CoLab Network

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Drugs | Health Technologies | Health Systems

Protocol

Drugs for Advanced Renal Cell Carcinoma: A Treatment Pattern Analysis

Final Project Protocol

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Abbreviations

CCRE	Canadian Cancer Real-world Evaluation
ICI	immune checkpoint inhibitor
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
mTOR	mammalian target of rapamycin
RCC	renal cell carcinoma
TKI	tyrosine kinase inhibitor

Abstract

Renal cell carcinoma (RCC) is the most common type of renal cancer and over the past 10 years, the treatment options have evolved substantially. In addition to mammalian target of rapamycin inhibitors (mTORs), tyrosine kinase inhibitors (TKIs) of VEGFRs and immune checkpoint inhibitors (ICIs) have been introduced. However, there is currently a paucity of real-world evidence on how these options are used and how long patients typically continue with various treatments. In this study, the Canadian Cancer Real-world Evaluation (CCRE) Platform will conduct a treatment pattern analysis to identify the sequence of treatments for patients with RCC who started publicly funded first-line renal cancer treatments. Results from this study will help inform discussions on system and resource planning, and potentially prompt future analyses relating to RCC treatments in Canada.

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Amendments and Updates

Table 1: Version History

Version	Version date	Location (e.g., heading, page)	Amendment description and rationale
1	May 8, 2024	NA – first draft	
2	May 21, 2024	Throughout document	Altered protocol based on PMDE comments on the version from May 8, 2024
3	July 2, 2024	Throughout document	Altered protocol based on clinical expert reviewer comments on the version from May 8, 2024, and made final editorial changes
4	July 8, 2024	Throughout document	Final editorial changes
5	March 4, 2025	Throughout document	Final style and editorial changes, changes to participant roles: • updated exclusion criterion 1.3 • updated "end of treatment after first/second/third drug exposure" variable definition • removed 4 variables pertaining to the fourth drug exposure since this was not reported • altered font on page 4 and changed some numbered lists to be bulleted lists • spelled out the word "multiplied" instead of using "x."

NA = not applicable; PMDE = Post-Market Drug Evaluation.

Background and Rationale

Condition

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 90% of all cases worldwide.[1] Approximately 8,100 Canadians were diagnosed with kidney and renal pelvis cancer in 2022, of which 85% of cases were attributed to RCC.[2] RCCs are further classified into different subtypes based on histology including clear cell (conventional or class), non-clear cell (papillary, chromophobe, collecting duct, or medullary), and unclassified. The clear cell component subtype is the most prevalent form of RCC and represents more than 70% of all RCC cases in practice.[3] More than one-third of patients are identified with metastatic disease at initial diagnosis, because most patients experience few or no symptoms at earlier stages.[4] Among those diagnosed at earlier stages, 30% of patients with stage I to III disease experience recurrence after surgical resection.[5] When patients experience symptoms, they commonly present with flank pain, visible blood in the urine, a noticeable mass in the abdomen, loss of appetite, fatigue, pain, and anemia.[6,7] Patients who develop metastatic disease are reported to have 5-year survival rates ranging from 0% to 20%.[6]

Drug Treatments

The last 2 decades have seen significant advancements in therapies for patients with treatment naive advanced clear cell RCC, particularly with the introduction of VEGFR tyrosine kinase inhibitors (TKIs) and, more recently, immune checkpoint inhibitors (ICIs) in this therapeutic area.[8-10] Treatment decisions are guided by prognostic risk models, particularly the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group classification (favourable, intermediate, and poor).[10] More than 80% of patients with metastatic cancer are classified in the intermediate-risk or poor-risk subgroups.[10] There is no standard therapy for non-clear cell RCC, and it is generally accepted that patients with non-clear cell histology should be treated similarly to patients with clear cell histology.

Before the introduction of ICIs, VEGFR TKIs were commonly used as first-line treatment. Presently, the use of an ICI in combination with another ICI (e.g., an anti–PD-1 with anti–CTLA-4 monoclonal antibody) or with a VEGFR TKI has been reported as a preferred treatment strategy in the first-line setting for patients with good performance status without significant comorbidities. These combinations may be followed by monotherapy with a VEGFR TKI upon disease progression. Funding criteria may limit treatment options beyond the second line. Before the emergence of these newer therapies, mammalian target of rapamycin (mTOR) inhibitors like everolimus and temsirolimus were commonly used to treat advanced RCC.[11]

Gaps in Knowledge

A broad range of systemic treatments and treatment combinations are available to patients with advanced RCC; however, there is a paucity of information on how these options are currently used and how long patients continue with these treatments. This study will identify patterns in the use of systemic treatment options, as patients progress through different lines of therapy, and describe treatment duration and dose for specific therapies.

Expected Contribution of This Study

The findings will be used to determine potential areas of drug funding pressures. The information from this study will be used to inform and focus system and resource planning and/or prompt development of other projects to address additional clinical and economic questions impacting treatment of advanced RCC.

Policy Question

1. How are drugs for advanced RCC currently used?

Policy Impact

The findings of this study will be used to determine the current drug utilization and treatment patterns for advanced RCC in the setting in Canada.

Research Questions

1. What is the volume of prescription drugs used in the treatment of advanced RCC in the past 5 years?
2. In what sequence are drugs used in treating advanced RCC?
3. How long, on average, are patients treated for each treatment episode?
4. What are the patient characteristics along the treatment sequence?

