clinical outcome-related variables for exploratory objective

Best response to 1L axitinib + pembrolizumab therapy	The best response to 1L axitinib + pembrolizumab therapy as charted in the medical (Complete response [CR], partial response [PR], stable disease, progressive disease, not assessed, unknown), and date of scan used to assess best response to treatment	Outcome
Progression during or following 1L axitinib + pembrolizumab therapy	Did patient experience progression during or following 1L axitinib + pembrolizumab therapy (yes/no), method of assessment (chart-based, scan-based, other), and the date of first progression during or following 1L axitinib + pembrolizumab therapy	Outcome

Table 8. Calculated endpoints/clinical outcomes for exploratory objective

Clinical Outcome	Operational definition
Duration of follow-up	Time from date of initiation of 1L axitinib + pembrolizumab therapy to date of last follow-up (calculated arithmetically)
Time from aRCC diagnosis to initiation of 1L axitinib + pembrolizumab therapy	Time from date of aRCC diagnosis to date of 1L index axitinib + pembrolizumab therapy initiation (months)
Real–world duration of treatment (rwDOT)	Time from initiation of line of therapy to discontinuation of line of therapy for any reason. To be calculated both arithmetically and via KM method. For KM analysis, patients will be censored on the last office visit with the provider during the respective line of therapy if still receiving therapy. For combination therapies, DOT will be calculated for each individual therapy only and both therapies (time to discontinuation of first therapy and last therapy).
Real-world overall response rate (rwORR)	Number of patients with CR or PR during 1L axitinib + pembrolizumab therapy over total number of patients with treatment response assessed during 1L index axitinib + pembrolizumab therapy
Time to response	Among patients with a documented response (CR or PR), time from initiation of 1L index axitinib + pembrolizumab therapy to best physician-reported response (CR or PR)
Real-world duration of response (rwDOR)	Time from physician-reported best response during 1L axitinib + pembrolizumab therapy to physician-reported disease progression or death. To be calculated both arithmetically and via KM method among patients with a documented response (CR or PR). For KM analysis, patients who did not progress or die will be censored at the start date of next line or date of last encounter, whichever comes first
Real-world treatment-free interval (rwTFI)	Time from discontinuation of line of therapy until initiation of subsequent therapy (up to 5L)
Real-world time to next treatment (rwTTNT)	Time between the initiation of line of therapy and next subsequent treatment. Patients who do not

Table 8. Calculated endpoints/clinical outcomes for exploratory objective

Clinical Outcome	Operational definition
	receive subsequent treatment will be censored at the date of last encounter or date of death.
Number of AEs associated with therapy modifications/discontinuation	Number of AEs reported per patient that were associated with a therapy modification or discontinuation.
Frequency of reported AEs (if applicable)*	Frequency of AE occurrence during 1L index axitinib + pembrolizumab therapy overall that resulted in a therapy modification or discontinuation
Recurrence of AE associated with therapy modifications/discontinuation	Among patients with a reported AE, total number of episodes of the same AE type that resulted in separate therapy modifications/discontinuation while on 1L index axitinib + pembrolizumab therapy
Time from 1L axitinib + pembrolizumab initiation to first AE occurrence associated with a therapy modification/discontinuation*	Among those who experienced at least 1 AE associated with a therapy modification/discontinuation: time from date of 1L index axitinib + pembrolizumab initiation to the date of first reported AE occurrence associated with a therapy modification/discontinuation (months)
Time from 1L axitinib + pembrolizumab initiation to first severe AE occurrence associated with a therapy modification/discontinuation *	Among those who experienced at least one severe AE (Grade 3+) associated with a therapy modification/discontinuation: time from date of 1L index axitinib + pembrolizumab initiation to the date of first reported severe AE occurrence associated with a therapy modification or therapy discontinuation (months)
Time from 1L axitinib + pembrolizumab initiation to first AE occurrence associated with a therapy modification*	Among those who experienced at least one AE associated with a therapy modification/discontinuation: time from date of 1L index axitinib + pembrolizumab initiation to the date of first reported AE occurrence associated with a therapy modification (months)
Time from 1L axitinib + pembrolizumab initiation to first AE occurrence associated with therapy discontinuation*	Among those who experienced at least one AE associated with a therapy modification/discontinuation: time from date of 1L index axitinib + pembrolizumab initiation to the

