NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

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
Version identifier of the study report	1.0
Date	08 APRIL 2025
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(-ies) of study	United States of America
Author	[redacted]

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1. ABSTRACT (STAND-ALONE DOCUMENT)

Title

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

Lead author: [redacted]

Rationale and background

Combination therapy using axitinib plus pembrolizumab (axitinib + pembrolizumab) is a standard of care in the first-line treatment of patients with aRCC. Axitinib (Inlyta®), a Pfizer product, was first approved by the United States (US) Food and Drug Administration (FDA) in January 2012, and subsequent FDA approval of 1L axitinib + pembrolizumab for aRCC in 2019 was based on results of the KEYNOTE-426 phase 3 trial, which showed benefit in both overall survival (OS) and median progression-free survival (PFS).[1] In an extended follow-up of the trial, potential treatment-related adverse events led to approximately one-fifth (20%) of patients discontinuing axitinib treatment and nearly two-thirds (62%) requiring treatment interruption.[2] A better understanding of treatment patterns, therapy management, and outcomes of patients with aRCC treated with 1L axitinib + pembrolizumab 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 (rwORR)

b. Real-world progression-free survival (rwPFS)
c. Real-world overall survival (rwOS)

Study design

This was a cohort study that included 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 recruited physicians to participate in the study through a proprietary network of community oncologists. Primary data was collected from participating physicians, who were asked to complete a one-time survey on treatment management approaches for aRCC. Participating physicians were then 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 were secondary data that was 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 US were eligible to participate in the study if they had treated at least 5 aRCC patients in the past year, were able to participate in research monitored/approved by a centralized independent institutional review board (IRB), and agreed to participate in data quality assurance (QA)/quality control (QC) procedures. For the retrospective chart abstraction, patients meeting the eligibility criteria were identified by oncologists in OPEN. These patients were adults diagnosed with aRCC who initiated axitinib + pembrolizumab as 1L treatment and had 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 axitinib + pembrolizumab); treatment management (dose holds, dose modifications, etc.)

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

Exploratory outcomes: rwORR, real-world progression-free survival, rwOS

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 were collected via a one-time physician survey. Retrospective patient data were abstracted and entered into an eCRF by patients' treating physicians or another physician in that patient's treating practice within the oncology network. The source documents were the patient chart/medical record data

housed within the electronic health records (EHRs) and accessed by the participating providers.

Study size

This study collected information from 25 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 was a descriptive analysis of physician survey data and patient-level data, and no formal hypotheses were specified *a priori*. Counts and frequencies were 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 was used for time-to-event estimates, accounting for right-censoring. All statistical analyses were conducted using Statistical Analysis Software (SAS v. 9.4).

Results

Physician Survey – Secondary Objective #2

Participating physicians (N=25) practiced in predominantly community settings (4 [16.0%] in small community practices; 4 [16.0%] in medium community practices; 11 [44.0%] in large community practices) and had a median 15.0 years in practice. Adverse events (AEs) and disease progression were the factors most frequently selected by providers as influencing dose modifications and/or treatment discontinuation for 1L axitinib + pembrolizumab. For AE management, only 16 providers (64.0%) had access to multispecialty consultations and 19 (76.0%) reported using published guidelines. Hepatotoxicity (14; 66.7%) and diarrhea (12; 57.1%) were the AEs the largest number of providers selected as the most concerning AEs they encounter when using 1L axitinib + pembrolizumab for aRCC.

Patient-Level Chart Abstraction

Primary Objective #1 – Treatment Patterns

For the N=300 patients with aRCC, median time from aRCC diagnosis to initiation of 1L axitinib + pembrolizumab was 0.5 months (min-max: 0.0-8.9 months). The primary reason for choosing 1L axitinib + pembrolizumab was its status as standard of care (99.3%) with patient choice also selected for 33 (11.0%) patients. Most patients (95.0%) began 1L axitinib + pembrolizumab on the standard 5 mg orally twice daily (BID). Dose modifications in 1L axitinib + pembrolizumab were reported for 111 (37.0%) patients, with 43 (14.3%) reporting an axitinib reduction, 26 (8.7%) reporting an axitinib increase, 41 (13.7%) reporting an axitinib interruption, and 18 (6.0%) reporting a pembrolizumab interruption. Median time to first modification was 2.7 months after 1L axitinib + pembrolizumab initiation. At last follow-up, 134 patients (44.7%) had discontinued 1L axitinib + pembrolizumab, with disease progression cited as the most common reason. Median duration of therapy for 1L axitinib + pembrolizumab was 18.6 months (95% confidence interval [CI]: 17.0-21.2). At last follow-up, the majority of patients (n=210/300; 70.0%) had not received treatment beyond 1L axitinib + pembrolizumab.

Median real-world time to next treatment (rwTTNT) from 1L to second-line treatment was 22.3 months (95% CI: 20.0-25.6).

Secondary Objective #2 – Patient Demographic & Clinical Characteristics

Median follow-up from initiation of 1L axitinib + pembrolizumab for N=300 patients with aRCC was 12.3 months. The majority of patients (n=238/300; 79.3%) were alive at last follow-up, and disease progression was the most common cause of death among those who had died (n=47/62; 75.8%). The majority of patients were male (61.0%), non-Hispanic (86.7%), and White (69.3%). Most patients had either Medicare (46.7%) or commercial (41.3%) insurance. Most patients with aRCC were initially diagnosed with metastatic disease (n=210/300; 70.0%) and median age at aRCC diagnosis was 66.7 years (min-max: 35.0-90.0). Sarcomatoid features were present for 34 patients (11.3%), and IMDC risk score at initiation of 1L axitinib + pembrolizumab was 54 (18.0%) favorable, 178 (59.3%) intermediate, 65 (21.7%) poor, and 3 (1.0%) unknown. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (n=235/300; 78.3%).

Exploratory Objective #1 – Clinical Outcomes

Physician-reported real world overall response rate (rwORR) among all patients in this study was 73.7% (95% CI: 68.5%-78.8%). At last follow-up, 114 patients (38.0%) patients had experienced progression while on 1L axitinib + pembrolizumab. For patients with a response of complete or partial response (CR or PR), median duration of response was 16.6 months (95% CI: 14.3-19.1). Median real-world progression-free survival (rwPFS) was 19.5 months (95% CI: 17.3-21.3), while the estimated probability of a patient being progression-free and alive 12 months post-initiation of 1L axitinib + pembrolizumab was 0.74 (95% CI: 0.68-0.79). Median rwOS was not reached in this study. Estimated probability of survival at 12-months post-initiation of 1L axitinib + pembrolizumab was 0.85 (95% CI: 0.80-0.89).

Discussion

The majority of patients were able to start 1L axitinib + pembrolizumab at the FDA-recommended initial dose and few required axitinib dose reductions, supporting that therapy management via dose modifications of 1L axitinib + pembrolizumab may affect only a minority of patients. rwDOT and rwPFS results in this study were higher than in a real-world study on 1L axitinib + pembrolizumab using electronic medical records and KEYNOTE-426, which may be due to the relatively short follow-up and high level of censoring in the present study.[1, 3] When managing AEs that may occur during 1L axitinib + pembrolizumab, some treating physicians did not have access to resources on AE management (e.g., guidelines, multispecialty consultation), highlighting a potential opportunity for further education on treatment management. Further prospective studies with longer follow-up are needed to understand the impact of 1L axitinib + pembrolizumab treatment modification on clinical outcomes for aRCC.

Milestones

Milestone	Planned Date	Actual Date	Comments
Completion of feasibility assessment	19 October 2022	19 October 2022	

IRB approval of original protocol		23 April 2024	
IRB approval of protocol after amendment		14 June 2024	
Registration in the HMA-EMA Catalogues of RWD studies register	18 July 2024	18 July 2024	
Start of data collection	30 July 2024	31 July 2024	
End of data collection	26 August 2024	22 August 2024	
Completion of data QC/validation	9 September 2024	18 September 2024	
Completion of data analysis	19 November 2024	20 December 2024	Extended period of results review, including generation of new figure
Final study slide deck	31 January 2025	24 January 2025	

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L, 2L, 3L, 5L	first-line, second-line, third-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
BID	twice daily
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
CTCAE	Common Terminology Criteria for Adverse Events
DCT	data collection tool
DOD	Department of Defense
EBRT	external beam radiation therapy
ECOG-PS	Eastern Cooperative Oncology Group performance status
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
IEC	independent ethics committee
I-O	immunotherapy
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQR	interquartile range
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
KPS	Karnofsky performance status
LOT	line of therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIS	non-interventional study
OPEN	Oncology Provider Extended Network

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PASS	Post-Authorization Safety Study
PD-1	programmed cell death – 1 protein
PFS	progression-free survival
PHI	protected health information
PR	partial response
PVD	peripheral vascular disease
QA	quality assurance
QC	quality control
RCC	renal cell carcinoma
RFA	radiofrequency ablation
RWD	real-world data
rwDOR	real-world duration of response
rwDOT	real-world duration of treatment
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
SAbR	stereotactic ablative body radiotherapy
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TKI	tyrosine kinase inhibitor
TNM	Tumor, node, metastasis
VEGFR	vascular endothelial growth factor receptor
UAT	user acceptance testing
US	United States
YRR	Your Reporting Responsibility

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

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*Affiliation at time of study support

4. OTHER RESPONSIBLE PARTIES

Research Team Members

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

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

*Affiliation at time of study support

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Completion of feasibility assessment	19 October 2022	19 October 2022	
IRB approval of original protocol		23 April 2024	
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Final study slide deck	31 January 2025	24 January 2025	

6. RATIONALE AND BACKGROUND

In the United States (US), an estimated 81,610 people are diagnosed with and 14,390 die from kidney cancer each year, the vast majority of which are renal cell carcinoma (RCC).[4] 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.[5] While mortality is high, overall survival (OS) 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.[6] 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.[7]

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, 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 US Food and Drug Administration (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 OS and objective response rate (ORR) compared to sunitinib alone.[8] 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 significantly higher OS at 12 months (89.9% vs. 78.3%) and 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.[1]

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 III 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.[2] More recently, a real-world 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.[3]

To date, few real-world studies of treatment patterns and outcomes for patients with aRCC treated with 1L axitinib + pembrolizumab have been published. Limited information is available on the clinical characteristics (e.g., tumor features) in a real-world setting, including on clear cell RCC, the most common RCC subtype accounting for approximately 75% of RCC diagnoses.[7] This study, while similar to the EHR-based study by Zakharia et al. (2022), contributes to the overall understanding of the real-world treatment and safety landscape for patients with aRCC on 1L axitinib + pembrolizumab. This study described general physician

treatment management strategies when prescribing 1L axitinib + pembrolizumab as well as detailed patient data on treatment patterns (including therapy management), demographics, and clinical outcomes for patients who received 1L axitinib + pembrolizumab for aRCC. These real-world data and real-world evidence can be used to inform treatment strategies for 1L axitinib + pembrolizumab.

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

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research 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?

7.2. Study objectives

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

7.2.1. 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

7.2.2. 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

7.2.3. 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 (rwORR)
    b. Real-world progression-free survival (rwPFS)
    c. Real-world overall survival (rwOS)

8. AMENDMENTS AND UPDATES

Table 7.2-1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	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.

9. RESEARCH METHODS

9.1. Study design

This was a non-interventional, observational cohort study based on a cross-sectional physician survey as well as a retrospective medical chart review (final protocol found in **Appendix 2**). Cardinal Health recruited oncologists within the Cardinal Health Oncology Provider Extended Network (OPEN) in the US to participate in the study. A study invitation was emailed to potential participants within OPEN that included physician and patient eligibility criteria for the study. A link was also included in the study invitation that physicians used to access and complete an adverse event (AE) training (see **Section 10.5**), after which physicians were directed to the study electronic case report form (eCRF). For the study eCRF, physicians first completed a one-time physician survey that included 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 then completed a patient-level chart abstraction (see below, Secondary Data Collection – Patient-Level Chart Abstraction).

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

Secondary Data Collection – Patient-Level Chart Abstraction

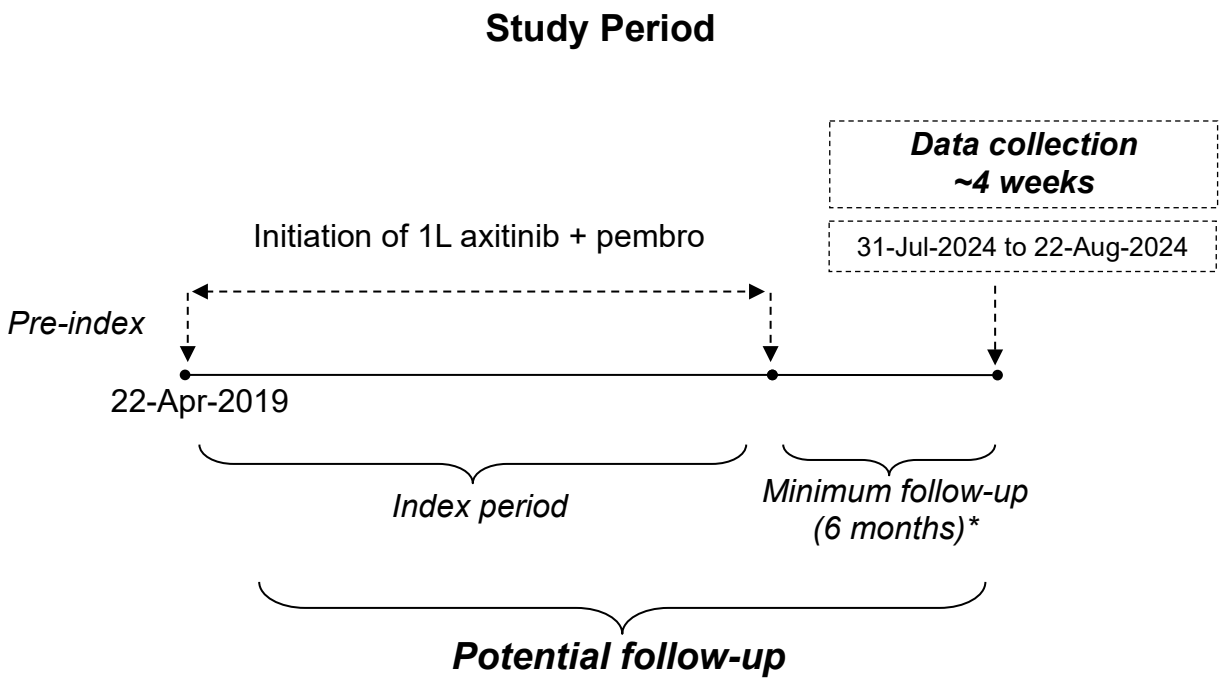
Participating physicians were asked to identify patients that meet the inclusion criteria of this study per documented information in their electronic medical records (EMRs), including notes, reports, scans, and other chart documentation. After the providers responded to questions regarding the eligibility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

The eCRF captured 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 captured included baseline clinical characteristics (e.g., 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 and details on any AEs cited as causing a therapy modification (e.g., cause, date of onset, management, and severity if applicable). Additional outcome-related variables collected were tumor response, progression, and date of death (if applicable). Exploratory clinical outcomes of interest (calculated) included rwORR, rwPFS, and rwOS. The study index date was the date of 1L axitinib + pembrolizumab therapy initiation (i.e., date patient was started actively receiving both drugs). The index date occurred between 22 April 2019 and 6 months before the start of data collection. These data were abstracted from the patients' EMRs into the eCRF relative to the time points as shown in **Figure 1.**

Providers completed the eCRF one time per patient, and the total follow-up time per patient varied based on the date that the provider completed the eCRF. However, all patients were required to have a minimum of 6 months follow-up, unless deceased, following initiation of 1L axitinib + pembrolizumab therapy. The sample size target for the retrospective chart-based study was N=300 patients. The Sponsor was 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 were 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 was being conducted.