Study Overview

Table 2: Study Objective

Objective	To describe real-world use and sequence of publicly funded systemic therapies in the treatment of patients with advanced RCC
Population	Individuals aged 18 years and older who start publicly funded systemic therapy (sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, nivolumab, cabozantinib, pembrolizumab + axitinib, or nivolumab + ipilimumab) for the treatment of advanced RCC.
Drug utilization measures	Rates and proportions of publicly funded first-line therapies; rates and proportions of identified subsequent therapies
Patient characteristics and subgroups	Descriptive patient characteristics: clinical and demographic characteristics Subgroups: time-era stratifications, age stratification (< 65 years or ≥ 65 years), stratification on first-line treatment or common sequences (exploratory or sample size permitting)
Time	Accrual period: January 1, 2017, to December 31, 2022 (Ontario) January 1, 2017, to December 31, 2021 (Alberta) January 1, 2017, to December 31, 2021 (British Columbia) Observation period: Between start date of first-line treatment (index date) and December 31, 2023. Patients are followed until death or end of study period.
Setting	This study will examine patients in the outpatient setting in Ontario, Alberta, and British Columbia.
Main measure of effect	The numbers and proportions of advanced RCC patients receiving specified first-line and post–first-line anticancer therapies.

RCC = renal cell carcinoma.

Research Methods

Study Design

A retrospective cohort study assessing patterns of treatment for patients with advanced RCC was used.