Table 8. Calculated endpoints/clinical outcomes for exploratory objective

Clinical Outcome	Operational definition
	date of first reported AE occurrence associated with therapy discontinuation (months)
Time from 1L axitinib + pembrolizumab initiation to first treatment change	Among those who experienced at least one treatment change (reduction, increase, interruption): time from date of 1L index axitinib + pembrolizumab initiation to date of first reported dose modification (months)
Time to AE resolution (if applicable)*	Time from date of AE onset to date of documented AE resolution/improvement (days) per each modification/discontinuation-associated AE occurrence during 1L index axitinib + pembrolizumab therapy
Real-world progression-free survival (rwPFS)	Time from initiation of 1L axitinib + pembrolizumab therapy to charted disease progression or death from any cause, whichever occurs first. Patient still receiving index therapy at last encounter will be censored on date of last encounter. Patients who discontinue index therapy without date of progression/date will be censored on date of discontinuation. rwPFS will be calculated using several definitions of discontinuation (i.e., discontinuation of axitinib; discontinuation of pembrolizumab; discontinuation of both).
Real-world overall survival (rwOS)	Time from 1L index axitinib + pembrolizumab therapy initiation and the date of death (event). Patients still alive at the end of follow-up/study end date will be censored on the date of last encounter. Median and survival point estimates will be calculated from the KM curve. If median survival cannot be estimated (e.g., median has not been reached due to data immaturity/high rate of censoring), the KM method will be used to estimate survival point estimates at 3, 6, 12, 18, and 24 months from treatment initiation as appropriate

*Only captured if providers list AEs as rationale for dose modification or treatment discontinuation and complete subsequent AE-related follow-up questions (Table 5).

9.4. Data Sources

Primary Data – Physician Survey
Primary data on physicians' treatment management approaches will be collected via a one-time physician survey as part of the patient-level, retrospective, chart-based data collection. Based on the study objectives, a preliminary outline of key variables and datapoints to be collected by the physician survey is included in Section 9.3 above.

Secondary Data – Chart Abstraction
For secondary data collection, patient data will be abstracted and entered into an eCRF by physicians within the OPEN. The source documents are the patient chart/medical record data housed within the EHRs and accessed by the participating providers. Data abstracted into the eCRFs must match those charts.

Through the chart review approach, data elements contained in unstructured fields of the EHR (e.g., clinical progress notes, radiographic scans/reports, pathology reports) or those elements requiring a provider's interpretation (e.g., date of progression) can be collected. The eCRF is a custom data abstraction tool allowing the provider chart abstractor to input de-identified data directly from the patient EHR into a secure, web-based platform. The data elements that can be collected are limited by the length of time required for the participating provider to conduct the data abstraction, which may vary depending upon the complexity of data elements required and the patient's health record. Based on the study objectives, a preliminary outline of key variables and datapoints to be abstracted into the eCRF by participating physicians is included in Section 9.3 above.

No source document verification can be conducted by Cardinal Health; however, data QC, QA, and validation processes will be performed as described. These processes and systems are vetted during field testing with volunteer physicians, as described in Section 9.8.

9.5. Study Size

This is a descriptive analysis of cross-sectional provider survey data and retrospective provider- and patient-level data. Given the descriptive nature, no hypotheses are specified a priori, and no formal hypothesis testing will be performed.

In a feasibility assessment conducted by Cardinal Health in October 2022 with physicians in Cardinal Health's OPEN network, 40 physicians, who had experience personally treating/managing patients with RCC, estimated that a total of 1,576 patients with RCC were treated/managed in their practice in the past 3 years (mean: 39.4 patients per provider; range: 5-102).

- Among the 1,576 patients with RCC that were treated/managed in their practice in the past 3 years, 1,057 (67%) patients were diagnosed with advanced/metastatic disease (mean: 26.4 patients per provider; range: 4-50).
  Among the 1,057 patients that have been treated/managed in their practice with aRCC in the past 3 years, 459 (43%) were treated with combination axitinib and I-O therapy (Mean: 11.8 patients per provider; Range: 1-35).