Figure 1. Study period diagram.



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

9.2. Setting

Patients that met eligibility criteria were identified by oncologists from the Cardinal Health OPEN in the US who were the patients' treating providers or worked 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. Providers practice predominantly in community practices (>75%), ranging in size from solo practitioners to physicians practicing in hospital systems; all were able to participate in research monitored by a central institutional review board (IRB).

After IRB approval of the research protocol, the physician survey and eCRF were pre-tested with 4 providers. Data collected as part of the pre-test was not used in the final analytic dataset. After testing and revisions (if necessary), providers from OPEN were contacted and asked to participate in the research. Additionally, these physicians provided an estimate of their total eligible patient population.

Data was collected between 31 Jul 2024 and 22 Aug 2024.

Primary Data Collection

For primary data collection on treatment management approaches, participating physicians were 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 was completed once per provider prior to participating in the patient-level, retrospective, chart-based data collection. A waiver of obtaining physician consent was obtained for the study given the minimal risk imposed by the data elements to be collected.

Secondary Data Collection

For secondary data collection, providers submitted a maximum of 15 eCRFs each. The maximum number of eCRFs per provider was originally set at 10 eCRFs each and was increased to achieve target patient numbers following pre-approval from Pfizer. Physicians were 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 were the patient chart/medical record data housed within the EHRs and accessed by the participating providers. Providers were compensated through honoraria payment for each completed and validated eCRF. A waiver of obtaining patient consent was obtained for the study.

The study population included 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 remained eligible for inclusion.

9.3. Subjects

9.3.1. Patient inclusion criteria - secondary data collection

Patients must have met 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.

9.3.2. Patient exclusion criteria - secondary data collection

Patients meeting any of the following exclusion criteria were not 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.

9.3.3. 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 IRB

- Agreement to participate in data quality assurance (QA)/quality control (QC) procedures

9.4. Variables

Primary Data Collection – Physician Survey (Secondary Objective #2)

The following de-identified provider-level variables/data elements were collected from physician surveys for Secondary Objective #2. Variable names/topics and roles were not shown as part of provider surveys. **Table 9.4-1** and **Table 9.4-2** include physician survey data elements of interest that were captured as part of the final data collection tool (DCT). **Table 9.4-2** includes additional data elements that were captured if providers selected AEs as a rationale for dose modification or treatment discontinuation.

Table 9.4-1. Physician survey variables – physician characteristics and treatment management approaches (Secondary Objective #2)

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 (please specify)	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)	Baseline characteristic	Physician reported

Table 9.4-1. Physician survey variables – physician characteristics and treatment management approaches (Secondary Objective #2)

Variable	Operational definition	Role	Data Source
	• West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)		
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 (please specify)	Baseline characteristic	Physician reported
Estimated caseload for patients with aRCC, patients w/aRCC who were treated with 1L axitinib + pembrolizumab therapy in the past year, and patients who were eligible for the study	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: • Complete response • Overall response rate • Overall survival • Number of contraindications • Patient compliance • Patient out-of-pocket cost • Patient preference • Practice reimbursement • Progression free survival • Quality of life • Safety profile • Treatment free interval • Trial follow-up time	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 +	Outcome	Physician reported

Table 9.4-1. Physician survey variables – physician characteristics and treatment management approaches (Secondary Objective #2)

Variable	Operational definition	Role	Data Source
	pembrolizumab for 1L treatment of aRCC [multiple select]: • Adverse events • Disease progression • Financial factors • Patient request to stop treatment • Other		

Table 9.4-2. Physician Survey - Follow-up questions for providers who listed AEs as a rationale for dose modifications or treatment discontinuation (Secondary Objective #2)

Variable	Operational Definition	Role	Data Source
AE management tools	What tools are available at your practice for AE management? • Laboratory testing (e.g., liver enzyme tests, complete blood count (CBC), renal function [e.g., creatinine], stool culture) • Multispecialty consultation (e.g., consult with nephrology) • 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) • Other (please specify)	Outcome	Physician reported
Most concerning AEs	Based on the known safety profile of the regimen, what are the most concerning AEs you encounter during your practice? • Constipation • Cough • Decreased appetite • Diarrhea • Dysphonia	Outcome	Physician reported

Table 9.4-2. Physician Survey - Follow-up questions for providers who listed AEs as a rationale for dose modifications or treatment discontinuation (Secondary Objective #2)

Variable	Operational Definition	Role	Data Source
	• Fatigue/asthenia • Hepatotoxicity • Hypertension • Hypothyroidism • Nausea • Palmar-plantar erythrodysesthesia • Rash • Stomatitis/mucosal inflammation		
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)	Outcome	Physician reported
AE-related treatment changes by severity	For the following AEs (separately by grade groups), which treatment changes (if any) would you typically make? **Grades**: 1-2 or 3-4 **AEs**: • Constipation • Cough • Decreased appetite • Diarrhea • Dysphonia • Fatigue/asthenia • Hepatotoxicity • Hypertension • Hypothyroidism • Nausea • Palmar-plantar erythrodysesthesia • Rash	Outcome	Physician reported

Table 9.4-2. Physician Survey - Follow-up questions for providers who listed AEs as a rationale for dose modifications or treatment discontinuation (Secondary Objective #2)

Variable	Operational Definition	Role	Data Source
	• Stomatitis/mucosal inflammation **Treatment Change Options**: • Continuation (no change) • Discontinuation of axitinib • Discontinuation of pembrolizumab • Dose reduction of axitinib • Dose reduction of pembrolizumab • Treatment interruption of axitinib • Treatment interruption of pembrolizumab • Prescribed concomitant medication		
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 discontinue therapy) (multiple select) • Availability of suitable subsequent line of therapy • Disease response prior to AE • First-time AE vs recurrent AE • Patient compliance • Patient comorbidities • Patient performance status • Patient preference • Probability the AE will fully resolve • Type of AE	Outcome	Physician reported

Table 9.4-2. Physician Survey - Follow-up questions for providers who listed AEs as a rationale for dose modifications or treatment discontinuation (Secondary Objective #2)

Variable	Operational Definition	Role	Data Source
	• Other (please specify)		

Secondary Data Collection Variables – Chart Abstraction

The following de-identified patient-level variables/data elements were 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 were not shown as part of chart abstraction. **Table 9.4-3** to **Table 9.4-7** represent data elements of interest that may be captured as part of the final DCT and **Table 9.4-8** includes the definition of endpoints/outcomes calculated from the collected data. **Table 9.4-4** includes additional data elements on AEs during 1L axitinib + pembrolizumab that were only captured if providers selected AEs as a reason for a patient dose modification and/or treatment discontinuation.

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
History of prior treatments	Type of treatment for RCC patient received prior to initiation of 1L axitinib + pembrolizumab therapy including surgery, radiation, none	Baseline characteristic	Patient medical records
Radiation received for RCC prior to index†	Type of radiation patient received for RCC prior to 1L axitinib + pembrolizumab, among those who received radiation: • External beam radiation therapy (EBRT) • Radiofrequency ablation (RFA) • Stereotactic ablative body radiotherapy (SAbR) • Other, please specify:	Baseline characteristic	Patient medical records
Surgery received for RCC	Type(s) and date(s) of surgical resection patient received among those who received surgery for RCC prior to initiation of 1L axitinib + pembrolizumab therapy including radical nephrectomy, partial nephrectomy,	Baseline characteristic	Patient medical records

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	cytoreductive surgery, or tumor ablation (radiofrequency/cryo). If patient had surgery, whether patient had residual disease (yes/no).†		
Radiation therapy during 1L axitinib + pembrolizumab therapy	Receipt of radiation therapy during 1L axitinib + pembrolizumab therapy (yes/no). 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. The initiation date of axitinib + pembrolizumab therapy will be the index date for this study. *Allowed for differing dates of discontinuation for axitinib and pembrolizumab.	Outcome	Patient medical records
Reason for initiating 1L axitinib + pembrolizumab >60 days after aRCC diagnosis†	If date of 1L axitinib + pembrolizumab initiation was more than 60 days after aRCC diagnosis, primary reason for delay: • Insurance factors • Patient choice • Patient comorbidities • Patient scheduling factors • Delay in diagnostic test results • Other (please specify)	Outcome	Physician reported

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
Reason(s) for index treatment selection	Reason(s) for selection of index including: • Insurance preference • Patient choice • Patient financial reasons • Method of administration • Standard of care/ National Comprehensive Cancer Network (NCCN) guidelines • Other (please specify)	Outcome	Physician reported
Initial dose/schedule of 1L therapy	Dosage and frequency/schedule of administration of 1L axitinib + pembrolizumab therapy at initiation.	Outcome	Patient medical records
Dose modifications for axitinib during 1L therapy	Type and number of dose modifications (up to 5 per type) for axitinib during 1L treatment including dose hold/interruption, dose/frequency increase, or dose/frequency reduction (multiple select).	Outcome	Patient medical records
Dose modifications for pembrolizumab during 1L therapy†	Type and number of dose modifications (up to 5 per type) for pembrolizumab during 1L treatment including dose hold/interruption, dose/frequency increase, or dose/frequency reduction (multiple select).	Outcome	Patient medical records
Reason(s) for dose/frequency reduction during 1L therapy†	Reason(s) for each dose/frequency reduction (up to 5) for 1L axitinib and/or pembrolizumab, including*: • Aggressive disease • Insurance/financial factors • Patient performance status • Patient comorbidities	Outcome	Physician reported

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	• To improve patient compliance • To improve patient tolerance • To increase efficacy/patient response • To follow recommended dosing guidelines • To titrate before eventual discontinuation • Adverse event/toxicity • Other (please specify) *Collected separately for axitinib and pembrolizumab		
Reason(s) for dose/frequency increase during 1L therapy†	Reason(s) for each dose/frequency increase (up to 5) for 1L axitinib and/or pembrolizumab, including*: • Aggressive disease • Dose titration • Insurance/financial factors • Patient performance status • Patient comorbidities • To increase efficacy/patient response • To follow recommended dosing guidelines • To return to original dose after resolution of AE • Resolution of adverse event/toxicity • Other (please specify)	Outcome	Physician reported

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	*Collected separately for axitinib and pembrolizumab		
Reason(s) for dose hold/interruption during 1L therapy†	Reason(s) for each dose hold/interruption (up to 5) for 1L axitinib and/or pembrolizumab, including*: • Aggressive disease • Insurance/financial factors • 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 • Adverse event/toxicity • Other (please specify) *Collected separately for axitinib and pembrolizumab	Outcome	Physician reported
Date of dose modification during 1L axitinib + pembrolizumab therapy	The date of each dose modification of each type of modification (i.e., dose hold/interruption, dose/frequency increase, or dose/frequency reduction)* *Collected different dates for axitinib and pembrolizumab	Outcome	Patient medical records

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
New dose/frequency after modification (increase, reduction)†	For dose/frequency increases and reductions, new dose and/or frequency* *Collected separately for axitinib and pembrolizumab	Outcome	Patient medical records
Length of treatment interruption	For reported dose holds/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* *Collected separate answers for axitinib and pembrolizumab	Outcome	Patient medical records
Reason(s) for index discontinuation	Reason(s) for discontinuing index: • Adverse event/toxicity • Death • Disease progression • Financial factors • Patient request to stop treatment • Scheduled duration of treatment complete • Other *Collected separate answers for axitinib and pembrolizumab	Outcome	Physician reported
Reason(s) patient did **NOT** initiate a LOT (line of therapy) post-1L axitinib + pembrolizumab	Reason(s) patient did <u>not</u> receive a subsequent LOT after discontinuation of 1L axitinib + pembrolizumab therapy, including: • Death • Financial factors • Patient choice • Poor drug availability • Other [please specify]	Outcome	Physician reported
Treatment regimen or drugs received for	Treatment(s) received following index (1L) treatment regimen (when applicable, up	Outcome	Patient medical records

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
aRCC after 1L axitinib + pembrolizumab therapy	to fifth-line [5L]) until data cut-off/end of follow-up. Subsequent treatments captured may include approved systemic treatments for aRCC.		
Date(s) of treatment initiation and discontinuation for second-line (2L) and later	Dates of treatment initiation and discontinuation (when applicable) for treatments received after index (up to 5L) treatment(s).	Outcome	Patient medical records
Reason for 2L and later treatment selection	Reason for selection of subsequent treatments including: • Patient choice • Financial reasons • Method of administration • Standard of care/NCCN guidelines • Disease progression • Metastasis • Other (please specify)	Outcome	Physician reported
Reason for 2L and later treatment discontinuation	Reason for discontinuing subsequent treatments after index (up to 5L): • Disease progression (defined clinically) • Disease progression (confirmed with scan) • Scheduled duration of therapy complete • Toxicity/intolerability • Patient choice • Death • Other (please specify)	Outcome	Physician reported
Vital status[†]	Vital status for patient at last follow-up (alive, deceased)	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	Outcome	Patient medical records

Table 9.4-3. Treatment pattern-related variables (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	• COVID-19 related • Unknown, data not available • Other (please specify)		
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
Disposition at data cut-off/end of follow-up	If alive, patient disposition at data cut-off/end of follow-up: • Patient is not receiving active therapy (including maintenance) or palliative care • Patient is receiving active therapy (including maintenance) • Patient is receiving palliative care • Patient was referred to hospice • Unknown, lost to follow-up • Other (please specify)	Outcome	Patient medical records

[†]Variables were added and/or modified during eCRF development and finalization and therefore may not match variables presented in the Protocol.

Table 9.4-4. Follow-up questions for providers who reported AEs as rationale for 1L axitinib + pembrolizumab dose modification or treatment discontinuation (Primary Objective #1)

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 axitinib + pembrolizumab therapy, including: • Asthenia • Constipation	Outcome	Patient medical records

Table 9.4-4. Follow-up questions for providers who reported AEs as rationale for 1L axitinib + pembrolizumab dose modification or treatment discontinuation (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	• Decreased appetite • Diarrhea • Dysphonia • Erythrodysesthesia (hand-foot) syndrome • Fatigue • Hypertension • Vomiting • Weight loss • Other		
Number of times per AE	Number of times each AE/toxicity caused a dose modification and/or treatment discontinuation	Outcome	Patient medical records
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 • Axitinib-related • Pembrolizumab-related • Non-treatment related • 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: • Emergency room (ER) admission • Hospitalization • No treatment • Supportive care (medication)	Outcome	Patient medical records

Table 9.4-4. Follow-up questions for providers who reported AEs as rationale for 1L axitinib + pembrolizumab dose modification or treatment discontinuation (Primary Objective #1)

Variable	Operational definition	Role	Data Source
	• Unknown • Other		
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 • Topical treatments • Other	Outcome	Patient medical records
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 appeared in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution was not inferred by a temporal relationship between drug administration and an AE but must have been 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 were 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

[†]Variables/response options were modified during eCRF development and finalization and therefore may not match variables presented in the Protocol.