Study Design Diagrams

Figure 1: Study Design Diagram for Ontario

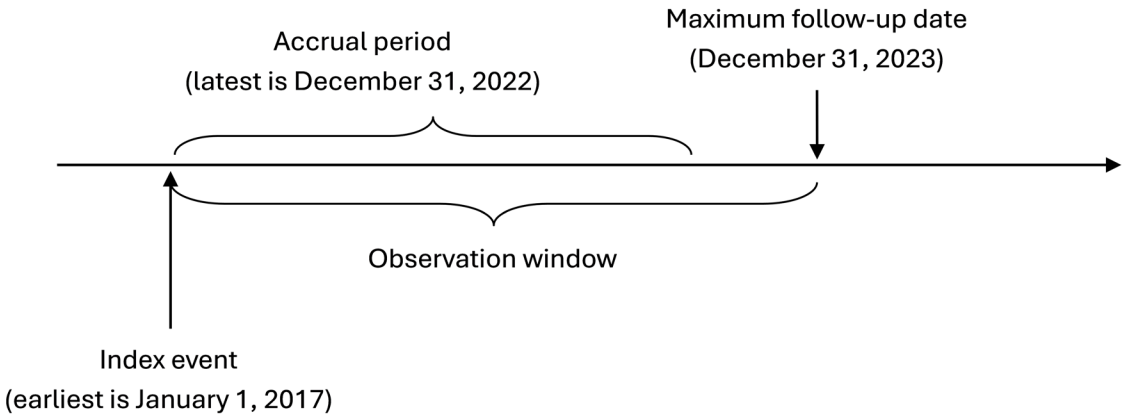

Figure 2: Study Design Diagram for Alberta

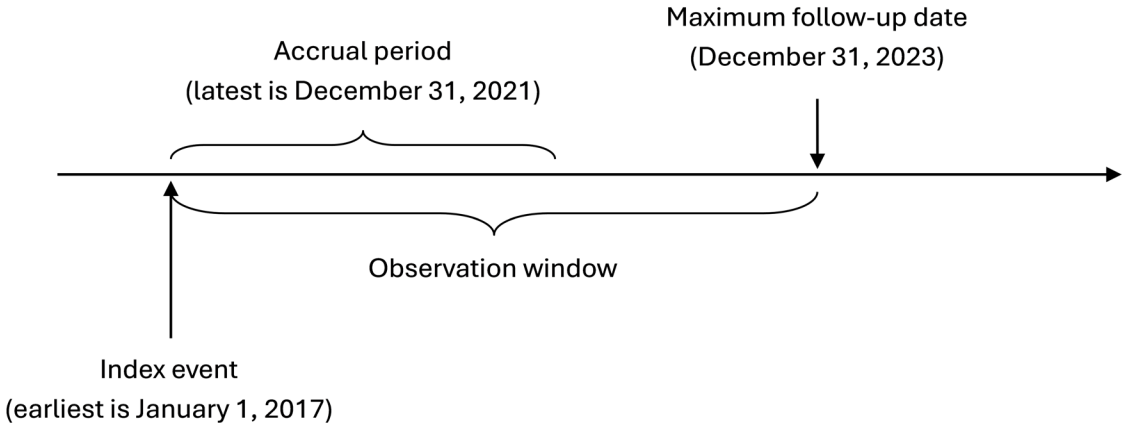

Figure 3: Study Design Diagram for British Columbia

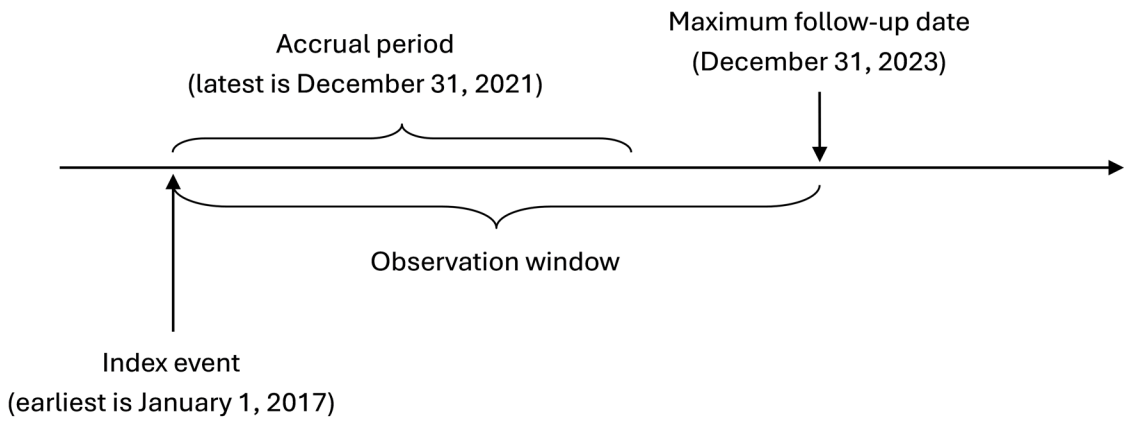

Table 3: Key Dates for Study Design by Province

Study design details	Key dates		
	Ontario	Alberta	British Columbia
Accrual window for patients	January 1, 2017, to December 31, 2022	January 1, 2017, to December 31, 2021	January 1, 2017, to December 31, 2021
Index date	Start date of publicly funded first-line therapy for advanced RCC (sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, nivolumab, cabozantinib, pembrolizumab + axitinib, or nivolumab + ipilimumab)		
Lookback window	Up to 5 years before the index date (earliest is January 1, 2012)		
Observation window	Between start date of first-line treatment (index date, earliest is January 1, 2017) and December 31, 2023.		
Maximum follow-up date	December 31, 2023		

RCC = renal cell carcinoma.

Study Population and Setting

Table 4: Study Population

Term	Criteria or definition
Index date (and rationale)	The index date in this study will be the first date of publicly funded first-line treatment for patients with RCC. This date was chosen because the objective of this study is to characterize patients who receive these treatments and to determine the subsequent treatment regimens they undergo. Therefore, it is pertinent for the patients of this study to enter the cohort on the first day they receive first-line treatment. This is an exposure-based method to build the cohort (i.e., identify treatment exposures, then ensure all patients in the group are diagnosed with RCC), in which we would ascertain a cohort of patients who started one of the publicly funded RCC treatments. Using this method, we would systemically exclude anyone who starts treatment using a non-publicly funded regimen (e.g., clinical trial or non-publicly funded combination of drugs). The authors considered a diagnosis-based approach (i.e., identify all individuals with RCC and then identify their first treatment) to capture the group of patients who may start renal cancer

Term	Criteria or definition
	treatment other than the specified publicly funded treatments (i.e., the other treatment category); however, the authors found that this will be a very small group based on a feasibility analysis conducted at the Ontario site of the CCRE Platform. Additionally, some patients who received other treatments may not be captured in our databases due to data limitations. Therefore, the authors (in consultation with PMDE and those who submitted the query), decided that the cohort for this study would be a homogenous group of individuals who started publicly funded RCC treatment.
Ontario cohort	
Inclusion criteria	The cohort will consist of patients with RCC who start publicly funded systemic treatment between January 1, 2017, and December 31, 2022, and had a diagnosis of RCC before the index treatment (ICD-O-3 site: C64.9, C65.9). **Step A:** Identify patients (and their treatment dates) who were exposed to RCC treatments between January 1, 2017, and December 31, 2022 (ODB, ALR, NDFP): • This includes treatment with sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipilimumab + nivolumab, cabozantinib, or pembrolizumab + axitinib (refer to the DIN list in Appendix 1). • Keep the earliest treatment within the accrual period as the index date. **Step B:** Among these patients who receive renal cancer treatments, identify those with an RCC diagnosis in OCR: • Identify patients from OCR to obtain diagnosis date and cancer characteristics for RCC (ICD-O-3 = C64.9, C65.9) (refer to Appendix 1 for histology codes). • If there are multiple RCC diagnosis dates, keep the first one.
Exclusion criteria	1. **Checkpoint:** Output the number of patients with an additional primary cancer diagnosis before the RCC diagnosis and after the RCC diagnosis: 1.1. For any patients with an additional non-RCC diagnosis after index date, censor on the non-RCC diagnosis date. Do not exclude these patients. 1.2. Exclude any patients with an additional non-RCC diagnosis between RCC diagnosis date and index date. 1.3. Exclude patients who have a non-RCC diagnosis within 5 years before the RCC diagnosis of interest. 2. **Checkpoint:** Output the number of patients who have additional treatments between index date and diagnosis date. This will help identify those who started first-line treatment outside of the accrual period. This group will be excluded. 3. Invalid patient identification number. 4. If less than 18 years of age. 5. Invalid death date (death before index date; RPDB). 6. Invalid sex (missing; RPDB). 7. Non-Ontario resident status on index date.
Alberta cohort	
Inclusion criteria	The cohort will include all patients in Alberta who were treated for RCC with sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipilimumab + nivolumab, cabozantinib, or pembrolizumab + axitinib, between January 1, 2017, and December 31, 2021, and had a diagnosis of RCC (ICD-O-3 site: C64.9, C65.9). **Step A:** Identify patients (and their treatment dates) who were exposed to RCC treatments between January 1, 2017, and December 31, 2021 (PIN): • This includes treatment with sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus,