Primary Data – Physician Survey
This study aims to collect information from at least N=30 providers who have treated at least 5 patients with aRCC in the past year and currently are treating at least one with 1L axitinib + pembrolizumab. Cardinal Health has performed prior research and feasibility assessments that support our capabilities to conduct this physician survey study through the OPEN and achieve the proposed research objectives and sample size.

Secondary Data – Patient-Level Chart Abstraction Study
This study aims to collect data abstracted from the medical charts of N=300 total patients with aRCC who received 1L axitinib + pembrolizumab therapy. The sample size target of 300 patients for the chart-review was determined considering the objectives of the research, prior feasibility assessment (as described above), anticipated provider recruitment, and the method of chart data abstraction. Additionally, Cardinal Health has performed prior research and feasibility assessments that support our capabilities to conduct this chart review study through the OPEN and achieve the proposed research objectives and sample size.

Considering the targeted sample size for the chart review study (N=300), the 95% confidence intervals (CIs) around point estimates of binary event probabilities based on various subgroup sizes are shown below. Any statistical comparisons will be exploratory; however, it is important to consider the precision and face validity of estimates in smaller populations or proportions. Table 9 provides the precision levels for point estimates by sample size calculated via normal approximation and the Fleiss method, where appropriate.

Table 9. 95% CIs for point estimates by sample size

Probability of event	95% Confidence Interval (CI) *Sample Size*						
	N=30	N=50	N=75	N=100	N=150	N=200	N=300
5%	0.6%-21.3%	1.1%-16.2%	1.5%-13.4%	1.9%-11.8%	1.2%-8.8%	1.7%-8.3%	2.4%-7.6%
20%	4.0%-36.0%	7.9%-32.1%	10.3%-29.7%	11.7%-28.3%	13.3%-26.7%	14.2%-25.8%	15.3%-24.7%
30%	11.9%-48.1%	16.3%-43.7%	19.0%-41.0%	20.5%-39.5%	22.3%-37.7%	23.4%-36.6%	24.6%-35.4%
40%	20.8%-59.2%	25.4%-54.6%	28.2%-51.8%	29.9%-50.1%	31.8%-48.2%	33.0%-47.0%	34.3%-45.7%
50%	30.4%-69.6%	35.1%-64.9%	38.0%-62.0%	39.7%-60.3%	41.7%-58.3%	42.8%-57.2%	44.2%-55.8%

9.6. Data Management

Primary & Secondary Data
Provider survey (primary) and patient-level (secondary) data are entered by the provider into the eCRF, a custom data abstraction tool for capturing deidentified patient-level data directly into a secure, web-based survey platform (Qualtrics). The eCRF structure and format are designed to allow providers to efficiently move through the EHR while documenting the patient journey throughout the course of disease. The eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of PHI. Limited and necessary to achieve study

objectives PHI (e.g., start and end of treatment dates, date of death) will be collected in the course of the chart review or stored in the eCRF.

The Cardinal Health research team is responsible for the programming, testing, and hosting of data from submitted eCRFs, and all data are stored on encrypted, password-protected, and HIPAA-compliant servers housed within the Cardinal Health electronic data storage infrastructure.
Participating physicians will be asked to complete the chart review individually, meaning that site research staff or support staff will not complete any data abstraction. Physicians are instructed to consult all available sources and indicate whether data points have been substantiated by source materials in the EHR. The study variables that can be collected are limited to those that can be captured within the allotted 45 to 60 minutes.

Following protocol finalization, a text version of the CRF will be created, and once finalized, an eCRF will be programmed in Qualtrics. Variables are captured in numeric and text format, as appropriate, and grouped according to the study objectives as described in the protocol. The Qualtrics interface used for data entry and management provides screens for data entry and includes study-specific programming checks to help control data quality, consistency, and validity. No source document verification can be conducted by Cardinal Health; however, data QC, QA, and validation processes will be performed as described. The raw data entered into Qualtrics will be vetted through QA, QC, and validation procedures as described in Section 9.8, and a Cardinal Health analyst will export them into SAS v9.4 for data transformation and analysis, which will be used for all manipulations of data. Pfizer will not have access to the individual data collected.