Table 9.4-5. Patient demographic characteristics (Secondary Objective #1)

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
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 (please specify)	Baseline characteristic	Patient medical records

Table 9.4-6. Patient clinical characteristics (Secondary Objective #1)

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 Acquired Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (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 • Unknown • Other (please specify)	Baseline characteristic	Patient medical records
Sarcomatoid Features	Presence of sarcomatoid features (yes/no/unknown)	Baseline characteristic	Patient medical records
Location of metastatic sites & number of lesions[†]	Sites of metastases & number of lesions at initiation of 1L axitinib + pembrolizumab therapy for aRCC • All sites where metastatic disease was detected 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) • Specific location within each selected site (write-in)	Baseline characteristic	Patient medical records

Table 9.4-6. Patient clinical characteristics (Secondary Objective #1)

Variable	Operational definition	Role	Data Source
	• Number of lesions at each site selected (1-2, 3-4, 5+)		
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
Height	Patient's height	Baseline characteristic	Patient medical records
Weight	Patient's weight	Baseline characteristic	Patient medical records
Body mass index (BMI)	Physician-reported BMI	Baseline characteristic	Patient medical records or calculated using height and weight
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: • 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-	Baseline characteristic	Patient medical records

Table 9.4-6. Patient clinical characteristics (Secondary Objective #1)

Variable	Operational definition	Role	Data Source
	care; totally confined to bed or chair. • Unknown		
Karnofsky Performance Status (KPS)†	If ECOG-PS was unknown, patient's most recent known KPS at or in the 90 days prior to the initiation of 1L axitinib + pembrolizumab therapy: • 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) • Cerebrovascular disease	Baseline characteristic	Patient medical records

Table 9.4-6. Patient clinical characteristics (Secondary Objective #1)

Variable	Operational definition	Role	Data Source
	• Chronic obstructive pulmonary disease (COPD) • Coronary artery disease • Congestive heart failure • Dementia • Diabetes with or without complications • Hepatitis B • Hepatitis C • Hypertension • Liver disease – mild or moderate/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

[†]Variables/response options were modified during eCRF development and finalization and therefore may not match variables presented in the Protocol.

Table 9.4-7. Clinical outcome-related variables (Exploratory Objective #1)

Variable	Operational definition	Role	Data Source

Table 9.4-7. Clinical outcome-related variables (Exploratory Objective #1)

Initial response to 1L axitinib + pembrolizumab therapy†	The initial response to 1L axitinib + pembrolizumab therapy as charted in the medical records (partial response [PR], stable disease, not assessed, unknown), and date of scan used to assess initial response to treatment	Outcome	Patient medical records
Best response to 1L axitinib + pembrolizumab therapy	The best response to 1L axitinib + pembrolizumab therapy as charted in the medical records (complete response [CR], PR, stable disease, progressive disease, not assessed, unknown), and date of scan used to assess best response to treatment	Outcome	Patient medical records
Progression during or following 1L axitinib + pembrolizumab therapy†	Progression experienced during 1L axitinib + pembrolizumab (assessed via scan) and the date of first progression during or following 1L axitinib + pembrolizumab therapy. Progression was also assessed if providers indicated progression as the reason for discontinuing therapy.	Outcome	Patient medical records

†Variables/response options were modified during eCRF development and finalization and therefore may not match variables presented in the Protocol.

Table 9.4-8. Calculated endpoints by objective

Calculated endpoint	Operational definition
Primary Objective #1 – Treatment Patterns	
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. Calculated both arithmetically and via Kaplan-Meier (KM) method. For KM analysis, patients were censored on the last office visit with the provider during the respective line of therapy if still receiving therapy. For combination therapies, rwDOT was calculated for each individual therapy

Table 9.4-8. Calculated endpoints by objective

Calculated endpoint	Operational definition
	only and both therapies (time to discontinuation of first therapy and last therapy).
Real-world treatment-free interval (rwTFI)	Time from discontinuation of line of therapy until initiation of subsequent therapy
Real-world time to next treatment (rwTTNT)	Time between the initiation of line of therapy and next subsequent treatment. Patients who did not receive subsequent treatment were 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.
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 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)

Table 9.4-8. Calculated endpoints by objective

Calculated endpoint	Operational definition
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. Calculated for three most commonly reported AEs.
Exploratory Objective #1 – Clinical Outcomes	
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 best response	Among patients with a documented best 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. 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 were censored at the start date of next line or date of last encounter, whichever came first
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 who had not experienced progression or death were censored on date of last encounter. The KM method was also used to estimate PFS point estimates at 3, 6, 12, 18, and 24 months from treatment initiation as appropriate
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 were censored on the date of last encounter. Median and survival point estimates were calculated from the KM curve. If median survival could not be estimated (e.g., median was not reached due to data immaturity/high rate of censoring), the KM method was used to estimate survival point estimates at 3, 6, 12, 18, and 24 months from treatment initiation as appropriate

*Only calculated if providers listed AEs as reason for dose modification or treatment discontinuation and completed subsequent AE-related follow-up questions (**Table 9.4-4**).

Table 9.4-8. Calculated endpoints by objective

Calculated endpoint	Operational definition

[†]Calculated variables may have been modified after finalization of the protocol, therefore definitions may vary slightly between this report and the protocol.

9.5. Data sources and measurement

Primary Data – Physician Survey

Primary data on physicians' treatment management approaches were collected via a one-time physician survey as part of the patient-level, retrospective, chart-based data collection. The one-time physician survey included questions on physician/practice characteristics, questions to confirm physician eligibility, and survey questions about treatment management approaches for aRCC. The key variables and datapoints collected by the physician survey is included in **Table 9.4-1** and **Table 9.4-2** above.

Secondary Data – Chart Abstraction

For secondary data collection, patient data were abstracted and entered into an eCRF by physicians from the OPEN. The source documents were the patient chart/medical record data housed within the EHRs and accessed by the participating providers. 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) were collected. The eCRF was 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 eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information (PHI). Based on the study objectives, the variables and datapoints that were abstracted into the eCRF by participating physicians are included in **Section 9.4** above.

No source document verification was conducted by Cardinal Health; however, data QC, QA, and validation processes were performed as described. These processes and systems are vetted during field testing with physicians, as described in **Section 9.10**.

9.6. Bias

For this study, the vendor Cardinal Health did not, and could not, conduct source document verification of data abstracted by physicians. Nevertheless, Cardinal Health required that all physicians that were not previously verified to 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 were subject to further review, and at the discretion of Cardinal Health, may have had all patient records submitted removed from the analytic dataset.

This study employed purposive sampling that selects physicians and patients based on pre-specified selection criteria and hence, the participants included in this study may not be representative of all patients within the cohorts of interest or representative of all physicians treating these patients. As such, treatment patterns reflected in the study represent 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 is available to describe non-participating providers or non-selected patients. While Cardinal Health could not verify that all patients who meet the study

eligibility criteria are included in the final dataset, participating providers were limited to submitting a maximum of 15 eCRFs in an aim to minimize provider bias. Additionally, to minimize bias related to selection of patient subsets within practices, physicians were 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.

This study may also be subject to bias due to missing data. Although physicians were 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 involved 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. Nevertheless, the eCRF was thoroughly tested both internally by the Cardinal Health team as well as during physician user acceptance testing (UAT) to ensure the questions and data points of interest were clear.

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.

9.7. Study size

This was a descriptive analysis of cross-sectional provider survey data and retrospective provider- and patient-level data. Given the descriptive nature of this study, no *a priori* hypotheses were specified, and no formal hypothesis testing was performed.

Primary Data – Physician Survey

This study collected information from N=25 physicians who treated at least 5 patients with aRCC in the past year. At start of data collection, up to N=30 physicians were expected, as the maximum number of charts allowed per physician was set at 10. With the increase of the allowed charts to 15 per provider on August 8, 2024, achievement of the N=300 patient quota was completed with fewer than N=30 physicians.

Secondary Data – Patient-Level Chart Abstraction Study

This study collected 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, a prior feasibility assessment (as described below), anticipated provider recruitment, and the method of chart data abstraction. Additionally, Cardinal Health performed prior research and feasibility assessments that supported conduct of this chart review study through the OPEN to achieve the research objectives and sample size.

The patient sample size in this study (N=300) was informed by a feasibility assessment conducted by Cardinal Health in October 2022 with physicians in Cardinal Health's OPEN network. In the feasibility, 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, physicians estimated that 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 were treated/managed in their practice with aRCC in the past 3 years, providers estimated that 459

(43%) were treated with combination axitinib and I-O therapy (Mean: 11.8 patients per provider; Range: 1-35).

Based on the targeted sample size of N=300 for the chart review study, the 95% confidence intervals (CIs) around point estimates of binary event probabilities based on various subgroup sizes are shown below. Any statistical comparisons were exploratory; however, it is important to consider the precision and face validity of estimates in smaller populations or proportions. **Table 9.7-1** provides the precision levels for point estimates by sample size calculated via normal approximation and the Fleiss method, where appropriate.

Table 9.7-1. 95% CIs for point estimates by sample size

Probability of event	95% 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%

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (**Appendix 4**).

9.9. Statistical methods

9.9.1. Main summary measures

This study included a descriptive analysis of provider survey data and retrospective patient-level data. Study results were reported in aggregate (i.e., across the entire study population) and for subgroups of interest depending on sample size. All variables were summarized using counts and frequencies for dichotomous and categorical variables, while measures of centrality (mean, median) and spread (minimum, maximum, standard deviation [SD], interquartile range [IQR], as appropriate) were used for continuous variables. Time-to-event outcomes were assessed using KM methods, which accounted for right-censoring by considering the events of interest as well as the end of follow-up/study end date (censored events). All data processing and analysis was performed in SAS v9.4. Detailed analyses by objective are included in the SAP (see **Appendix 4**).

9.9.2. Main statistical methods

Please refer to SAP document in Appendix 4.

9.9.3. Missing values

The number of missing or unknown observations were described for both categorical and numeric variables. No data imputation was conducted. Patients with missing/unknown data were reported.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

Cardinal Health was responsible for the programming, testing, and hosting of data from submitted eCRFs. Testing included 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 was field-tested with 4 providers to ensure its functionality during UAT, 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 were reviewed by Cardinal Health with Pfizer. No data from the pre-testing phase were used in the current study. Additionally, prior to data collection (prior to the field test and actual study launch), Cardinal Health completed internal testing, 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 and internal testing were included in the data QC log. Any changes made to the case report form (CRF) and eCRF document as a result of the pre-tests required the resubmission of the CRF and study protocol to the IRB.

Participating providers were informed in their contractual agreement that follow-up with Cardinal Health may be required and were contacted for query resolution and/or data validation as needed. For medical queries and random data validation, providers were asked to create a 4-digit unique identifier for each patient, which was transmitted to Cardinal Health and used for identifying the patient record for data validation. Data was reviewed by a licensed HCP employee of Cardinal Health to identify medical queries. Data was 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). Issues flagged for potential data validation were resolved with the providers directly on a case-by-case basis. All eCRFs flagged during QC were reviewed by the team to determine the level of follow-up needed. No eCRFs were removed during QC for this study.

Random data validation was conducted by selecting a random eCRF from each provider submitting a patient. Providers subjected to random validation were asked to complete a 3 data point-validation exercise for the patient, whereby the provider was given the unique patient identifier but no other information. The provider was then asked to re-enter the following data elements: date of initial RCC diagnosis, date of aRCC diagnosis, and date of 1L axitinib + pembrolizumab initiation. Providers who had been previously verified by Cardinal Health were not subject to random validation. A verified provider was any physician abstractor who had 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 was still required to answer questions regarding patients with data flagged by Cardinal Health's research operations or research analytics teams. A provider who failed to

validate all data points for a selected patient was required to submit to further clinical data review. No eCRFs were removed during QC and validation processes for this study.

After completion of QC/QA reviews and for all completed eCRFs, the study database was locked, and all data was downloaded and stored on a secured server housed within the Cardinal Health Information Technology infrastructure.

9.11. Protection of human subjects

Subject information and consent

Primary Data Collection

Primary data was reported by participating physicians via survey. Pfizer was not responsible for ensuring that the appropriate consenting processes or consenting waivers were in place, as this responsibility was deferred to the vendor Cardinal Health.

Secondary Data Collection

As this study did not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer was not required. A central IRB found that this research meets the requirement for a waiver of consent under 45 CFR 46 116(f)[2018 Requirements] 45 CFR 46.116(d) [Pre-2018 Requirements].

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

The final protocol, any amendments, and CRF were reviewed and approved by a central IRB for participating in the study. Each provider acknowledged he/she could participate in research approved by a central IRB. No site IRBs evaluated the final protocol or eCRF.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

10. RESULTS

10.1. Participants

During data collection from July 31, 2024 to August 22, 2024, 25 providers completed one-time physician surveys and submitted eCRFs for 300 aRCC patients who received 1L axitinib + pembrolizumab treatment. No eCRFs were excluded after data QC and validation.

10.2. Descriptive data

10.2.1. Provider characteristics (primary data)

In total, 25 providers from OPEN practices in the US volunteered to participate and submitted patient-level data for this study (**Table 10.2-1**). These 25 providers submitted eCRFs for at least one aRCC patient treated with 1L axitinib + pembrolizumab. All providers were practicing

medical oncologists, and represented all US regions including Northeast (n=4, 16.0%), Midwest (n=7, 28.0%), South (n=7, 28.0%) and West (n=7, 28.0%). Participating physicians had a median 15.0 years in practice at time of survey. Practice types included urban (n=16, 64.0%), suburban (n=8, 32.0%) and rural (n=1, 4.0%) settings.

Table 10.2-1. Provider characteristics

	All Physicians N=25
Practice setting (n, %)	
Small private community practice (2-5 physicians)	2 (8.0)
Small private community practice (2-5 physicians) owned by a hospital	2 (8.0)
Medium-sized private community practice (6-10 physicians)	3 (12.0)
Medium-sized private community practice (6-10 physicians) owned by a hospital	1 (4.0)
Large private community practice (> 10 physicians)	9 (36.0)
Large private community practice (> 10 physicians) owned by a hospital	2 (8.0)
Community practice owned by an academic center	3 (12.0)
Academic medical center	3 (12.0)
US region of practice (n, %)	
Northeast (CT, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT)	4 (16.0)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)	7 (28.0)
South (AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV)	7 (28.0)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)	7 (28.0)
Practice type (n, %)	
Urban: a densely populated region within or near a city with 50,000+ inhabitants	16 (64.0)
Suburban: a less densely populated residential area near a city with 2,500+ inhabitants	8 (32.0)
Rural: a region with a low population density and <2,500 inhabitants	1 (4.0)
Number of years in practice	
Mean (SD)	14.6 (7.3)
Median (P25-P75)	15.0 (9.0-20.0)
Min, Max	4.0, 30.0
Medical specialty (n, %)*	
Medical oncology	25 (100.0)
Hematology	1 (4.0)

Table 10.2-1. Provider characteristics

	All Physicians N=25
Number of patient charts abstracted for final data set	
Mean (SD)	12.0 (4.5)
Median (P25-P75)	15.0 (10.0-15.0)
Min, Max	2.0, 15.0
Estimated number of aRCC patients treated in practice in the past year	
Mean (SD)	28.8 (16.0)
Median (P25-P75)	25.0 (18.0-35.0)
Min, Max	5.0, 70.0
Estimated number of patients meeting study eligibility criteria	
Mean (SD)	19.4 (11.0)
Median (P25-P75)	16.0 (12.0-22.0)
Min, Max	7.0, 50.0
Estimated number of aRCC patients personally treated with 1L axitinib plus pembrolizumab in the past year	
Mean (SD)	10.9 (6.8)
Median (P25-P75)	10.0 (7.0-13.0)
Min, Max	2.0, 30.0

*Multiple responses were allowed.