Term	Criteria or definition
	nivolumab, ipilimumab + nivolumab, cabozantinib, or pembrolizumab + axitinib (refer to the DIN list in Appendix 1). • Keep the earliest treatment within the accrual period as the index date. **Step B:** Among these patients who receive renal cancer treatments, identify those with an RCC diagnosis in ACR: • Identify patients from ACR to obtain diagnosis date and cancer characteristics for RCC (ICD-O-3 = C64.9, C65.9) (refer to Appendix 1 for histology codes). • If there are multiple RCC diagnosis dates, keep the first one.
Exclusion criteria	1. Invalid patient identification number. 2. **Checkpoint:** Output the number of patients with an additional primary cancer diagnosis before the RCC diagnosis and after the RCC diagnosis: 2.1. For any patients with an additional non-RCC diagnosis after index date, censor on the non-RCC diagnosis date. Do not exclude these patients. 2.2. Exclude any patients with an additional non-RCC diagnosis between RCC diagnosis date and index date. 2.3. Exclude patients who have a non-RCC diagnosis within 5 years before the RCC diagnosis of interest. 3. **Checkpoint:** Output the number of patients who have additional treatments between index date and diagnosis date. This will help identify those who started first-line treatment outside of the accrual period. This group will be excluded. 4. Not referred (i.e., not in pharmacy or patient records). 5. Invalid date of death (death before index date). 6. Non-Alberta resident on index date.
British Columbia cohort	
Inclusion criteria	The cohort will include all patients treated for RCC with sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipilimumab + nivolumab, cabozantinib, or pembrolizumab + axitinib for RCC between January 1, 2017, and December 31, 2021, and had a diagnosis of RCC (ICD-O-3 site: C64.9, C65.9). **Step A:** Identify patients (and their treatment dates) who were exposed to RCC treatments between January 1, 2017, and December 31, 2021 (BC Cancer Pharmacy database): • This includes treatment with sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipilimumab + nivolumab, cabozantinib, or pembrolizumab + axitinib (refer to the DIN list in Appendix 1). • Keep the earliest treatment within the accrual period as the index date. **Step B:** Among these patients who receive renal cancer treatments, identify those with an RCC diagnosis in the BC Cancer Registry: • Identify patients from the BC Cancer Registry to obtain diagnosis date and cancer characteristics for RCC (ICD-O-3 = C64.9, C65.9) (refer to Appendix 1 for histology codes). • If there are multiple RCC diagnosis dates, keep the first one.
Exclusion criteria	1. Non-RCC histology (refer to Appendix 1 for histology codes). 2. **Checkpoint:** Output the number of patients with an additional primary cancer diagnosis before the RCC diagnosis and after the RCC diagnosis: 2.1. For any patients with an additional non-RCC diagnosis after index date, censor on the non-RCC diagnosis date. Do not exclude these patients. 2.2. Exclude any patients with an additional non-RCC diagnosis between RCC diagnosis date and

Term	Criteria or definition
	index date. 2.3. Exclude patients who have a non-RCC diagnosis within 5 years before the RCC diagnosis of interest. 3. **Checkpoint:** Output the number of patients who have additional treatments between index date and diagnosis date. This will help identify those who started first-line treatment outside of the accrual period. This group will be excluded. 4. Non-British Columbia resident at start of first-line therapy. 5. Aged 18 years or less at diagnosis. 6. Diagnosis date before January 1, 2002.

ACR = Alberta Cancer Registry; ALR = Activity Level Report; CCRE = Canadian Cancer Real-world Evaluation; DIN = drug identification number; NDFP = New Drug Funding Program; ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; OCR = Ontario Cancer Registry; ODB = Ontario Drug Benefits; PIN = Pharmaceutical Information Network; PMDE = Post-Market Drug Evaluation; RPDB = Registered Persons Database; RCC = renal cell carcinoma.

Study Variables

Table 5: Baseline Variables

Variable	Variable definition	Variable output
Age	**Definition:** age in years **Assessment period:** index date **Database:** RPDB (Ontario), ACR (Alberta), BC Cancer Registry (British Columbia)	1 continuous variable
Sex	**Definition:** sex categorized as male, female **Assessment period:** index date **Database:** RPDB (Ontario), ACR (Alberta), BC Cancer Registry (British Columbia)	1 categorical variable with 2 levels
Income quintile	**Definition:** neighbourhood income quintile **Assessment period:** index date **Database:** RPDB (Ontario), Census Tract (Alberta)	1 categorical variable with 6 levels (1 lowest, 2, 3, 4, 5 highest, missing)
Rurality	**Definition:** urban versus rural area of residence **Assessment period:** index date **Database:** RPDB (Ontario), Census Tract (Alberta)	1 categorical variable with 3 levels: yes, no, missing
Charlson Comorbidity Index score	**Definition:** Charlson Comorbidity Index score for 2 years before index date. Exclude category 14 (cancer) from total, to capture only comorbidities unrelated to cancer diagnosis. **Assessment period:** up to 2-year lookback period before index date **Database:** CIHI-DAD (Ontario, Alberta)	1 categorical variable with 4 levels: 0, 1, 2+, or missing
Year of RCC cancer diagnosis	**Definition:** year of cancer diagnosis **Assessment period:** any time before index date (Alberta, Ontario); 2002 onward (British Columbia) **Database:** OCR (Ontario), ACR (Alberta), BC Cancer Registry (British Columbia)	1 categorical variable (levels to be defined based on frequency distribution)

Variable	Variable definition	Variable output
Time from diagnosis to index	**Definition:** time from diagnosis date to index date in days **Assessment period:** from diagnosis date to index date **Database:** OCR (Ontario), EMRs (Alberta), BC Cancer Registry (British Columbia)	1 continuous variable
Stage at diagnosis	**Definition:** highest stage at diagnosis **Assessment period:** at diagnosis date Databases: BC Cancer Registry (British Columbia)	1 categorical variable with 5 levels: 1, 2, 3, 4, or missing
Tumour histology	**Definition:** tumour histology at diagnosis Refer to Appendix 1 for grouping of ICD-O-3 histology codes **Assessment period:** at diagnosis date **Database:** OCR (Ontario), ACR (Alberta), BC Cancer Registry (British Columbia)	1 categorical variable with 4 levels (clear cell, papillary, chromophobe, other)
Nephrectomy (partial or radical)	**Definition:** indicator for surgical resection of primary cancer CIHI intervention (CCI) or procedure (CCP) codes and service date received by patient before index date and after diagnosis date Refer to Appendix 1 for diagnosis and procedure codes. **Assessment period:** from diagnosis date to index date **Database:** CIHI-DAD, CIHI-SDS, OCR (Ontario), BC Cancer Surgery Network database (British Columbia), ACR (Alberta)	1 categorical variable with 3 levels: yes, no, missing

ACR = Alberta Cancer Registry; BC = British Columbia; CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CIHI-DAD = Canadian Institute for Health Information – Discharge Abstract Database; CIHI = Canadian Institute for Health Information; CIHI-SDS = Canadian Institute for Health Information – Same Day Surgery; ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; OCR = Ontario Cancer Registry; PIN = Pharmaceutical Information Network; RCC = renal cell carcinoma; RPDB = Registered Persons Database.