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

Primary Data Collection

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

A completed CRF is required for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. Cardinal Health shall ensure that the CRFs are securely stored in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Cardinal Health has ultimate responsibility for the collection and reporting of all data entered on the CRFs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRF serves as the source document. Any corrections to entries made in the CRFs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Secondary Data Collection

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

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

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Cardinal Health and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

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

9.6.2. Record Retention

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

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

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study unless Cardinal Health and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

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

9.7. Data Analysis

This study is an observational cohort study of cross-sectional provider and retrospective provider-abstracted patient -level data. Given the observational nature, no hypotheses are specified *a priori,* and no formal hypothesis testing will be performed. Study results will be reported in aggregate overall (i.e., across the entire study population) and for subgroups of interest depending on sample size. All respondent data will be de-identified, and physicians and patients will remain anonymous to Pfizer, and vice-versa. All data processing and analysis will be performed in SAS v9.4.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Analysis plan for primary objectives

Secondary Data – Patient-Level Chart-Abstracted Data

The primary objectives of this study are descriptive and aim to describe and summarize among patients with aRCC who received 1L axitinib + pembrolizumab therapy (1) treatment patterns and sequences of 1L axitinib + pembrolizumab therapy and beyond (e.g., regimens received, rationale for treatment initiation/discontinuation, dose modifications, duration of treatment, time to next treatment) and (2) patient-level real-world treatment management of 1L axitinib + pembrolizumab therapy. Results for these objectives will be reported via descriptive analyses; frequencies and proportions will be used for dichotomous and categorical variables, and measures of centrality (mean, median) and spread (min, max, standard deviation, interquartile range, as appropriate) will be used for continuous variables. Treatment patterns, including regimens received, rationale for treatment initiation/discontinuation, and duration of treatment will be reported by line of therapy. Dose modification results will be reported for 1L axi+pembro only. Estimated incidence of AEs experienced during index therapy that resulted in a therapy modification or discontinuation will be descriptively summarized (overall) as the frequency of occurrence among all patients on axitinib + pembrolizumab therapy, if applicable.

Analysis plan for secondary/exploratory objectives

Primary Data – Physician Survey

Secondary objective 3 aims to characterize physician perceptions and treatment management approaches using the provider survey. These results will be reported via descriptive analyses as counts and frequencies for dichotomous and categorical variables and as measures of centrality (mean, median) and spread (min, max, SD, IQR, as appropriate) for continuous variables.

Secondary Data – Patient-Level Chart Abstraction

Secondary objective 1 aims to describe patient demographic and clinical characteristics based on chart review. These results will be reported via descriptive analyses as counts and

frequencies for dichotomous and categorical variables and as measures of centrality (mean, median) and spread (min, max, SD, IQR, as appropriate) for continuous variables.

Exploratory analyses will consist of describing real-world clinical outcomes including real-world overall response rate (rwORR), time to treatment response (rwTTR), duration of response (rwDOR), treatment-free interval (rwTFI), time to next treatment (rwTTNT), progression-free survival (rwPFS) and overall survival (rwOS). The rwORR, rwTTR, and rwDOR variables will be based on the reported dates of radiographic studies made during therapy. No independent blinded review of radiologic studies will be conducted. Clinical outcomes will be described arithmetically and time to event outcomes will be calculated using the KM method to allow for right-censoring. The KM method will be used to generate estimates of median time to event and associated 95% CIs; unadjusted comparisons in median time to event across cohorts will be made by log-rank tests. If median survival cannot be estimated (e.g., median has not been reached due to data immaturity/high rate of censoring), the KM method will be used to estimate survival point estimates at 3, 6, 12, 18, and 24 months from treatment initiation as appropriate.

Subgroups will be identified following the completion of data collection and data validation. Potential analysis groups of interest may include, but are not limited to, medical specialty of abstracting physician, patient race/ethnicity, patient risk assessment at baseline, severity of AE, AE type, or type of 1L axi+pembro dose modification. Additional subgroups may be identified upon completion of data collection and analysis and selection of subgroups for analyses will be dependent on adequate sample size.