10.2.2. Patient characteristics (secondary data)

In this study, patients who received 1L axitinib + pembrolizumab for treatment of aRCC were a median age of 66.7 years at aRCC diagnosis, majority male (61.0%), majority White (69.3%) with 22.7% identifying as Black or African-American, and majority non-Hispanic (86.7%; **Table 10.2-2).** Median follow-up from initiation of 1L axitinib + pembrolizumab was 12.3 months, with approximately half of patients still on 1L axitinib + pembrolizumab at data collection (49.0%). Most patients were alive at data collection (79.3%), with the most common cause of death being disease progression.

Table 10.2-2. Patient characteristics

	All (n=300)
Age at aRCC diagnosis (years)	
Mean (SD)	66.0 (9.3)
Median (P25-P75)	66.7 (60.0-72.8)

Table 10.2-2. Patient characteristics

	All (n=300)
Min, Max	35.0, 90.0
Sex at birth (n, %)	
Male	183 (61.0)
Female	117 (39.0)
Race (n, %)*	
American Indian or Alaska Native	1 (0.3)
Asian	20 (6.7)
Black or African-American	68 (22.7)
Native Hawaiian or Other Pacific Islander	3 (1.0)
White	208 (69.3)
Unknown	0 (0.0)
Ethnicity (n, %)	
Hispanic or Latino	23 (7.7)
Not Hispanic or Latino	260 (86.7)
Unknown	17 (5.7)
Follow-up from initiation of 1L axitinib + pembrolizumab (months)	
Mean (SD)	17.5 (13.4)
Median (P25-P75)	12.3 (8.1-21.6)
Min, Max	0.9, 61.7
1L axitinib + pembrolizumab therapy status at data collection (n, %)	
Still on 1L axitinib + pembrolizumab	147 (49.0)
Discontinued 1L axitinib + pembrolizumab	134 (44.7)
Discontinued 1L axitinib only (i.e., still on 1L pembrolizumab)	7 (2.3)
Discontinued 1L pembrolizumab only (i.e., still on 1L axitinib)	12 (4.0)
Patient vital status at data collection (n, %)	
Alive	238 (79.3)
Deceased	62 (20.7)
Cause of death, among patients who were deceased at data collection (n, %)	
Disease progression	47 (75.8)
Toxicity related to treatment	1 (1.6)

Table 10.2-2. Patient characteristics

	All (n=300)
COVID-19 related	1 (1.6)
Unknown, data not available	5 (8.1)
Other†	8 (12.9)

*Multiple responses were allowed.
†Full write-in responses can be found in the compendium.

10.3. Main results

10.3.1. Primary objective #1 – Treatment patterns

10.3.1.1. Pre-index treatment

The majority of patients (66.0%) had not received any prior treatment for aRCC before receiving 1L axitinib + pembrolizumab, with 26.0% and 9.7% having received surgery and radiation, respectively (**Table 10.3-1**). Among patients who received radiation prior to 1L axitinib + pembrolizumab (n=29), stereotactic ablative body radiotherapy (44.8%) and external beam radiation therapy (41.4%) were the most common. For patients who had undergone surgery for aRCC prior to 1L axitinib + pembrolizumab (n=78), the majority underwent radical nephrectomy surgery (70.5%). Among patients who underwent surgery, median time from surgery to initiation of 1L axitinib + pembrolizumab was 12.0 months.

Table 10.3-1. Pre-index treatments

	All Patients (N=300)
Treatment types received prior to initiation of 1L axitinib + pembrolizumab for aRCC (n, %)*	
Radiation	29 (9.7)
Surgery	78 (26.0)
None	198 (66.0)
Type of radiation therapy received prior to initiation of 1L axitinib + pembrolizumab, among patients who received radiation (n, %)	
External beam radiation therapy (EBRT)	12 (41.4)
Radiofrequency ablation (RFA)	3 (10.3)
Stereotactic ablative body (SAbR) radiotherapy	13 (44.8)
Other†	1 (3.4)
Type of surgical resection received prior to initiation of 1L axitinib + pembrolizumab, among patients who underwent surgery (n, %)	
Cytoreductive surgery	8 (10.3)
Partial nephrectomy	9 (11.5)

Table 10.3-1. Pre-index treatments

	All Patients (N=300)
Radical nephrectomy	55 (70.5)
Tumor ablation (radiofrequency/cryo)	3 (3.8)
Other†	3 (3.8)
Time from prior surgery to initiation of 1L axitinib + pembrolizumab, among patients who underwent surgery prior to 1L axitinib + pembrolizumab initiation (months)	
n (%)	78 (26.0)
Mean (SD)	25.2 (29.9)
Median (P25-P75)	12.0 (2.9-39.7)
Min, Max	0.3, 156.4
Patient had residual disease post-surgery for RCC, among patients who underwent surgery prior to 1L axitinib + pembrolizumab initiation (n, %)	
Yes	21 (26.9)
No	55 (70.5)
Unknown	2 (2.6)

†Full write-in responses can be found in the study compendium.

10.3.1.2. Index therapy – dosing and modifications

Median time from aRCC diagnosis to initiation of 1L axitinib + pembrolizumab was 0.5 months (**Table 10.3-2**). The primary reason for choosing 1L axitinib + pembrolizumab was its position as a SOC (99.3%), while 11.0% cited patient choice. Most providers initiated 1L axitinib on the standard dosing schedule of 5 mg orally twice daily (BID). Overall, 37.0% (n=111) of patients reported at least one treatment modification during 1L axitinib + pembrolizumab, with a median time to first modification of 2.7 months after initiation. For patients who experienced a reduction in axitinib (n=43), median time to first reduction was 2.3 months. Most common reasons for that first reduction included AEs and patient intolerance. At the first reduction in axitinib, most patients reduced to 3 mg BID. Overall, 26 patients (8.7%) were able to increase axitinib, with a median time to first increase of 0.5 months. Most common reasons for that first increase included following dosing guidelines and to increase efficacy. At the first increase in axitinib, most patients increased to 7 mg BID. A minority of patients (13.7%) experienced an axitinib interruption, with a median time to first interruption of 2.8 months. The most common reason for that first axitinib interruption was AE/toxicity. Median duration of first axitinib interruption was 15.0 days (min-max: 2.0-45.0).

Table 10.3-2. 1L axitinib + pembrolizumab dosing and modifications

	All Patients (N=300)
Primary reason(s) 1L axitinib + pembrolizumab was selected for this patient (n, %)*	
Insurance preference	12 (4.0)
Patient choice	33 (11.0)
Method of administration	10 (3.3)
Standard of care/NCCN guidelines	298 (99.3)
Other†	3 (1.0)
Time from aRCC diagnosis to initiation of 1L axitinib + pembrolizumab (months)	
Mean (SD)	0.7 (1.0)
Median (P25-P75)	0.5 (0.3-0.7)
Min, Max	0.0, 8.9
Patient received radiation as treatment for aRCC during 1L axitinib + pembrolizumab therapy (n, %)	
Yes	14 (4.7)
No	286 (95.3)
Time from initiation of 1L axitinib + pembrolizumab to first dose of radiation therapy while on 1L axitinib + pembrolizumab, among patients who received radiation while on 1L axitinib + pembrolizumab (months)	
n (%)	14 (4.7)
Mean (SD)	1.6 (4.6)
Median (P25-P75)	0.4 (0.1-0.7)
Min, Max	0.0, 17.5
Site(s) of radiation therapy, among patients who received radiation while on 1L axitinib + pembrolizumab (n, %)*	
Brain	2 (14.3)
Bone	11 (78.6)
Other metastatic site†	1 (7.1)
Starting dose and frequency of axitinib at initiation of 1L axitinib + pembrolizumab (n, %)	
5 mg orally twice daily until progression	285 (95.0)
3 mg BID	11 (3.7)

Table 10.3-2. 1L axitinib + pembrolizumab dosing and modifications

	All Patients (N=300)
2 mg BID	4 (1.3)
Starting dose and frequency of pembrolizumab at initiation of 1L axitinib + pembrolizumab (n, %)	
200 mg intravenously once every 3 weeks	269 (89.7)
400 mg intravenously once every 6 weeks	31 (10.3)
Time from initiation of 1L axitinib + pembrolizumab therapy to first treatment modification (axitinib or pembrolizumab), among patients with at least one treatment modification (months)	
n (%)	111 (37.0)
Mean (SD)	4.7 (6.6)
Median (P25-P75)	2.7 (1.2-5.3)
Min, Max	0.3, 48.9
Total number of dose/frequency reductions in axitinib, among patients with at least one reported reduction	
n (%)	43 (14.3)
Mean (SD)	1.2 (0.4)
Median (P25-P75)	1.0 (1.0-1.0)
Min, Max	1.0, 3.0
Total number of dose/frequency increases in axitinib, among patients with at least one reported increase	
n (%)	26 (8.7)
Mean (SD)	1.2 (0.4)
Median (P25-P75)	1.0 (1.0-1.0)
Min, Max	1.0, 2.0
Total number of dose holds/interruptions in axitinib, among patients with at least one reported hold/interruption	
n (%)	41 (13.7)
Mean (SD)	1.1 (0.4)
Median (P25-P75)	1.0 (1.0-1.0)
Min, Max	1.0, 2.0
Axitinib dose/frequency reductions	

Table 10.3-2. 1L axitinib + pembrolizumab dosing and modifications

	All Patients (N=300)
Time to first axitinib dose/frequency reduction from initiation of 1L axitinib + pembrolizumab therapy, among patients with at least one axitinib reduction (months)	
n (%)	43 (14.3)
Median (P25-P75)	2.3 (1.4-3.7)
Reason(s) for first axitinib dose/frequency reduction, among patients with at least one axitinib reduction (n, %)*	
Patient performance status	2 (4.7)
To improve patient compliance	1 (2.3)
To improve patient tolerance	14 (32.6)
To follow recommended dosing guidelines	3 (7.0)
Adverse event/toxicity	36 (83.7)
Other†	1 (2.3)
New axitinib dose and frequency after first axitinib reduction, among patients with at least one axitinib reduction (n, %)	
3 mg orally twice a day	36 (83.7)
2 mg orally twice a day	6 (14.0)
Other†	1 (2.3)
Axitinib dose/frequency increases	
Time to first axitinib dose/frequency increase from initiation of 1L axitinib + pembrolizumab, among patients with at least one axitinib increase (months)	
n (%)	26 (8.7)
Median (P25-P75)	0.5 (0.5-2.8)
Reason(s) for first axitinib dose/frequency increase, among patients with at least one axitinib increase (n, %)*	
Aggressive disease	1 (3.8)
Dose titration	2 (7.7)
To increase efficacy/patient response	11 (42.3)
To follow recommended dosing guidelines	15 (57.7)
New axitinib dose and frequency after first axitinib increase, among patients with at least one axitinib increase (n, %)	
7 mg orally twice a day	22 (84.6)

Table 10.3-2. 1L axitinib + pembrolizumab dosing and modifications

	All Patients (N=300)
10 mg orally twice a day	4 (15.4)
Axitinib holds/interruptions	
Time to first axitinib dose hold/interruption from initiation of 1L axitinib + pembrolizumab, among patients with at least one axitinib hold/interruption (months)	
n (%)	41 (13.7)
Median (P25-P75)	2.8 (1.4-5.3)
Reason(s) for first axitinib hold/interruption, among patients with at least one axitinib hold/interruption (n, %)*	
Insurance/financial factors	1 (2.4)
Patient performance status	2 (4.9)
Patient comorbidities	4 (9.8)
To improve patient tolerance	8 (19.5)
Adverse event/toxicity	29 (70.7)
Other†	8 (19.5)
Duration of first axitinib hold/interruption, among patients with at least one axitinib hold/interruption (days)	
n (%)	41 (13.7)
Median (P25-P75)	15.0 (9.0-21.0)
Pembrolizumab holds/interruptions	
Total number of dose holds/interruptions in pembrolizumab, among patients with at least one hold/interruption	
n (%)	18 (6.0)
Median (P25-P75)	1.0 (1.0-1.0)
Time to first pembrolizumab dose hold/interruption from initiation of 1L axitinib + pembrolizumab, among patients with at least one pembrolizumab hold/interruption (months)	
n (%)	18 (6.0)
Median (P25-P75)	3.3 (2.3-9.5)
Reason(s) for first pembrolizumab hold/interruption, among patients with at least one pembrolizumab hold/interruption (n, %)*	
To improve patient tolerance	1 (5.6)
To increase efficacy/patient response	1 (5.6)

Table 10.3-2. 1L axitinib + pembrolizumab dosing and modifications

	All Patients (N=300)
To return to original dose after resolution of AE	1 (5.6)
Adverse event/toxicity	12 (66.7)
Other†	4 (22.2)
Duration of first pembrolizumab hold/interruption, among patients with at least one pembrolizumab hold/interruption (days)	
n (%)	18 (6.0)
Median (P25-P75)	21.0 (14.0-35.0)

†Full write-in responses can be found in the study compendium.

*Multiple responses were allowed.

10.3.1.3. Discontinuation of index and duration of index therapy

At last follow-up, 44.7% of patients had discontinued 1L axitinib + pembrolizumab (**Table 10.3-3**). Disease progression was the most common reason for discontinuing axitinib and pembrolizumab. Only 7.8% and 9.6% of patients discontinued axitinib or pembrolizumab, respectively, due to AEs. Median rwDOT for 1L axitinib + pembrolizumab was 18.6 months (95% CI: 17.0 - 21.2; **Figure 2**), with the 12-month probability of a patient being on 1L axitinib + pembrolizumab estimated as 0.73. Median rwTTNT from 1L to 2L therapy was 22.3 months (95% CI: 20.0-25.6).