Table 6: Outcome Variables of Interest

Variable	Variable definition	Variable output
Death date	**Definition:** date of death for patients who died during observation period **Assessment period:** observation period **Database:** RPDB (Ontario) BC Cancer Registry (British Columbia), ACR (Alberta)	1 indicator variable (1 = died, 0 = death not observed) 1 date variable; missing if death not observed
Censor date	**Definition:** date of last follow-up for patients not observed to die during observation period Follow-up ends at the earliest of: • end of observation period • date of last contact, if patient is no longer a provincial resident	1 date variable; missing if death is observed

Variable	Variable definition	Variable output
	• date of additional non-RCC diagnosis. **Assessment period:** observation period **Database:** RPDB (Ontario), BC Cancer Registry (British Columbia), ACR (Alberta)	
Survival time	**Definition:** time in days from index date to death or censoring **Assessment period:** observation period **Database:** constructed from death date, censor date	1 continuous variable
First drug exposure category	**Definition:** indicator for the specific treatment used as the first treatment exposure: sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipililumab + nivolumab, cabozantinib, or pembrolizumab + axitinib **Assessment period:** index date **Database:** ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 categorical variable with 10 levels: sunitinib, pazopanib, sorafenib, axitinib, everolimus, temsirolimus, nivolumab, ipililumab + nivolumab, cabozantinib, or pembrolizumab + axitinib 1 date variable
Duration of first drug exposure	**Definition:** Time in days from index date to last dispensing or administration date of first drug exposure. Total duration of first drug exposure, including any breaks or gaps in treatment. If treatment is an oral medication, add the days' supply of the last dispensing date to the dispensing date. If treatment is IV, indicate cycle length in days. **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable
Time on treatment during first drug exposure	**Definition:** treated time, in days, during first drug exposure, excluding any gaps or breaks in treatment If treatment is an oral medication, sum of the total days supply dispensed during the first exposure period. If treatment is IV, sum of the total days treated (number of dispensed cycles × cycle length). **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable
Total dose during first drug exposure	**Definition:** total dose of drug during first exposure **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), BC Cancer Pharmacy database (British Columbia)	1 continuous variable

Variable	Variable definition	Variable output
End of treatment after first drug exposure	**Definition:** Indicator for whether a patient has ended treatment after first-line treatment or if they have ongoing treatment. Patients were considered to have ended treatment if they died following first drug exposure, or if they were not observed to start a subsequent therapy (second drug exposure) and had at least 30 days of observation between the end of first drug exposure and end of follow-up (censor date). **Assessment period:** observation period **Databases:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 binary variable (1 = ended treatment, 0 = ongoing treatment)
Second drug exposure	**Definition:** indicator for initiation of second drug exposure Flag individuals who received a second drug exposure, defined as the drug name after dispensed or administered after the first-line therapy. For oral medications, start of second line may occur before the end of the dispensing date + days supply of the first line therapy. For IV drugs, it will be after the administration of first-line therapy. **Assessment period:** observation period, following first-line **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 indicator variable (1 = initiated second line; 0 = no second-line therapy)
Start of second drug exposure	**Definition:** start date for second drug exposure Start of second drug, defined as the first dispending record following the end of first drug exposure. **Assessment period:** from end of first drug to death or censoring **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 date variable; NA if patient did not initiate second drug exposure
Duration of second drug exposure	**Definition:** Time in days from start of second drug exposure (previously mentioned) to last dispensing or administration date of second-line therapy. Total duration of second drug exposure, including any breaks or gaps in treatment. If treatment is an oral medication, add the days supply of the last dispensing to the dispensing date. If treatment is IV, indicate cycle length in days. **Assessment period:** observation period **Database:** constructed from ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable; NA if patient did not initiate second drug exposure

Variable	Variable definition	Variable output
Time on treatment during second drug exposure	**Definition:** treated time, in days, during second drug exposure, excluding any gaps or breaks in treatment If treatment is an oral medication, sum of the total days' supply dispensed during the second exposure period. If treatment is IV, sum of the total days treated (number of dispensed cycles multiplied by cycle length). **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable
Total dose during second drug exposure	**Definition:** total dose of drug during second exposure **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), BC Cancer Pharmacy database (British Columbia)	1 continuous variable
End of treatment after second drug exposure	**Definition:** Indicator for whether a patient has ended treatment after second drug exposure or if they have ongoing treatment. Patients were considered to have ended treatment if they died following second drug exposure, or if they were not observed to start a subsequent therapy (third drug exposure) and had at least 30 days of observation between end of second drug exposure and end of follow-up (censor date). **Assessment period:** observation period **Databases:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 binary variable (1 = ended treatment, 0 = ongoing treatment)
Second drug exposure category	**Definition:** Indicator for the specific treatment used as the second drug exposure. Categorized by drug name: • single-agent nivolumab • single-agent axitinib • single-agent cabozantinib • single-agent pazopanib • single-agent sunitinib • others: any other anticancer treatment that is not listed in the previously mentioned 5 groups. This includes mTOR inhibitors. **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 categorical variable with 6 levels; NA if patient did not initiate second drug exposure