9.8. Quality Control

Cardinal Health will be responsible for the programming, testing, and hosting of data from submitted CRFs. Testing includes ensuring functionality across web-based user environments, looping logic to ensure proper alignment of data-related fields (required responses to certain fields prior to entering data into subsequent field), and other programmatic checks to reduce input of erroneous data (such as specifying maximums for year of birth or initiation of index treatment within the dates of the enrollment period).

In addition, the eCRF will be field-tested with 4 providers to ensure its functionality, the correct interpretation of the questions in relation to the data points of interest, and the proper length of time for completion of data abstraction on a single patient. The pre-test results will be reviewed by Cardinal Health with Pfizer. No data from the pre-testing phase will be used in the current study. Additionally, prior to data collection (during the field test and actual study launch), Cardinal Health will complete the previously described user acceptance testing (UAT), inputting various clinical scenarios and identifying function edit checks and checks that are required to be made manually post-data collection. Results of the UAT will be included in the data QC log. Any changes made to the CRF document as a result of the pre-test will require the resubmission of the CRF and study protocol to the IRB.

Participating providers are informed in their contractual agreement that follow-up with Cardinal Health may be required and are contacted for query resolution and/or data validation as needed. For medical queries and random data validation, providers will be

asked to create a 4-digit unique identifier for each patient, which will be transmitted to Cardinal Health and used for identifying the patient record for data validation. Data will be reviewed by a licensed HCP employee of Cardinal Health to identify medical queries. Data will be further reviewed by an analyst and scientist to check for face validity of aggregate results (e.g., statistical outliers; eCRF completion in an unexpectedly short time; treatment regimens unknown to be used for the disease under study; individual provider responses compared with aggregate responses; laboratory, pathology, and radiology results inconsistent with known clinical parameters; other clinical data inconsistent with known standards and outcomes; and distribution and content of key variables needed for analysis). Issues flagged for potential data validation will be resolved with the providers directly on a case-by-case basis. Any eCRF flagged during QC will be reviewed by the team to determine the level of follow-up needed. Individual eCRFs that cannot be validated will be removed from the dataset, and the respective provider will not be compensated for the eCRF that is removed.

Random data validation occurs by selecting a random eCRF from each provider submitting a patient. Providers subjected to random validation are asked to complete a 3 data point-validation exercise for the patient, whereby the provider is given the unique patient identifier but no other information. The provider is then asked to re-enter the data elements. The 3 data points may include: month/year of treatment initiation, stage at diagnosis, and date of treatment discontinuation (or date of last treatment/prescription if patient is still on therapy). Providers who had been previously verified by Cardinal Health will not be subject to random validation. A verified provider is any physician abstractor who has completed at least 2 of the following: (1) completed and acknowledged Cardinal Health web-based chart data abstraction training in the past 2 years, (2) participated in a chart review pre-test with screen sharing, (3) participated in two previous chart review studies in the past 2 years and accurately validated data, and (4) completed a phone interview with the Cardinal Health team for data validation. Despite a provider having been verified, however, he or she will still be required to answer questions regarding patients with data flagged by the research operations or research analytics teams. A provider who fails to validate all data points for a selected patient will be required to submit to further clinical data review. No resampling to replace any excluded eCRF will be conducted.

After completion of QC/QA reviews and for all completed eCRFs, the study database will be locked, and all data will be downloaded and stored on a secured server housed within the Cardinal Health Information Technology infrastructure. Analyses for all research objectives will be performed at that time.