Table 10.3-3. Discontinuation of index and duration of index therapy

	All Patients (N=300)
1L axitinib + pembrolizumab therapy status at data collection (n, %)	
Still on 1L axitinib + pembrolizumab	147 (49.0)
Discontinued 1L axitinib + pembrolizumab	134 (44.7)
Discontinued 1L axitinib only (i.e., still on 1L pembrolizumab)	7 (2.3)
Discontinued 1L pembrolizumab only (i.e., still on 1L axitinib)	12 (4.0)
Patient's most recent dose of axitinib if still on therapy or dose at time of discontinuation (n, %)	
1 mg orally twice daily until progression	1 (0.3)
2 mg orally twice daily until progression	12 (4.0)
3 mg orally twice daily until progression	40 (13.3)

Table 10.3-3. Discontinuation of index and duration of index therapy

	All Patients (N=300)
5 mg orally twice daily until progression	218 (72.7)
7 mg orally twice daily until progression	19 (6.3)
10 mg orally twice daily until progression	8 (2.7)
Other[†]	2 (0.7)
Patient's most recent dose of pembrolizumab if still on therapy or dose at time of discontinuation (n, %)	
200 mg intravenously once every 3 weeks	246 (82.0)
400 mg intravenously once every 6 weeks	54 (18.0)
Reason(s) for discontinuation of 1L axitinib, among those who discontinued 1L axitinib (n, %)*	
Adverse event/toxicity	11 (7.8)
Death	13 (9.2)
Disease progression	111 (78.7)
Financial factors	2 (1.4)
Patient request to stop treatment	11 (7.8)
Scheduled duration of treatment complete	3 (2.1)
Other	3 (2.1)
Reason(s) for discontinuation of 1L pembrolizumab, among those who discontinued 1L pembrolizumab (n, %)*	
Adverse event/toxicity	14 (9.6)
Death	14 (9.6)
Disease progression	110 (75.3)
Patient request to stop treatment	5 (3.4)
Scheduled duration of treatment complete	8 (5.5)
Other	3 (2.1)
rwDOT for 1L axitinib + pembrolizumab using KM methods (months)[a]	
N of Censored (%)	166 (55.3)
N of events (%)	134 (44.7)

Table 10.3-3. Discontinuation of index and duration of index therapy

	All Patients (N=300)
KM Median [95% CI]	18.6 [17.0-21.2]
3-month rwDOT of 1L axitinib + pembrolizumab	
N at Risk (%)	291 (97.0)
Point Estimate [95% CI]	0.97 [0.94-0.98]
6-month rwDOT of 1L axitinib + pembrolizumab	
N at Risk (%)	274 (91.3)
Point Estimate [95% CI]	0.94 [0.90-0.96]
12-month rwDOT of 1L axitinib + pembrolizumab	
N at Risk (%)	137 (45.7)
Point Estimate [95% CI]	0.73 [0.67-0.78]
18-month rwDOT of 1L axitinib + pembrolizumab	
N at Risk (%)	67 (22.3)
Point Estimate [95% CI]	0.53 [0.45-0.60]
24-month rwDOT of 1L axitinib + pembrolizumab	
N at Risk (%)	31 (10.3)
Point Estimate [95% CI]	0.35 [0.27-0.43]
rwTTNT from 1L to 2L (months)[b]	
N of Censored (%)	210 (70.0)
N of events (%)	90 (30.0)
KM Median [95% CI]	22.3 [20.0-25.6]

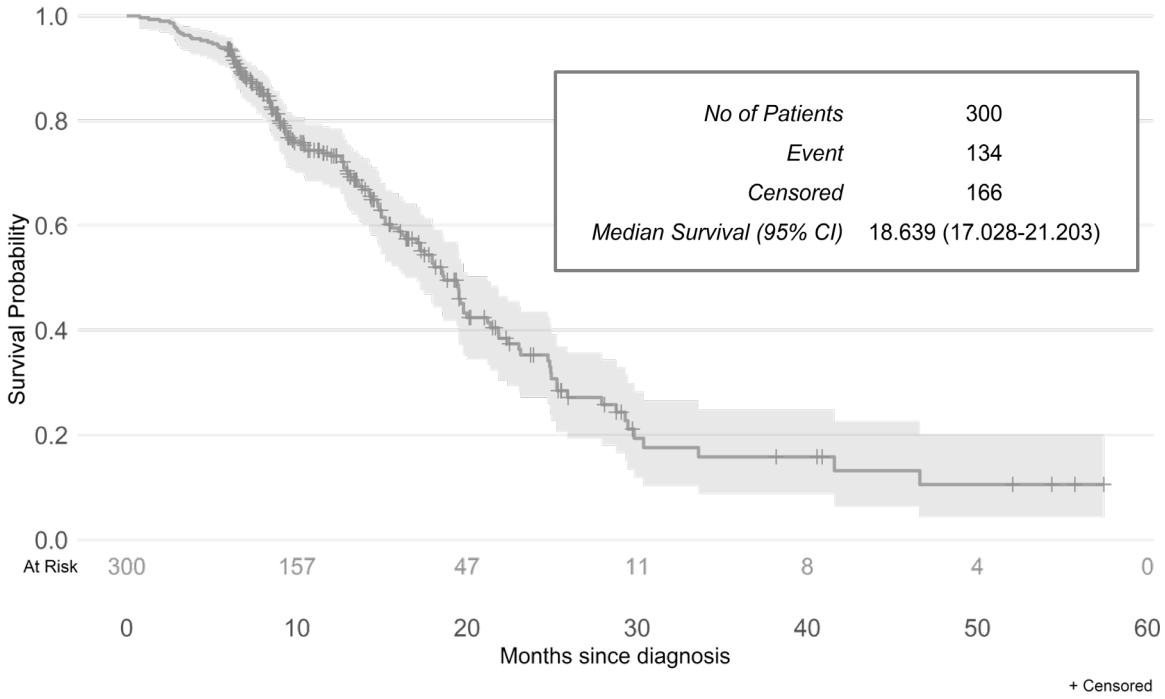
*Multiple responses were allowed.

[†]Full write-in responses can be found in the compendium.

[a]Time from initiation of 1L axitinib + pembrolizumab to the last occurring discontinuation of pembrolizumab or axitinib for any reason (event) or last day of communication for patients still on 1L axitinib + pembrolizumab (censored).

[b]Time from initiation of 1L axitinib + pembrolizumab to initiation of 2L treatment (event) or for patients who do not receive 2L therapy, date of last encounter or death (censored).

Figure 2. KM curve for rwDOT for 1L axitinib + pembrolizumab.



10.3.1.4. Post-index treatments

At last follow-up, the majority of patients (70.0%) had not received further treatment beyond 1L axitinib + pembrolizumab (**Table 10.3-4**). For patients who discontinued 1L axitinib + pembrolizumab but did not go on to receive a 2L therapy (n=44), the most common reasons were death (59.1%) and patient choice (40.9%). The median rwTFI between 1L and 2L therapy was 0.5 months. Among patients who received 2L therapy (n=90; 30.0%), the majority received cabozantinib (65.6%; **Figure 3**). At last follow-up, only 9.3% of patients (n=28) had received 3 lines of therapy or more.

Table 10.3-4. Post-index treatments

	All Patients (N=300)
Number of LOTs received after 1L axitinib + pembrolizumab therapy for aRCC (n, %)	
0	210 (70.0)
1	62 (20.7)
2	26 (8.7)
3	1 (0.3)
4	1 (0.3)

Table 10.3-4. Post-index treatments

	All Patients (N=300)
Reason(s) patient did not receive 2L therapy, among patients who did not receive 2L following discontinuation of 1L therapy (n, %)*	
Death	26 (59.1)
Patient choice	18 (40.9)
Other[†]	4 (9.1)
2L therapy	
Patient received 2L therapy (n, %)	
Yes	90 (30.0)
rwTFI between 1L and 2L therapy, among patients who initiated 2L (months)[a]	
n (%)	90 (30.0)
Median (P25-P75)	0.5 (0.4-0.7)
2L therapy received, among patients who received 2L therapy (n, %)	
Cabozantinib	59 (65.6)
Everolimus	2 (2.2)
Ipilimumab plus nivolumab	3 (3.3)
Lenvatinib plus everolimus	12 (13.3)
Nivolumab	8 (8.9)
Nivolumab plus cabozantinib	2 (2.2)
Temsirolimus	4 (4.4)
Primary reason for selecting 2L therapy, among patients who received 2L therapy (n, %)	
Patient choice	4 (4.4)
Method of administration	1 (1.1)
Standard of care/NCCN guidelines	54 (60.0)
Disease progression	31 (34.4)
rwDOT for 2L therapy, among patients who discontinued 2L (months)	
n (%)	46 (15.3)
Median (P25-P75)	6.5 (4.0-11.6)
rwDOT for 2L therapy, using KM Methods[c]	

Table 10.3-4. Post-index treatments

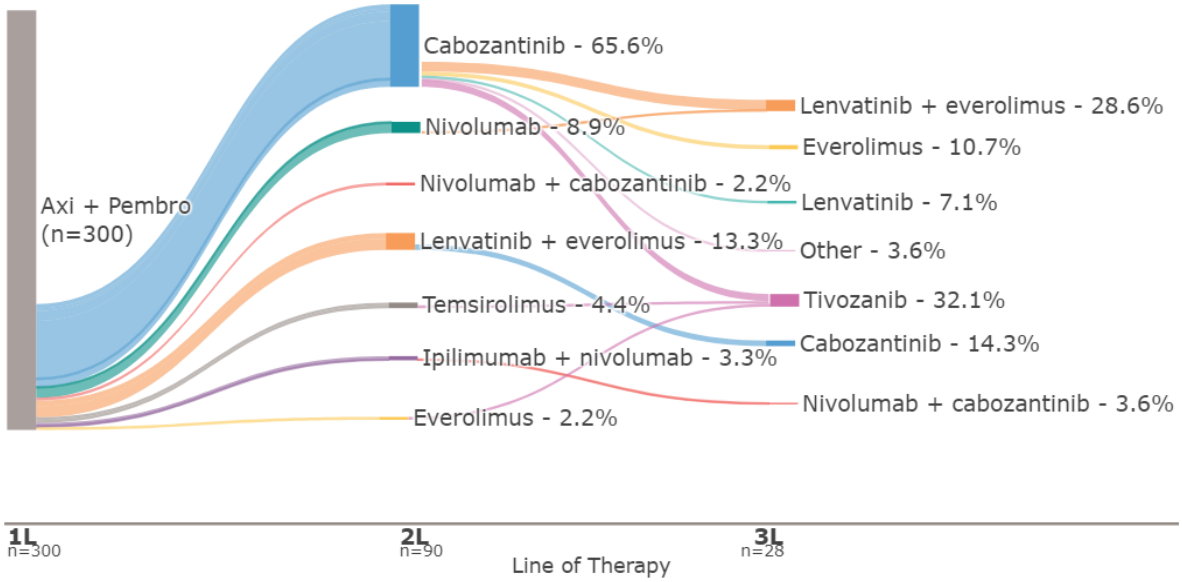
	All Patients (N=300)
N of Censored (%)	44 (48.9)
N of events (%)	46 (51.1)
KM Median [95% CI]	11.6 [7.8-16.3]
Primary reason for discontinuation of 2L therapy, among patients who discontinued 2L therapy (n, %)	
Disease progression (defined clinically)	2 (4.3)
Disease progression (confirmed with scan)	38 (82.6)
Toxicity/intolerability	3 (6.5)
Death	3 (6.5)
Third-line (3L) therapy	
Patient received 3L therapy (n, %)	
Yes	28 (9.3)
3L therapy received, among patients who received 3L therapy (n, %)	
Cabozantinib	4 (14.3)
Everolimus	3 (10.7)
Lenvatinib	2 (7.1)
Lenvatinib plus everolimus	8 (28.6)
Nivolumab plus cabozantinib	1 (3.6)
Tivozanib	9 (32.1)
Other[†]	1 (3.6)
Primary reason for selecting 3L therapy, among patients who received 3L therapy (n, %)	
Method of administration	1 (3.6)
Standard of care/NCCN guidelines	19 (67.9)
Disease progression	8 (28.6)
Primary reason for discontinuation of 3L therapy, among patients who discontinued 3L therapy (n, %)	
Disease progression (defined clinically)	2 (14.3)
Disease progression (confirmed with scan)	10 (71.4)
Toxicity/intolerability	1 (7.1)
Death	1 (7.1)

Table 10.3-4. Post-index treatments

	All Patients (N=300)

*Multiple responses were allowed.
†Full write-in responses can be found in the compendium.

Figure 3. Sankey diagram of 1L-3L treatment sequencing



10.3.2. Secondary objective #1 – Patient characteristics

10.3.2.1. Patient-level demographic characteristics

Overall, the majority of patients were male (61.0%), non-Hispanic (86.7%), and White (69.3%; **Table 10.3-5)**. Median age at aRCC diagnosis was 66.7 years. Most patients had either Medicare (46.7%) or commercial (41.3%) insurance.

Table 10.3-5. Patient baseline demographic characteristics.

	All Patients (n=300)
Age at initial RCC diagnosis (years)	
Median (P25-P75)	65.1 (58.6-71.9)
Age at aRCC diagnosis (years)	
Median (P25-P75)	66.7 (60.0-72.8)
Sex at birth (n, %)	

Table 10.3-5. Patient baseline demographic characteristics.

	All Patients (n=300)
Male	183 (61.0)
Female	117 (39.0)
Race (n, %)*	
American Indian or Alaska Native	1 (0.3)
Asian	20 (6.7)
Black or African-American	68 (22.7)
Native Hawaiian or Other Pacific Islander	3 (1.0)
White	208 (69.3)
Ethnicity (n, %)	
Hispanic or Latino	23 (7.7)
Not Hispanic or Latino	260 (86.7)
Unknown	17 (5.7)
Most recent primary insurance at data collection (n, %)	
Medicare	140 (46.7)
Medicaid	27 (9.0)
Commercial	124 (41.3)
Military	8 (2.7)
Self-pay	1 (0.3)
US region of residence (n, %)	
Northeast (CT, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT)	59 (19.7)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)	91 (30.3)
South (AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV	85 (28.3)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)	65 (21.7)

*Multiple responses were allowed.

10.3.2.2. Patient-level baseline clinical characteristics

Most patients' initial RCC diagnosis was metastatic (70.0%), while 26.0% had stage II or stage III disease at initial diagnosis (**Table 10.3-6**). At initiation of 1L axitinib + pembrolizumab, the majority of patients (59.3%) had an intermediate IMDC risk score, with 18.0% having favorable and 21.7% having poor risk scores. A minority of patients (11.3%) had sarcomatoid tumor features, and the most common tumor grades at aRCC diagnosis were grade 2 (36.0%) and grade 3 (33.7%). Lung (64.3%), bone (34.3%), liver (32.7%), and regional/distal lymph nodes (29.0%) were the most common sites of metastases prior to 1L axitinib + pembrolizumab.

Hypertension was the most common comorbidity reported for patients in this study (45.0%) followed by diabetes (22.7%). Most patients had relatively high performance, with the majority (78.3%) having an ECOG score of 0 or 1.