Variable	Variable definition	Variable output
Third drug exposure	**Definition:** indicator for initiation of third drug exposure Flag individuals who received a third drug exposure, defined as the drug name after dispensed or administered after the second drug exposure. For oral medications, start of third-line therapy may occur before the end of the dispensing date + days supply of the second-line therapy, but for IV drugs, it will be after the administration of second drug exposure. **Assessment period:** observation period, following second drug exposure **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 indicator variable (1 = initiated third line; 0 = no third drug exposure)
Start of third drug exposure	**Definition:** start date for third drug exposure Start of third drug exposure, defined as the first dispending record following the end of second drug exposure. **Assessment period:** from end of second drug exposure to death or censoring **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 date variable; missing if patient did not initiate third drug exposure
Duration of third drug exposure	**Definition:** Time in days from start of third drug exposure to last dispensing date of third drug exposure or administration date of drug exposure. Total duration of third drug exposure, including any breaks or gaps in treatment. If treatment is an oral medication, add the days supply of the last dispensing to the dispensing date. If treatment is IV, indicate cycle length in days. **Assessment period:** observation period **Database:** constructed from ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable; NA if patient did not initiate third drug exposure
Time on treatment during third drug exposure	**Definition:** treated time, in days, during third drug exposure, excluding any gaps or breaks in treatment If treatment is an oral medication, sum of the total days supply dispensed during the third exposure period. If treatment is IV, sum of the total days treated (number of dispensed cycles multiplied by cycle length). **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 continuous variable

Variable	Variable definition	Variable output
Total dose during third drug exposure	**Definition:** total dose of drug during third exposure **Assessment period:** observation period **Database:** constructed from ODB, ALR and NDFP (Ontario), BC Cancer Pharmacy database (British Columbia)	1 continuous variable
End of treatment after third drug exposure	**Definition:** Indicator for whether a patient has ended treatment after third drug exposure or if they have ongoing treatment. Patients were considered to have ended treatment if they died following third drug exposure, or if they were not observed to start a subsequent therapy (fourth drug exposure) and had at least 30 days of observation between the end of third drug exposure and end of follow-up (censor date). **Assessment period:** observation period **Databases:** constructed from ODB, ALR and NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 binary variable (1 = ended treatment, 0 = ongoing treatment)
Third drug exposure category	**Definition:** Indicator for the specific treatment used in the third line. Categorized by drug name: • single-agent nivolumab • single-agent axitinib • single-agent cabozantinib • others: any other anticancer treatment that is not listed in the previously mentioned 5 groups. This includes mTOR inhibitors. **Database:** ODB (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 categorical variable with 4 levels; missing if patient did not initiate third drug exposure
Fourth drug exposure	**Definition:** indicator for initiation of fourth drug exposure Flag individuals who received a fourth drug exposure, defined as the drug name after it was dispensed or administered after third-line therapy. For oral medications, start of fourth line may occur before the end of the dispensing date + days supply of the third-line therapy. For IV drugs, it will be after the administration of third drug exposure. **Assessment period:** observation period, following third drug exposure **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	1 indicator variable (1 = initiated third line; 0 = no additional therapy past third drug exposure)
Start of fourth drug exposure	**Definition:** start date for fourth drug exposure Start of fourth drug exposure, defined as the first dispending record following the end of third drug exposure. **Assessment period:** from end of third drug	1 date variable; NA if patient did not initiate fourth drug exposure

Variable	Variable definition	Variable output
	exposure to death or censoring **Database:** ODB, ALR, NDFP (Ontario), PIN (Alberta), BC Cancer Pharmacy database (British Columbia)	

ACR = Alberta Cancer Registry; ALR = Activity Level Reporting; BC = British Columbia; mTOR = mammalian target of rapamycin; NA = not applicable; NDFP = New Drug Funding Database; ODB = Ontario Drug Benefits; PIN = Pharmaceutical Information Network; RCC = renal cell carcinoma; RPDB = Registered Persons Database.

Data Analysis

Table 7: Descriptive Analyses

Descriptive measure	Details
Exposure	Treatment with publicly funded first-line treatment for RCC
Measures of interest	1. The numbers and proportions of patients with RCC receiving different classes of anticancer therapies by year and line of therapy. 2. Sequencing of therapies after first-line treatment. 3. We will summarize treatment progression and sequencing in a flow diagram. To account for censoring at the end of the follow-up period, the progression of patients through lines of therapy will be presented 2 ways: with censoring as a separate state in the flow diagram, and with the frequency distributions weighed using the inverse probability of censoring.
Analytic software	SAS 9.4 (Ontario, British Columbia) R (v.4.3.2 in Alberta)
Sampling and weighting	NA
Missing data methods	NA
Bias due to loss to follow-up	Our cohort will be subject to uninformative censoring at the end of the follow-up period. Patients will be censored if they are alive at the end of the study period (December 31, 2023) or are diagnosed with a new primary cancer during the study period. Survival analysis methods that account for censoring will be used in the analysis of time-to-event data. Median and restricted mean treatment duration for each treatment exposure will be estimated using the Kaplan-Meier method, using the longest available time horizon (tau) common to all provinces. We will account for censoring in our analysis of treatment sequencing in 2 ways: by treating censoring as a separate health state, and by weighting observed patients by the inverse probability of censoring. The probability of being observed (i.e., not censored) at each treatment exposure will be estimated using Kaplan-Meier survival methods. Observed individuals will then be reweighted using these probabilities to represent individuals who are not observed due to right censoring.