9.9. Limitations of the Research Methods

Strengths

The extensive Cardinal Health network of oncologists/hematologists is geographically diverse, EHR/GPO-agnostic, and inclusive of multiple settings of community oncology care, thus lending external validity and representativeness of the data. Retrospective medical chart review provides in-depth knowledge of biomarker testing, diagnostic testing, treatment patterns, clinical outcomes, and rationale for treatment decisions using an efficient, reliable, and verifiable method. Chart review studies are therefore well suited for oncology as these clinical parameters are important to assess the patient journey, especially with the current

focus on targeted, precision, and personalized medicine. Further, data are abstracted by providers for patients under their care, ensuring high data quality as the abstractor does not have to make assumptions about data elements. The majority of physicians invited to participate in this study have undergone various training sessions with Cardinal Health staff related to abstraction of data from patients' medical charts and completion of eCRFs and are well versed with the chart abstraction process. Furthermore, selection bias in patient inclusion should be minimized because physicians will be instructed to identify all eligible patients and to select patients chronologically starting with eligible patients who initiated the index treatment the earliest within the study index period. Finally, many of the data elements of interest are often not available in structured or unstructured EHR fields, and physician-abstracted chart review allows for collection of these difficult-to-retrieve patient-level data elements. Inclusion of a cross-sectional physician survey also provides insight into real-world treatment management strategies following initiation of axitinib + pembrolizumab therapy and requiring providers to have treated at least 5 RCC patients in the past year will ensure providers have experience in the RCC-treatment space.

Limitations

As is a limitation of any observational research study, not all patient characteristics will be included in the data collection (e.g., income and other variables that may influence physician prescribing behavior or treatment decisions), thereby allowing for potential unmeasured and residual confounding that cannot be accounted for in descriptive, univariate, multivariate, or subgroup analyses.

Cardinal Health does not, and cannot, conduct source document verification. Cardinal Health requires that all physicians submit to at least 1 random data validation check during the study whereby they are asked to re-enter 3 data points regarding a patient. Physicians failing to correctly re-enter data are subject to further review, and at the discretion of Cardinal Health, may have all patient records submitted removed from the analytic dataset.

This study employs purposive sampling that selects physicians and patients based on pre-specified selection criteria and hence, this may not be representative of all patients within the cohorts of interest or representative of all physicians treating these patients. Physicians invited to participate in this study will represent a subset of OPEN physicians. Importantly, treatment patterns reflected in the study will represent only the practices of physicians who have volunteered to participate, and may vary from non-responding physicians (i.e., those who refused study participation or who did not respond to the screening invitation). No data will be available to describe non-participating providers or non-selected patients. Cardinal Health cannot verify that all patients who meet the study eligibility criteria are included in the final dataset, and participating providers will initially be limited to submitting a maximum of 10 eCRFs in an aim to minimize provider bias (this maximum number of eCRFs may be increased if necessary, to aid in recruitment following prior approval from Pfizer). However, based on estimates of eligible patients reported by physicians who participated in the short chart review study, we expect the majority of providers to manage 10 or fewer eligible patients. Although bias related to selection of patient subsets within practices may occur, physicians will be instructed to identify all eligible patients and to select patients chronologically starting with eligible patients who initiated the index treatment the

earliest within the study index period. Additionally, these data will describe outcomes only for patients, who by design, have initiated the selected, approved 1L axitinib + pembrolizumab therapy. As such and coupled with a small sample size, outcomes may not be generalizable to all patients with aRCC.

Additionally, this study may be subject to bias due to missing data. Although physicians will be required to record all relevant patient experiences in the medical charts, there may be undercounting of events that are unknown to them due to having occurred outside the office/clinical setting. Further, loss to follow-up may occur if patients transfer care to other providers or clinics. As such, treatments, visits, and outcomes occurring after the date of last visit may be missing. Further, this study involves retrospective extraction of data from medical records. Thus, the accuracy and completeness of the data collected are limited by the quality and nature of data available in the EHR and abstracted into the eCRF. Further, loss to follow-up may occur if patients transfer care to other providers or clinics. As such, treatments, visits, and outcomes occurring after the date of last visit may be missing. Additionally, the follow-up period may not be long enough to observe all disease progression events during therapy.

Finally, findings from this study may be impacted by a lack of uniform assessment timepoints or imaging criteria for certain variables such as identification of metastasis or disease progression documentation in an EMR.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

At all times, patient PHI is kept confidential in accordance with HIPAA. The eCRF will not capture any data related to the patient's name, full date of birth, social security number, health insurance plan number, medical record number, or other such PHI. However, date of disease diagnosis, date(s) of treatment(s) administered (including dates of treatment), date of development of health states of interest (e.g., disease progression), and dates of death (if available) will be collected. These items are considered PHI under HIPAA. At no time will Pfizer be provided with PHI in the form of a dataset or otherwise; all study results will be reported in aggregate. Additionally, exact dates (e.g., of dose changes) will not be reported during analysis but will be used to calculate intervals of time between relevant anchor date and end dates of interest.