Table 10.3-6. Patient-level pre-index clinical characteristics

	All Patients (N=300)
Stage at initial RCC diagnosis (n, %)	
Stage I	12 (4.0)
Stage II	39 (13.0)
Stage III	39 (13.0)
Stage IV	210 (70.0)
Tumor grade at time of diagnosis of aRCC prior to initiation of 1L axitinib + pembrolizumab (n, %)	
G1: The cells are well differentiated	20 (6.7)
G2: The cells are moderately differentiated	108 (36.0)
G3: The cells are poorly differentiated	101 (33.7)
G4: The cells are undifferentiated	42 (14.0)
Unknown	29 (9.7)
Sarcomatoid features present in patient's tumor (n, %)	
Yes	34 (11.3)
No	262 (87.3)
Unknown	4 (1.3)
Site(s) of metastases identified prior to initiation of 1L axitinib + pembrolizumab for aRCC (n, %)*	
Adrenal gland	59 (19.7)
Bone	103 (34.3)
Brain	11 (3.7)
Local lymph node(s)	30 (10.0)
Regional/distal lymph node(s)	87 (29.0)
Skin/soft tissue	4 (1.3)
Gastrointestinal system	4 (1.3)
Genitourinary system	2 (0.7)
Ovary	2 (0.7)
Liver	98 (32.7)

Table 10.3-6. Patient-level pre-index clinical characteristics

	All Patients (N=300)
Lung	193 (64.3)
Pleura, pericardial, and/or peritoneal cavity	22 (7.3)
Most recent IMDC risk score at or prior to initiation of 1L axitinib + pembrolizumab therapy (n, %)	
Favorable risk	54 (18.0)
Intermediate risk	178 (59.3)
Poor risk	65 (21.7)
Unknown	3 (1.0)
Body mass index at initiation of 1L axitinib + pembrolizumab (kg/m^2)	
Median (P25-P75)	26.6 (24.0-29.1)
Comorbidities or chronic conditions present at initiation of 1L axitinib + pembrolizumab therapy for aRCC (n, %)*	
Cerebrovascular disease (CVD)	12 (4.0)
Chronic obstructive pulmonary disease (COPD)	42 (14.0)
Congestive heart failure (CHF)	24 (8.0)
Coronary artery disease	63 (21.0)
Dementia	4 (1.3)
Diabetes (with or without complications)	68 (22.7)
Hepatitis B	1 (0.3)
Hepatitis C	8 (2.7)
Hypertension	135 (45.0)
Liver disease (mild)	24 (8.0)
Myocardial infarction - history	21 (7.0)
Peptic ulcer disease	18 (6.0)
Peripheral vascular disease (PVD)	11 (3.7)
Renal disease	23 (7.7)
Rheumatologic disease	5 (1.7)
Other†	30 (10.0)
None of the above	83 (27.7)
Patient has CKD, among patients who had renal disease (n, %)	

Table 10.3-6. Patient-level pre-index clinical characteristics

	All Patients (N=300)
Yes	21 (91.3)
No	2 (8.7)
Stage of CKD, among patients who had CKD (n, %)	
Stage 1 with normal or high GFR (GFR > 90 mL/min)	1 (4.8)
Stage 2 Mild CKD (GFR = 60-89 mL/min)	11 (52.4)
Stage 3A Moderate CKD (GFR = 45-59 mL/min)	5 (23.8)
Stage 3B Moderate CKD (GFR = 30-44 mL/min)	4 (19.0)
Stage 4 Severe CKD (GFR = 15-29 mL/min)	0 (0.0)
Stage 5 End Stage CKD (GFR <15 mL/min)	0 (0.0)
NCI Comorbidity Index (continuous)	
Median (P25-P75)	0.1 (0.0-0.5)
ECOG-PS at time of or within 90 days prior to initiation of 1L axitinib + pembrolizumab therapy for aRCC (n, %)[§]	
0 - Fully active; no restriction	73 (24.3)
1 - Restricted in strenuous physical activities; fully ambulatory and able to carry out light work.	162 (54.0)
2 - Capable of all self-care but unable to carry out any work activities; up and about >50 percent of waking hours.	59 (19.7)
3 - Capable of only limited self-care; confined to bed or chair >50 percent of waking hours.	6 (2.0)
4 – Completely disabled; could not carry out any self-care; totally confined to bed or chair.	0 (0.0)

*Multiple responses were allowed.

[†]Full write-in responses can be found in the compendium.

[§]KPS was included in the eCRF for collection should any patient be missing ECOG-PS. As all patients had ECOG-PS data available, KPS was empty and is not presented here.

10.3.3. Secondary objective #2 – Provider perspectives

10.3.3.1. Physician-identified factors influencing selection of initial therapy for aRCC

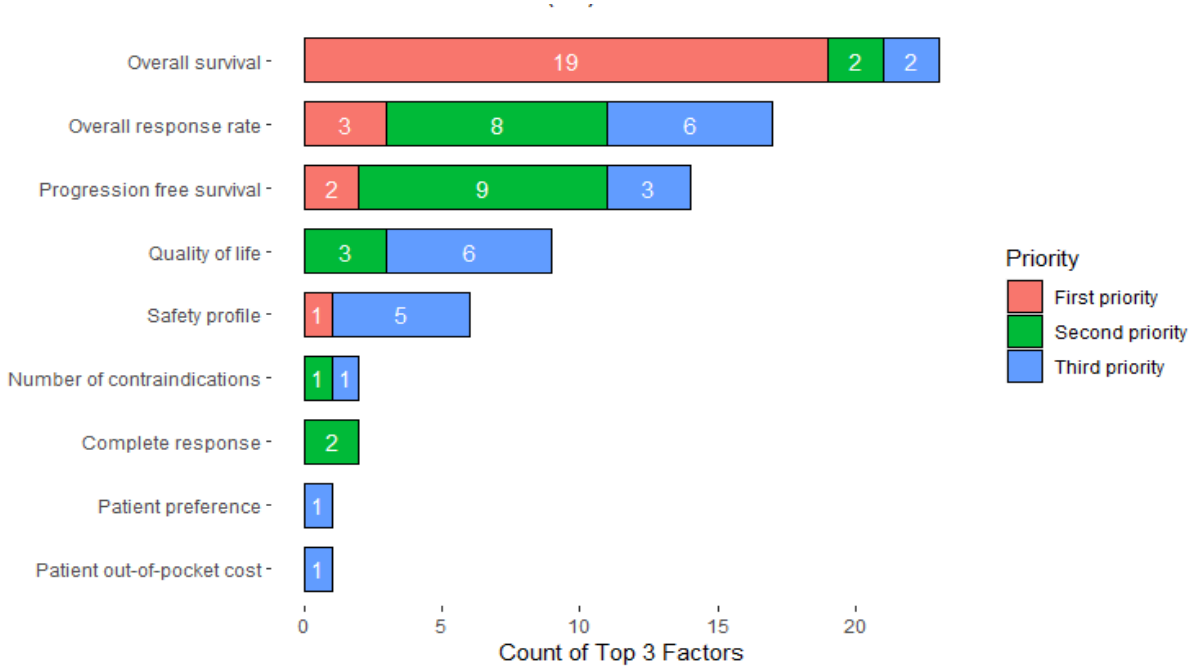
When surveyed on the three most influential factors in their selection of 1L axitinib + pembrolizumab for aRCC, most providers selected OS (92.0%), with high response levels also apparent for ORR (68.0%) and PFS (56.0%; **Table 10.3-7**). The most common top factor (i.e., ranked as the most influential) was OS, as 76.0% of providers selected this as their top choice (**Figure 4**).

Table 10.3-7. Provider perspectives on 1L treatment selection

	All Providers (N=25)
Top three factors that influence choice of 1L axitinib + pembrolizumab treatment for aRCC, times reported overall (n, %)[a]	
Complete response	2 (8.0)
Overall response rate	17 (68.0)
Overall survival	23 (92.0)
Number of contraindications	2 (8.0)
Patient compliance	0 (0.0)
Patient out-of-pocket cost	1 (4.0)
Patient preference	1 (4.0)
Practice reimbursement	0 (0.0)
Progression-free survival	14 (56.0)
Quality of life	9 (36.0)
Safety profile	6 (24.0)
Treatment-free interval	0 (0.0)
Trial follow-up time	0 (0.0)
Times factor was reported as most important in selection of top three factors that influence choice of 1L axitinib + pembrolizumab treatment for aRCC (n, %)[a]	
Overall response rate	3 (12.0)
Overall survival	19 (76.0)
Progression free survival	2 (8.0)
Safety profile	1 (4.0)

[a]Providers were allowed to select three top factors

Figure 4. Provider-identified top 3 factors influencing choice of axitinib + pembrolizumab as 1L treatment for aRCC.



10.3.3.2. Treatment management approaches for 1L axitinib + pembrolizumab

Providers most frequently cited adverse events and disease progression (84.0%) as factors that influence dose modifications and/or discontinuation for 1L axitinib + pembrolizumab, with almost half of providers also citing patient request to stop treatment (48.0%; **Table 10.3-8**). For tools in managing AEs, most providers had access at their practice to laboratory testing (84.0%), but only 64.0% reported having access to multispecialty consultation. Providers most frequently identified hepatotoxicity (66.7%), diarrhea (57.1%), and fatigue/asthenia (47.6%) as the most concerning AEs during 1L axitinib + pembrolizumab. Interruption in axitinib treatment was the most commonly used tool in distinguishing AE etiology, and when deciding whether to modify treatment versus discontinue after an AE of moderate severity, patient comorbidities (76.2%) and patient performance status (71.4%) were the most frequently reported influential factors. When managing grade 1/2 AEs (**Figure 5**), providers selected the most treatment management actions for hepatotoxicity, with treatment interruptions in pembrolizumab being the most common (66.7%) followed by interruption of axitinib (52.4%), and dose reduction of axitinib (33.3%). Similarly for Grade 3/4 AEs (**Figure 6**), the largest number of typical treatment management actions were observed for hepatoxicity followed by rash and diarrhea.

Table 10.3-8. Provider perspectives on 1L axitinib + pembrolizumab treatment management

	All Providers (N=25)
Factors, other than completion of scheduled treatment duration or death, that influence dose modifications and/or treatment discontinuations for 1L axitinib + pembrolizumab for aRCC (n, %)*	
Adverse events	21 (84.0)
Disease progression	21 (84.0)
Financial factors	5 (20.0)
Patient request to stop treatment	12 (48.0)
Tool(s) available at provider's practice used for AE management (n, %)*	
Laboratory testing (e.g., liver enzyme tests, CBC, renal function [e.g., creatinine], stool culture)	21 (84.0)
Multispecialty consultation (e.g., consult with nephrology)	16 (64.0)
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)	19 (76.0)
Most concerning AEs encountered during provider's practice, based on the known safety profile of the regime, among providers who cited AEs as a reason for dose modifications and/or treatment discontinuations for 1L axitinib + pembrolizumab in aRCC (n, %)*	
Cough	1 (4.8)
Decreased appetite	4 (19.0)
Diarrhea	12 (57.1)
Fatigue/asthenia	10 (47.6)
Hepatotoxicity	14 (66.7)
Hypertension	9 (42.9)
Hypothyroidism	6 (28.6)
Nausea	2 (9.5)
Palmar-plantar erythrodysesthesia	9 (42.9)
Rash	2 (9.5)
Stomatitis/mucosal inflammation	8 (38.1)
Tool(s) used to distinguish AE etiology to determine if AE is related to 1L axitinib + pembrolizumab vs. immune-related, among providers who cited AEs as a reason for dose modifications and/or treatment discontinuations for 1L axitinib + pembrolizumab in aRCC (n, %)*	

Interruption of axitinib treatment	21 (100.0)
Laboratory tests	18 (85.7)
Resolution of AE with corticosteroids	16 (76.2)
Most influential factors in decision to modify, as opposed to discontinue 1L axitinib + pembrolizumab therapy, if a patient experiences an AE of moderate severity while being treated for aRCC, among providers who cited AEs as a reason for dose modifications and/or treatment discontinuations for 1L axitinib + pembrolizumab in aRCC (n, %)*	
Availability of suitable subsequent line of therapy	10 (47.6)
Disease response prior to AE	6 (28.6)
First-time AE vs recurrent AE	13 (61.9)
Patient compliance	7 (33.3)
Patient comorbidities	16 (76.2)
Patient performance status	15 (71.4)
Patient preference	8 (38.1)
Probability the AE will fully resolve	14 (66.7)
Type of AE	14 (66.7)

*Multiple responses were allowed.

Figure 5. Typical therapy management chosen by providers (N=21) in response to grade 1/2 adverse events during first-line axitinib + pembrolizumab treatment for patients with aRCC

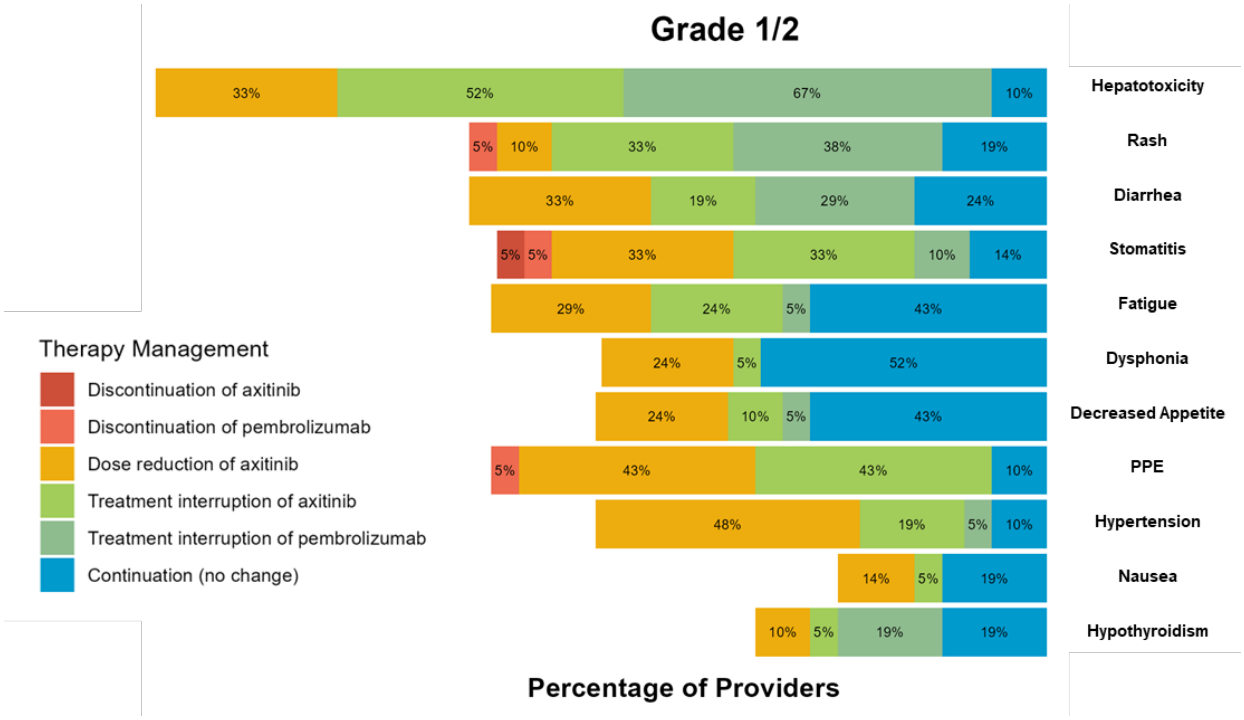
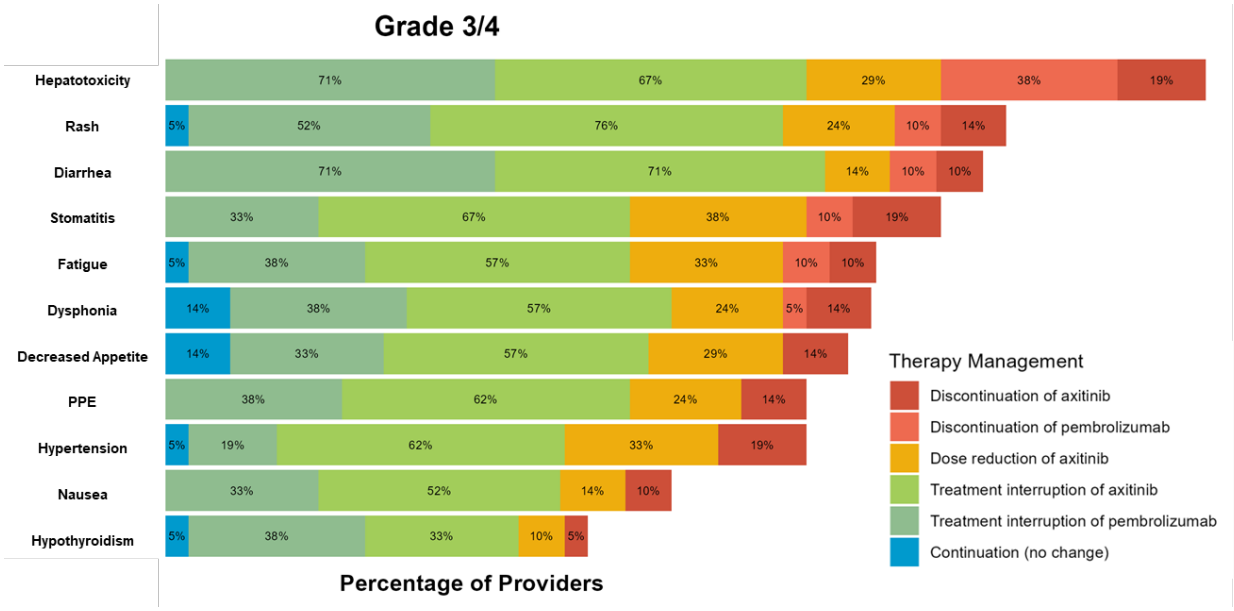