NA = not applicable; RCC = renal cell carcinoma.

Data Sources

Table 8: Data Sources by Province

Province and data type	Data sources
Ontario	
Cohort creation	• **ODB database:** all records of publicly funded medications in Ontario • **ALR database:** records of visits to oncology centres in Ontario • **NDFP:** all records of new and expensive injectable cancer drugs administered in

Province and data type	Data sources
	hospital settings in Ontario • **OCR:** records of cancer diagnoses • **RPDB:** demographics data
Clinical and demographic characteristics	• **CIHI-DAD:** all records of procedures and diagnoses that occur in an inpatient setting • **CIHI-SDS:** records of same day surgeries • **OHIP:** all records of procedures and diagnoses that occur in an outpatient setting • **NDFP** • **OCR** • **ODB** • **ALR** • **RPDB**
Outcomes	• **CIHI-NACRS database:** all records of procedures and diagnoses that occur in the ambulatory setting • **CIHI-DAD** • **OHIP** • **CIHI-SDS** • **ODB** • **RPDB**
Alberta	
Cohort creation	PIN database: all records of prescription medications dispensed in Alberta for all payers Alberta Cancer Registry: records of patient demographics, cancer diagnosis, and mortality
Clinical and demographic characteristics and outcomes	Alberta Cancer Registry: records of patient demographics, cancer diagnosis, and mortality
British Columbia	
Cohort creation	• **BC Provincial Systemic Therapy Program (pharmacy database):** pharmacy dispensing records for all publicly funded systemic therapies • **BC Cancer Registry:** records of patient demographics, cancer diagnosis, and mortality
Clinical and demographic characteristics and outcomes	• **BC Cancer Registry:** records of patient demographics, cancer diagnosis, and mortality • **BC Provincial Systemic Therapy Program (pharmacy database):** pharmacy dispensing records for all publicly funded systemic therapies • **BC Cancer Surgery database:** records of all surgical procedures received by patients living in British Columbia with cancer from 6-months before diagnosis onward

ALR = Activity Level Report Reporting; BC = British Columbia; CIHI-DAD = Canadian Institute for Health Information – Discharge Abstract Database; CIHI-NACRS = Canadian Institute for Health Information – National Ambulatory Care Reporting System; CIHI-SDS = Canadian Institute for Health Information – Same Day Surgery; NDFP = New Drug Funding Program; OCR = Ontario Cancer Registry; ODB = Ontario Drug Benefits; OHIP = Ontario Health Insurance Plan; PIN = Pharmaceutical Information Network; RPDB = Registered Persons Database.

Study Size, Precision, and Feasibility

A power or sample size calculation is not required for this utilization study.

Limitations

Ontario:

- No staging information for RCC.
- Elements required to calculate IMDC score is not available for all patients and therefore the IMDC score for patients in this cohort will not be reported.
- VEGFR TKIs are oral medications, which can only be identified among patients eligible for public drug funding. Therefore, we may underreport the overall number of patients in Ontario who receive these medications. However, this does capture individuals who are eligible for the Ontario public drug program.

Alberta:

- Alberta Cancer Registry data complete to the end of 2021. Data on the IMDC score is unavailable.
- No dosing information was available for RCC.

British Columbia:

- BC Cancer Registry data complete to the end of 2021.
- No data available on drugs received through patient support programs or private payment (off-label).
- Data on the IMDC score was unavailable.

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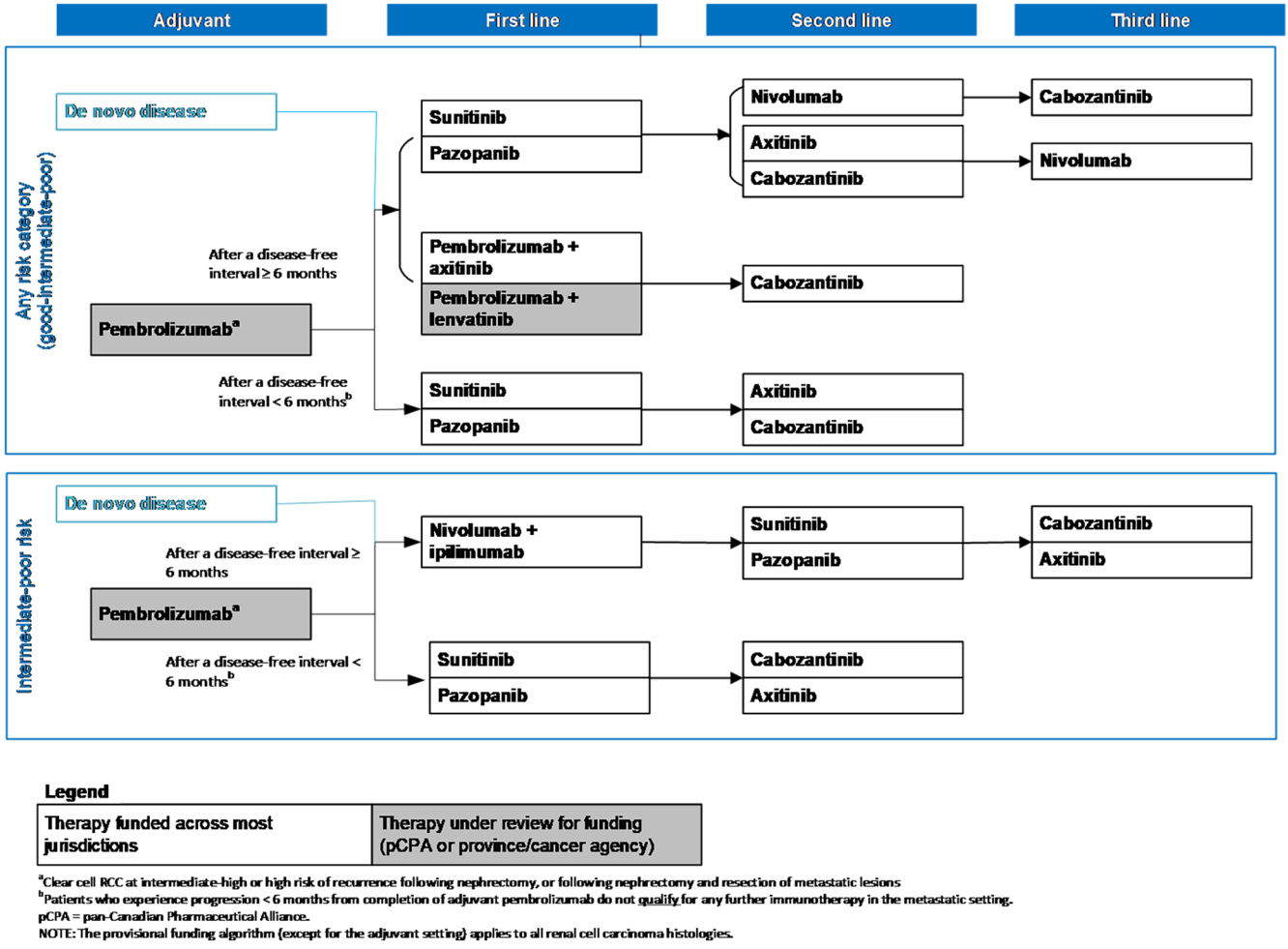
Appendix 1: Additional or Supporting Information