10.1. Patient Information

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

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the

study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

10.2. Patient Consent

Primary Data Collection

Primary data will be reported by participating physicians via survey. Pfizer will not be responsible for ensuring that the appropriate consenting processes or consenting waivers are in place for physicians and will defer this responsibility to the vendor Cardinal Health.

Secondary Data Collection

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

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPPs), Public Policy Committee of the International Society for Pharmacoepidemiology (ISPE 2008), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Primary Data Collection

This study does not involve data collection on individual patients by their treating healthcare professionals and the physician survey used in this study does not intend to identify product safety information. The physician survey for this study will be completed online via a secure website. The physician survey does not provide a free text field where study participants

could specify information that may constitute product safety information. Further, routine communication with study participants via email or phone with the study vendor is not expected during the conduct of the study. However, it is possible that a study participant may volunteer product safety information to study vendor while in conversation about the physician survey for any other reason (e.g., seeking information about the purpose of the study); this information must be reported as described below.

The following safety events must be reported on the NIS AEM Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

For exposure during pregnancy in studies of pregnant women, data on the exposure to axitinib during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

In the event that a study participant volunteers product safety information, study vendor must complete the non-interventional study (NIS) adverse event monitoring (AEM) Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

Study vendor who will serve to be available to study participants to answer questions during study participant completion of the data collection tool must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRRs) with Supplemental Topics".*

These trainings must be completed by study vendor prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training statements to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

Secondary Data Collection

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

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

The requirements for reporting safety events on the NIS AEM Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

- For exposure during pregnancy in studies of pregnant women, data on the exposure to Pfizer product during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

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

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

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

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

- *“Your Reporting Responsibilities (YRRs) with Supplemental Topics.”*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a “Confirmation of Training Statement” (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 statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results from the final analysis may be submitted in the form of peer-reviewed publications and/or presented as an abstract or poster at scientific conferences.

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 party responsible for collecting data from the participant 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.

13. REFERENCES

1. Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. (2022). Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. *G Ital Nefrol, 39*(3). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/35819037

2. Motzer, R. J., Tannir, N. M., McDermott, D. F., Aren Frontera, O., Melichar, B., Choueiri, T. K., . . . CheckMate, I. (2018). Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med, 378*(14), 1277-1290. doi:10.1056/NEJMoa1712126

3. Padala, S. A., Barsouk, A., Thandra, K. C., Saginala, K., Mohammed, A., Vakiti, A., . . . Barsouk, A. (2020). Epidemiology of Renal Cell Carcinoma. *World J Oncol, 11*(3), 79-87. doi:10.14740/wjon1279

4. Powles, T., Plimack, E. R., Soulieres, D., Waddell, T., Stus, V., Gafanov, R., . . . Rini, B. I. (2020). Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol, 21*(12), 1563-1573. doi:10.1016/S1470-2045(20)30436-8

5. Rini, B. I., Plimack, E. R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., . . . Investigators, K.-. (2019). Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med, 380*(12), 1116-1127. doi:10.1056/NEJMoa1816714

6. Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA Cancer J Clin, 73*(1), 17-48. doi:10.3322/caac.21763

7. Surveillance Research Program, N. C. I. (2023). SEER*Explorer: An interactive website for SEER cancer statistics. Retrieved from https://seer.cancer.gov/statistics-network/explorer/. Retrieved 08/01/2023 https://seer.cancer.gov/statistics-network/explorer/

8. Zakharia, Y., Thomaidou, D., Li, B., Siu, G., Levin, R., Vlahiotis, A., . . . Zanotti, G. (2022). Real-World Therapy Management and Outcomes of First-Line Axitinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma in the United States. *Front Oncol, 12*, 861189. doi:10.3389/fonc.2022.861189

14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.