Figure 6. Typical therapy management chosen by providers (N=21) in response to grade 3/4 adverse events during first-line axitinib + pembrolizumab treatment for patients with aRCC



10.3.4. Exploratory objective #1 – Clinical outcomes

10.3.4.1. Real-world response

Physician-reported response data to 1L axitinib + pembrolizumab were available for 98.0% of patients (**Table 10.3-9**). Initial response to 1L axitinib + pembrolizumab was reported for 27.3% of patients, with 13.3% reporting a PR and 4.0% reporting stable disease. Most patients had a reported best response (90.3%), with the majority reporting PR (61.3%) followed by stable disease (16.7%) and CR (12.3%). Physician-reported rwORR among all patients in this study was 73.7% (95% CI: 68.5%-78.8%). For patients with a response of CR or PR, median rwDOR was 16.6 months (95% CI: 14.3-19.1).

Table 10.3-9. Real-world response during 1L axitinib + pembrolizumab

	All Patients (N=300)
Patients with any disease response scans (initial, best, progression) assessed during 1L axitinib + pembrolizumab (n, %)	
Yes	294 (98.0)
Initial response to 1L axitinib + pembrolizumab therapy (n, %)	
Partial response	40 (13.3)
Stable disease	12 (4.0)
Not reported/available	248 (82.7)

Table 10.3-9. Real-world response during 1L axitinib + pembrolizumab

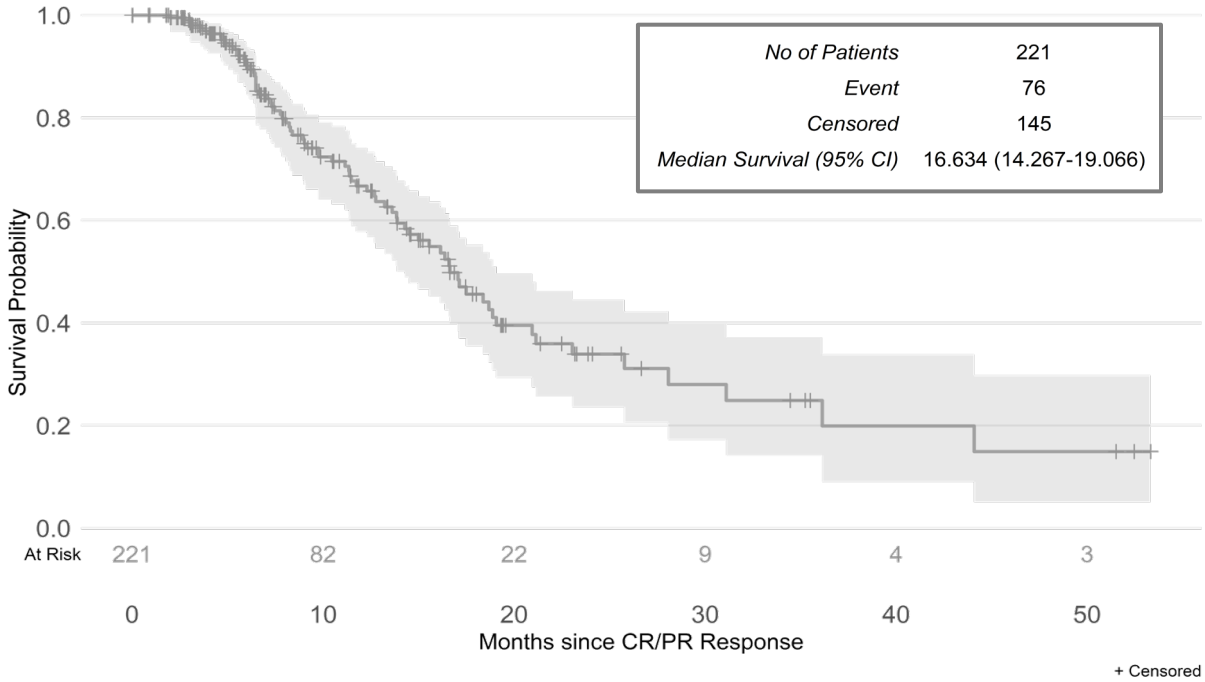
	All Patients (N=300)
Best response to 1L axitinib + pembrolizumab therapy (n, %)	
Complete response	37 (12.3)
Partial response	184 (61.3)
Stable disease	50 (16.7)
Not reported/available	29 (9.7)
rwORR for 1L axitinib + pembrolizumab, among patients with disease response scans (n, %)[a]	
N (%)	221 (75.2)
95% CI	[70.1-80.3]
rwORR for 1L axitinib + pembrolizumab, among all patients (n, %)[a]	
N (%)	221 (73.7)
95% CI	[68.5-78.8]
Time to response (CR or PR) during 1L, among patients with a documented best response of PR or CR (months)[b]	
n (%)	221 (81.6)
Median (P25-P75)	4.2 (3.0-7.4)
rwDOR using KM Methods (months)[c]	
N of Censored (%)	145 (65.6)
N of events (%)	76 (34.4)
KM Median [95% CI]	16.6 [14.3-19.1]

[a]Number of patients with CR or PR during 1L axitinib + pembrolizumab therapy divided by the total number of patients with treatment response assessed (initial, best, progression) during 1L index axitinib + pembrolizumab therapy

[b]Among patients with a documented best response of CR or PR, time from initiation of 1L index axitinib + pembrolizumab therapy to best physician-reported response (CR or PR)

[c]Among patients with a documented best response of CR or PR, time from physician-reported best response during 1L axitinib + pembrolizumab therapy to physician-reported disease progression or death (events) or start date of next line or date of last encounter, whichever comes first (censored)

Figure 7. KM curve for rwDOR from date of best response (CR or PR)



10.3.4.2. Real-world progression-free survival

At last follow-up, 38.0% of patients had experienced progression while on 1L axitinib + pembrolizumab (**Table 10.3-10**). In this study, median rwPFS was estimated as 19.5 months (95% CI: 17.3-21.3; **Figure 8**). Per the point estimate of rwPFS at 12 months post-initiation of 1L axitinib + pembrolizumab, the probability of a patient having not experienced progression or death by 12 months was estimated as 0.75 (95% CI: 0.67-0.79).

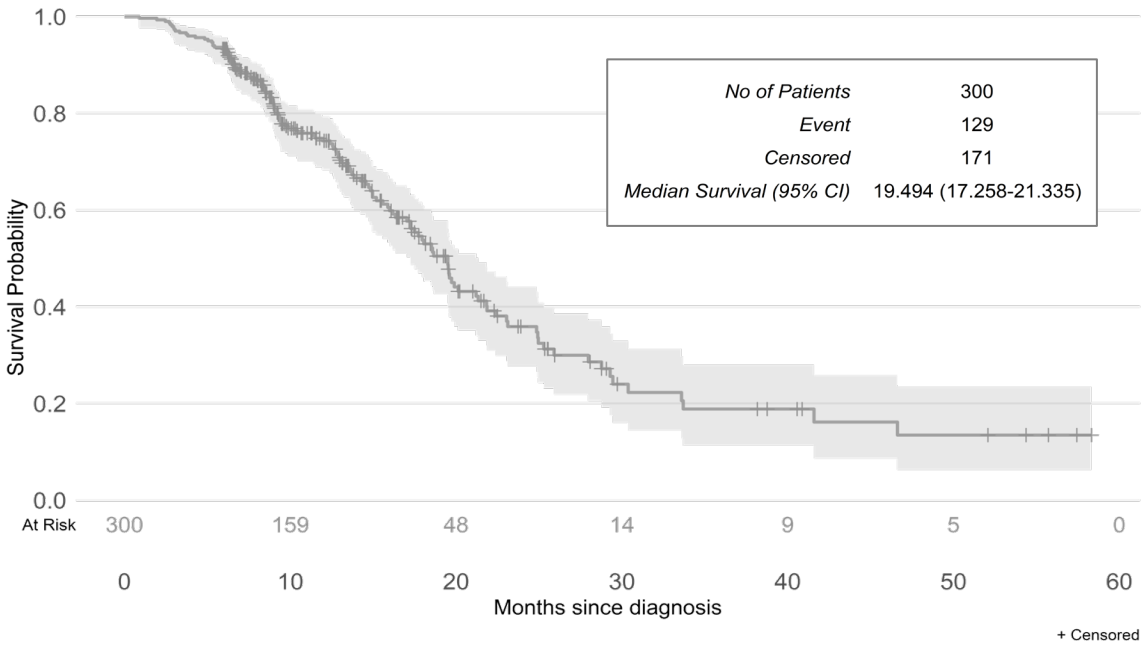
Table 10.3-10. Real-world progression-free survival (rwPFS)

	All Patients (N=300)
Patient progressed while on 1L axitinib + pembrolizumab (n, %)	
Yes	114 (38.0)
rwPFS from initiation of 1L (months)[a]	
N of Censored (%)	171 (57.0)
N of events (%)	129 (43.0)
KM Median [95% CI]	19.5 [17.3-21.3]
3-month rwPFS from initiation of 1L	
N at Risk (%)	292 (97.3)
Point Estimate [95% CI]	0.97 [0.95-0.99]
6-month rwPFS from initiation of 1L	

N at Risk (%)	274 (91.3)
Point Estimate [95% CI]	0.93 [0.90-0.96]
12-month rwPFS from initiation of 1L	
N at Risk (%)	138 (46.0)
Point Estimate [95% CI]	0.74 [0.68-0.79]
18-month rwPFS from initiation of 1L	
N at Risk (%)	67 (22.3)
Point Estimate [95% CI]	0.54 [0.46-0.61]
24-month rwPFS from initiation of 1L	
N at Risk (%)	31 (10.3)
Point Estimate [95% CI]	0.36 [0.28-0.44]

[a]Time from initiation of 1L axitinib + pembrolizumab to disease progression or death from any cause, whichever occurred first (events) or last date of communication (censored).

Figure 8. KM curve for rwPFS from initiation of 1L axitinib + pembrolizumab



10.3.4.3. Real-world overall survival

At last follow-up, 20.7% of patients (n=62) had died, with the most common cause of death being disease progression (75.8%; **Table 10.3-11**). Median rwOS was not reached in this

study (**Figure 9**), with the probability of a patient surviving 12-months post-initiation of 1L axitinib + pembrolizumab of 0.85 (95% CI: 0.80-0.89).

Table 10.3-11. rwOS

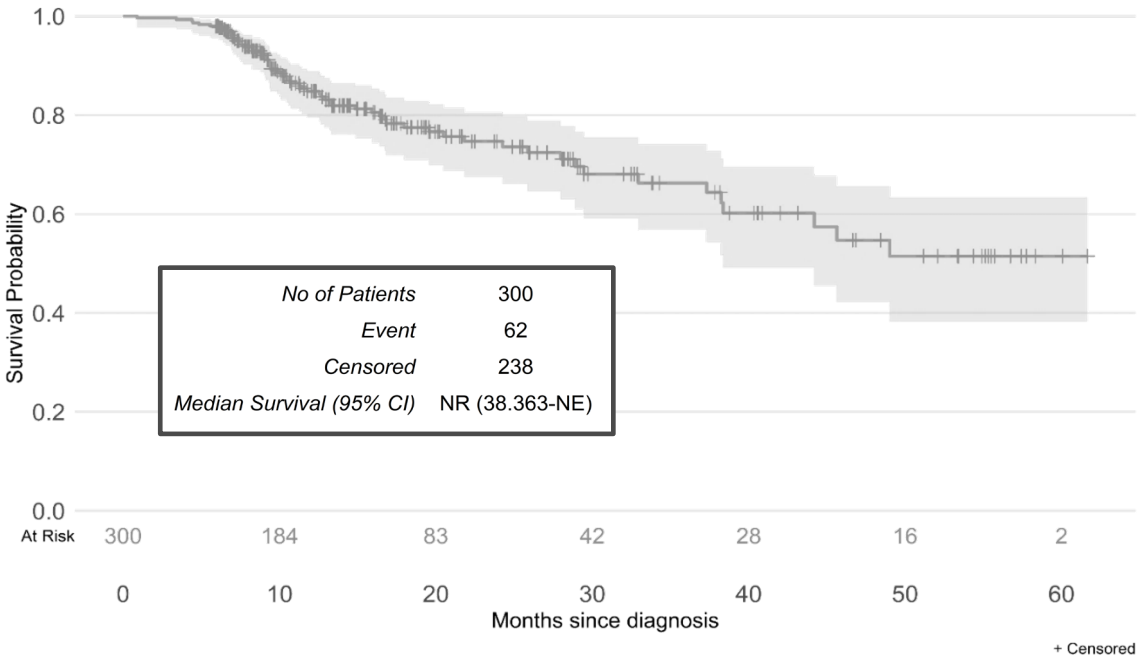
	All Patients (N=300)
Patient vital status at data collection (n, %)	
Alive	238 (79.3)
Deceased	62 (20.7)
Cause of death, among patients who were deceased at data collection (n, %)	
Disease progression	47 (75.8)
Toxicity related to treatment	1 (1.6)
COVID-19 related	1 (1.6)
Unknown, data not available	5 (8.1)
Other[†]	8 (12.9)
rwOS from initiation of 1L axitinib + pembrolizumab (months)[a]	
N of Censored (%)	238 (79.3)
N of events (%)	62 (20.7)
KM Median [95% CI]	NR [38.4-NE]
3-month rwOS from initiation of 1L axitinib + pembrolizumab	
N at Risk (%)	299 (99.7)
Point Estimate [95% CI]	1.00 [0.98-1.00]
6-month rwOS from initiation of 1L axitinib + pembrolizumab	
N at Risk (%)	286 (95.3)
Point Estimate [95% CI]	0.98 [0.96-0.99]
12-month rwOS from initiation of 1L axitinib + pembrolizumab	
N at Risk (%)	157 (52.3)
Point Estimate [95% CI]	0.85 [0.80-0.89]
18-month rwOS from initiation of 1L axitinib + pembrolizumab	
N at Risk (%)	97 (32.3)
Point Estimate [95% CI]	0.78 [0.71-0.83]

24-month rwOS from initiation of 1L axitinib + pembrolizumab	
N at Risk (%)	69 (23.0)
Point Estimate [95% CI]	0.75 [0.67-0.81]

[†]Full write-in responses can be found in the compendium.