Please note that this appendix has not been copy-edited

Figure 4: Provisional Funding Algorithm Diagram for Renal Cell Carcinoma



Source: Provisional Funding Algorithm, Indication: Renal Cell Carcinoma. Ottawa, ON: CDA-AMC; February 2024. https://www.cda-amc.ca/renal-cell-carcinoma

Table 9: Summary of Funding Dates

Drug name	ON	AB	BC
Sunitinib	November 2007	February 2008	July 2007
Sorafenib	August 2007	October 2009	August 2007
Everolimus	February 2011	February 2011	February 2011
Temsirolimus	June 2010	November 2010	July 2007
Pazopanib	November 2012	February 2012	September 2011

Drug name	ON	AB	BC
Pembrolizumab + axitinib	March 2021	February 2021	March 2021
Nivolumab + ipilimumab	May 2019	July 2019	May 2019
Nivolumab (single agent)	March 2017	April 2017	March 2017
Axitinib (single agent)	December 2013	March 2014	March 2014
Cabozantinib	May 2020	April 2020	January 2020
Pembrolizumab + lenvatinib	August 2023	June 2023	October 2023

AB = Alberta; BC = British Columbia; ON = Ontario.

Table 10: List of DIN for Targeted Therapies in Advanced or Metastatic NSCLC (As of April 19, 2024)

Drug name	DIN
Sunitinib	02532190
	02532204
	02532212
	02532220
	02539284
	02532840
	02532867
	02532875
	02532883
	02280795
	02280809
	02280817
	02328607
	02524058
	02524066
	02524074
	02524082
	02526204
	02526212
	02526220
Sorafenib	02490641
	02284227
Everolimus	02339501
	02339528

Drug name	DIN
	02369257
	02450267
	02425645
	02425653
	02425661
	02375907
	02375915
	02375923
	02530090
	02530104
	02530112
	02530120
	02504677
	02504685
	02504693
	02532409
	02532417
	02532425
	02532433
	02492911
	02492938
	02492946
	02463229
	02463237
	02463245
	02463253
Temsirolimus	02441810
	02304104
Pazopanib	02525666
	02521180
	02352303
	02352311
Pembrolizumab	02441152
	02456869
Axitinib	02389630

Drug name	DIN
	02389649
	02422883
	02422891
Nivolumab	02446626
	02446634
	02541416
Ipilimumab	02379384
Cabozantinib	02480824
	02480832
	02480840

DIN = drug identification number; NSCLC = non–small cell lung cancer.

Table 11: List of ICD-O Codes for RCC

RCC histology types	Code
Clear cell	8310
Papillary	8050, 8260, 8342
Chromophobe	8270, 8317
Other	8318, 8319,8290, 8510 8312 (this one refers to unclassified/not otherwise specified, may include this)

ICD-O = International Classification of Diseases for Oncology; RCC = renal cell carcinoma.

Source: Lichtensztajn D, Hofer BM, Leppert JT, et al. Associations of renal cell carcinoma subtype with patient demographics, comorbidities, and neighbourhood socioeconomic status in the California population. *Cancer Epidemiol Biomarkers Prev*. 2023 February 06; 32(2): 202 to 207. doi:10.1158/1055-9965.EPI-22-0784.

Table 12: Procedure Codes for Radical and Partial Nephrectomy

Description	CCI/CCP CODE
Open radical nephrectomy	**CCI:** 1PC89/91LB, 1PC89/91PF, 1PC89/91QF **CCP:** 6741, 6742, 6744
Laparoscopic radical nephrectomy	**CCI:** 1PC91DA, 1PC89DA, 1PC91AB
Open partial nephrectomy	**CCI:** 1PC87LA, 1PC87LAXXE, 1PC587LAXXG, 1PC87NQ
Laparoscopic partial nephrectomy	**CCI:** 1PC87DA

CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures.

Source: https://tspace.library.utoronto.ca/bitstream/1807/43344/1/Yap_Stanley_A_201311_MSc_thesis.pdf.

For more information on CoLab and its work, visit the **CoLab website**.

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CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.