[a]Time from initiation of 1L axitinib + pembrolizumab to death (event) or, if patient is still alive, date of last encounter (censored).

Figure 9. KM curve for rwOS from initiation of 1L axitinib + pembrolizumab



10.4. Outcome data

Not applicable.

10.5. Adverse events / adverse reactions

10.5.1. Treatment of AEs during data collection

Primary Data Collection

The physician survey used in this study was not intended to identify product safety information. The physician survey for this study was completed online via a secure website. The physician survey did 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 was not expected during the conduct of the study. However, if a study participant volunteered 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 was reported as described below.

The following safety events were reported on the non-interventional study (NIS) adverse event monitoring (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, were not reportable unless associated with serious or non-serious adverse events.

In the event that a study participant volunteered product safety information, the study vendor completed the NIS AEM Report Form and submitted it to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form was the study participant's contact information; as complete of contact information as possible was 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.

The study vendor who was available to study participants to answer questions during completion of the data collection tool completed the following Pfizer training requirements:

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

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

Re-training was completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issued an updated safety training program, including during the course of a calendar year, vendor ensured all vendor personnel completed the updated safety training within sixty (60) calendar days of issuance by Pfizer.

Secondary Data Collection

This study required 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 was obligated to report AEs with explicit attribution to any Pfizer drug that appeared in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution was not inferred by a temporal relationship between drug administration and an AE but was 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 were as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appeared in the reviewed information must have been 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 have been 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, were 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 was captured in the Event Narrative section of the report form, and constituted all clinical information known regarding these AEs. No follow-up on related AEs were conducted.

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

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “Drug Name” were 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 completed the following Pfizer training requirements:

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

These trainings were completed by research staff members prior to the start of data collection. All trainings included a “Confirmation of Training Statement” (for signature by the trainee) as a record of completion of the training, which was kept in a retrievable format. Copies of all signed training statements were provided to Pfizer.

Re-training was completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issued an updated safety training program, including during the course of a calendar year, vendor ensured all vendor personnel completed the updated safety training within sixty (60) calendar days of issuance by Pfizer.

10.5.1.1. Aggregated AE data

In this study, secondary data was collected on AEs that resulted in a 1L axitinib + pembrolizumab dose modification and/or discontinuation (**Table 10.5-1**). A minority of patients (n=58; 19.3%) experienced an AE that caused a dose modification and/or discontinuation of 1L axitinib + pembrolizumab, with the most common reported AE being fatigue (n=21; 7.0%). Detailed information (date of onset, highest grade, care received, cause, resolution, treatment management) on AEs resulting in a dose modification and/or discontinuation was collected, with the exception of AEs that were not explicitly included in the provided list of AEs but instead selected as “Other.” The median time from initiation of 1L axitinib + pembrolizumab to first AE that resulted in a dose modification/discontinuation was 1.7 months, with a slightly shorter time to first severe AE (Grade 3+) resulting in a dose modification/discontinuation (1.2 months). Median time from initiation of 1L axitinib + pembrolizumab to first AE-associated

dose modification was 1.4 months, whereas the median time from 1L initiation to AE-associated discontinuation was longer (8.4 months).

Table 10.5-1. Adverse events during 1L axitinib + pembrolizumab that resulted in a dose modification and/or discontinuation

	All Patients (n=300)
Patient experienced an AE that caused a dose modification and/or discontinuation of 1L axitinib + pembrolizumab therapy (n,%)	
Yes	58 (19.3)
No	242 (80.7)
AE/toxicity that caused a dose modification and/or discontinuation of 1L axitinib + pembrolizumab therapy (n, %)*	
Asthenia	4 (1.3)
Decreased appetite	9 (3.0)
Diarrhea	14 (4.7)
Dysphonia	2 (0.7)
Erythrodysesthesia (hand-foot) syndrome	8 (2.7)
Fatigue	21 (7.0)
Hypertension	11 (3.7)
Vomiting	2 (0.7)
Weight loss	7 (2.3)
Other¥	16 (5.3)
Number of AEs that caused a dose modification and/or discontinuation of 1L axitinib + pembrolizumab therapy per patient, among patients who experienced at least one AE that caused a dose modification and/or discontinuation	
n (%)	58 (100.0)
Median (P25-P75)	2.0 (1.0-2.0)
Time from 1L axitinib + pembrolizumab initiation to first AE that caused a dose modification and/or discontinuation, among patients who experienced at least one AE that resulted in a dose modification and/or discontinuation (months)¥	
n (%)	45 (77.6)
Median (P25-P75)	1.7 (0.8-3.0)

Table 10.5-1. Adverse events during 1L axitinib + pembrolizumab that resulted in a dose modification and/or discontinuation

	All Patients (n=300)
Time from 1L axitinib + pembrolizumab initiation to first severe AE (Grade 3+) that caused a dose modification and/or discontinuation, among patients who experienced at least one severe AE that resulted in a dose modification and/or discontinuation (months)¥	
n (%)	24 (41.4)
Median (P25-P75)	1.2 (0.7-2.4)
Time from 1L axitinib + pembrolizumab initiation to first AE that caused a dose modification, among patients who experienced at least one AE that resulted in a dose modification (months)¥	
n (%)	42 (72.4)
Median (P25-P75)	1.4 (0.7-3.0)
Time from 1L axitinib + pembrolizumab initiation to first AE that caused a discontinuation, among patients who experienced at least one AE that resulted in a discontinuation (months)¥	
n (%)	10 (17.2)
Median (P25-P75)	8.4 (1.7-25.0)

¥If "Other" was selected for the AE/toxicity that caused a dose modification and/or discontinuation, no further details about the AE beyond the number of times experienced were collected; overall, 13/58 patients with a reported AE had experienced only a non-listed (i.e., "other") AE.

*Multiple responses were allowed.

10.6. Other analyses

In addition to results for all patients, exploratory stratified results were generated and presented in the study compendium for the following subgroups, which were selected after reviewing the initial descriptive results for all patients:

- By sex (Male; Female)
- By age at aRCC diagnosis (≤70 years; >70 years)
- By race (White; Non-White)
- By IMDC risk score (Favorable; Intermediate/Poor)

11. DISCUSSION

11.1. Key results

Primary Objective #1

The majority of patients were able to start 1L axitinib + pembrolizumab at the FDA-recommended initial dose and few required axitinib dose reductions, supporting that therapy management via dose modifications of 1L axitinib + pembrolizumab may affect only a minority

of patients. Nevertheless, the frequency of dose modifications/treatment discontinuation due to AEs reported in this study is lower than that observed in the KEYNOTE-426 trial[1] as well as a recent real-world study on 1L axitinib + pembrolizumab.[3] In KEYNOTE-426, 25.9% of patients (111/429) experienced an AE that led to treatment discontinuation, 20.0% of patients (86/426) experienced an AE that led to an axitinib reduction, and 62.2% of patients (267/429) experienced an AE that led to a treatment interruption.[1] Similarly, a prior real-world study observed that 31.3% of patients (92/294) underwent a first dose hold, 8.2% of patients (24/294) a first dose change, and 15.0% of patients (44/294) their first discontinuation due to treatment-related toxicity.[3] These numbers are higher than those observed in this study (42/300 [14.0%] who experienced an AE that resulted in a dose modification [reduction or hold]; 10/300 [3.3%] who experienced an AE that led to treatment discontinuation). As this study only collected toxicity-related information on AEs that resulted in treatment changes, it is not possible to compare the overall frequency of AEs reported between studies. Nevertheless, any cross-study comparisons should be done cautiously, as no adjustments for patient baseline characteristics have been made and comparisons may not reflect true differences in treatment results.

In this study, the observed rwDOT was longer than that observed in KEYNOTE-426 (18.6 months [95% CI: 17.0-21.2] vs. 10.4 months [range: 0.0-21.2]). These differences may reflect the high level of censoring at relatively low follow-up present in the current study as well as that participating providers may not treat and/or have abstracted a representative sample of the full population of patients with aRCC receiving 1L axitinib + pembrolizumab. These limitations should be kept in mind when interpreting the clinical outcome results and further follow-up to allow the data to mature for these outcomes is recommended.

Secondary Objective #1

In terms of patient demographics, patients included in this study were majority male (61.0%), non-Hispanic (86.7%), and White (69.3%), which is broadly similar to demographics reported in the prior real-world study (e.g., 69.6% male; 67.9% White) and the KEYNOTE-426 trial (e.g., 71.3% male; no race reported).[1, 3] The current study included patients with intermediate/poor performance status (21.7% with ECOG-PS of 2+), which were not included in the KEYNOTE-426 trial based on the eligibility criteria. While the recent real-world study also included patients with higher ECOG-PS scores (14.4% with ECOG-PS of 2+), it should be noted that missingness in the ECOG-PS variable for that study was relatively high (17.6%). Similarly, the current study included more patients with intermediate/poor IMDC scores than prior studies. With the presence of less healthy patients in the current study, the broadly positive results observed support use of 1L axitinib + pembrolizumab even in patient groups not well-represented in the KEYNOTE-426 trial.

Secondary Objective #2

Providers were most concerned about hepatotoxicity, diarrhea, and fatigue when managing patients receiving 1L axitinib + pembrolizumab, and hepatotoxicity was the AE for which providers indicated the most therapy management actions (e.g., interruptions, reductions, discontinuations). When managing AEs that may occur during 1L axitinib + pembrolizumab, some treating physicians also indicated that did not have access to resources on AE management (e.g., guidelines, multispecialty consultation), highlighting a potential opportunity for further education on treatment management.

While median rwOS was not reached in the current study, 12-month rwOS (12-month: 0.85 [95% CI: 0.80-0.89]) was broadly similar to results observed in a prior real-world study (12-month rwOS: 0.74 [no 95% CI provided])[3] and KEYNOTE-426 (12-month rwOS: 0.90 [95% CI: 0.86-0.92].[2] Nevertheless, rwPFS observed in this study (12-month rwPFS: 0.74 [95% CI: 0.68-0.79]) was higher than in a real-world study on 1L axitinib + pembrolizumab using electronic medical records (e.g., rwPFS at 12-months: 0.39 [no 95% CI provided])[3] and KEYNOTE-426 (12-month PFS: 0.60 [95% CI: 0.55-0.65]).[2] Similarly, the rwORR was higher in the current study versus in KEYNOTE-426. As mentioned above, these differences may reflect the high level of censoring at relatively low follow-up present in the current study as well as that participating providers may not treat a representative sample of the full population of patients with aRCC receiving 1L axitinib + pembrolizumab. These limitations should be kept in mind when interpreting the clinical outcome results and further follow-up to allow the data to mature for these outcomes is recommended.

11.2. Strengths and limitations of the research methods

The extensive Cardinal Health network of oncologists/hematologists is geographically diverse, EMR/GPO-agnostic, and inclusive of multiple settings of community oncology care. Physician-abstracted retrospective medical chart review also provides in-depth knowledge of treatment patterns, clinical outcomes, and rationale for treatment decisions by physicians for patients under their care, ensuring high quality by reducing reliance on assumptions. Physician study participants represented the major US regions (Midwest, Northeast, South, West); small, medium and large practice sizes; mostly urban and suburban settings, and approximately 75% were community-based oncology practices and 25% were associated with an academic center. Data from this study may also contribute insights regarding under-represented patient groups, as 30% of patients were non-White.

While this study has several strengths, as a retrospective observational study of secondary data, there is the potential for multiple biases which may impact the findings. Patients were selected by participating physicians based on pre-specified eligibility criteria and the recruitment of physicians was limited to those in Cardinal Health's OPEN network who met requirements for participating in the study. Hence, findings may not be generalizable to all patients who received 1L axitinib + pembrolizumab or all US physicians treating patients with this regimen. Additionally, the median follow-up time in our study was relatively short at 12.3 months. Any future study will be designed to further evaluate long-term outcomes. Source document verification was not conducted; however, data was subjected to rigorous quality control measures and all physicians were required to submit to data validation checks, with failure to correctly validate data resulting in exclusion. Data related to events occurring outside of the treating physician's practice or that were not captured in the medical record may have been missing from this analysis, potentially impacting the findings.

11.3. Interpretation

Overall, the observed frequency of dose modifications and/or discontinuations, including due to treatment-related toxicity, was lower in this study than in prior studies. As this study only collected toxicity-related information on AEs that resulted in treatment changes (modifications or discontinuation), it is not possible to compare the overall frequency of AEs reported between studies. Nevertheless, any cross-study comparisons should be done cautiously, as no adjustments for patient baseline characteristics have been made and comparisons may not reflect true differences in treatment results. rwDOT was also longer in the present study,

and as mentioned above, this difference may reflect the high level of censoring at relatively low follow-up present in the current study as well as that participating providers may not treat a representative sample of the full population of patients with aRCC receiving 1L axitinib + pembrolizumab (i.e., patient populations are not directly comparable with unadjusted methods). These limitations should be kept in mind when interpreting the clinical outcome results and further follow-up to allow the data to mature for these outcomes is recommended.

Patients in this study were potentially less healthy than in other prior studies, and the broadly positive results therefore support use of 1L axitinib + pembrolizumab even in patients who were not included in the KEYNOTE-426 trial. While most providers indicated that they utilize therapy management in response to occurrence of AEs, providers did not all have access to laboratory testing, multispecialty consultation, and published guidelines, highlighting that these areas may be potential targets for improving therapy management for patients receiving 1L axitinib + pembrolizumab. Time-to-event results, while estimable for several outcomes, were in line or higher than those observed in prior studies. As there was a high frequency of censoring in this study, particularly in the 6 to 12-month post-initiation period, longer follow-up would be recommended to let the data further mature.

11.4. Generalizability

This study employed purposive sampling that selects physicians and patients based on pre-specified selection criteria and hence, our findings may not be representative of all patients with aRCC treated with axitinib + pembrolizumab or representative of all physicians treating patients with this regimen. Treatment patterns reflected in the study represent only the practices of physicians who have agreed 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 are available to describe non-responders.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

This study provides insights into provider perspectives on treatment management for 1L axitinib + pembrolizumab as well as real-world treatment patterns for patients with aRCC treated with 1L axitinib + pembrolizumab in the US community setting. When managing AEs that may occur during 1L axitinib + pembrolizumab, some treating physicians did not have access to resources on AE management (e.g., guidelines, multispecialty consultation), highlighting a potential opportunity for further education on treatment management. Further studies with longer follow-up are needed to understand the potential impact of 1L axitinib + pembrolizumab treatment modification on clinical outcomes for aRCC, particularly with the high levels of censoring in the current study.

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15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable.