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Drugs Health Technologies Health Systems

Drug Utilization Study

Drugs for Advanced Renal Cell Carcinoma: A Treatment Pattern Analysis

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This Drug Utilization Study was conducted by the Canadian Cancer Real-world Evaluation (CCRE) Platform team through the Post-Market Drug Evaluation CoLab Network.

Key Messages

Renal cell carcinoma (RCC) is the most common type of kidney cancer and can be difficult to treat, as it is often diagnosed at a later stage.

Significant advancements have been made in systemic therapies to treat advanced RCC, with recent clinical trials showing benefits when using dual immunotherapy or combining immune checkpoint inhibitors with VEGFR inhibitors.

However, there is limited information on how these treatments are currently used and their durations in real-world settings. Understanding these treatment patterns can help optimize clinical guidelines and resource planning for clinical practice over time.

This study aimed to characterize the use of systemic treatments for advanced RCC across 3 provinces in Canada (Ontario, Alberta, and British Columbia), including treatment sequences, duration, and dose across different lines of therapy.

We used population-based data from Ontario, Alberta, and British Columbia to follow patients diagnosed with RCC and who started treatment on publicly funded systemic therapies.

Among 2,224 patients, the average age at diagnosis was 67 years and the majority of patients were male.

Since their introduction, combination ipilimumab plus nivolumab and combination axitinib plus pembrolizumab have dominated as the first treatment option (first-line treatment) for advanced RCC, almost entirely replacing older drugs like pazopanib and sunitinib.

The average duration of first-line treatment ranged from 10 to 13 months, while second-line and third-line therapies were generally shorter, ranging from 6 to 8 months.

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Abbreviations

CCRE	Canadian Cancer Real-world Evaluation
ICI	immune checkpoint inhibitor
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
OS	overall survival
PFS	progression-free survival
PSP	patient support program
RCC	renal cell carcinoma
TKI	tyrosine kinase inhibitor

Introduction and Rationale

Background

RCC is the most common type of kidney cancer, accounting for approximately 90% of all such cases worldwide.[1] In 2022, approximately 8,100 Canadians were diagnosed with kidney and renal pelvis cancer, of which, 85% were RCC.[2] RCC is categorized into subtypes based on histology: clear cell (conventional or class), non-clear cell (papillary, chromophobe, collecting duct, or medullary), and unclassified. The clear cell subtype is the most prevalent form of RCC, representing more than 70% of RCC cases.[3]

A significant challenge in RCC treatment is that more than one-third of patients are diagnosed with metastatic disease, as early-stage RCC is typically asymptomatic.[4] Among those diagnosed at early stages (stage I to III), about 30% experience recurrence following surgical resection.[5] When patients do experience symptoms, they commonly present with visible blood in the urine, loss of appetite, fatigue, pain, or anemia.[6,7] Patients with metastatic RCC have poor 5-year survival rates, ranging from 0% to 20%.[6]

The last 2 decades have seen significant advancements in therapies for patients who have 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] Before 2005, cytoreductive nephrectomy followed by cytokine therapies to reduce the tumour burden and improve survival was the standard of care for advanced RCC. This changed around 2005, following the approval of VEGFR-targeted therapies (e.g., sunitinib). These drugs offered better outcomes compared to cytokines and led to discussions on the necessity of nephrectomy for all patients.[11] The SURTIME trial showed that initial systemic therapy followed by delayed nephrectomy could improve outcomes for patients with more aggressive disease compared to immediate nephrectomy.[12] This trial encouraged a selective approach to nephrectomy, especially for patients with poor-risk features. The CARMENA trial was a major turning point; demonstrating noninferior outcomes among patients treated with sunitinib alone (without nephrectomy) compared to those who underwent surgery followed by sunitinib.[13] As a result, the routine use of nephrectomy in RCC began to decline for patients with intermediate-risk and poor-risk disease. Around 2010, mammalian target of rapamycin inhibition through rapalogs such as everolimus and temsirolimus was introduced. However, rapalogs did not provide strong anticancer benefits in patients with RCC despite clear implications of the mammalian target of rapamycin signalling pathway in RCC tumour genesis.[14] The CheckMate 214 trial led to the approval of nivolumab plus ipilimumab (both ICIs) as a frontline therapy in 2018.[15] This combination showed significant survival advantages over sunitinib in patients who have 1 or more risk predictors based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score. This further reduced the need for nephrectomy, particularly for patients who could not tolerate surgery or had high metastatic burden. More recently, the KEYNOTE-426 trial demonstrated significant benefits by combining ICIs with VEGFR inhibitors, such as the pembrolizumab plus axitinib combination.[15] Such combination treatments improved progression-free survival (PFS) and overall survival (OS) compared to TKIs alone. Since 2019, these and other ICI VEGFR combinations have become widely used in the first-line treatment of advanced RCC globally. For example, the CLEAR trial evaluated lenvatinib plus pembrolizumab versus sunitinib in previously untreated patients with advanced RCC.[16] The CheckMate

9ER trial assessed cabozantinib combined with nivolumab against sunitinib in the same population.[17] These combinations showed significant improvements in PFS and OS compared to sunitinib and led to their approval as first-line treatment options recently.

Based on data from recent clinical trials showing benefits in PFS and OS, 11 systemic therapies have been approved by Health Canada for advanced RCC, 7 of which were designated for first-line treatment.[18] The decision to initiate treatment using systemic therapy is based on several factors, including a patient's IMDC risk group, comorbidities, and patient preference. The IMDC risk group classification categorizes patients into favourable-risk, intermediate-risk, and poor-risk groups.[10] Notably, more than 80% of patients with metastatic RCC fall into the intermediate-risk or poor-risk subgroups.[10] While there is no standardized therapy for non-clear cell RCC, treatment approaches generally mirror those for clear cell RCC. Currently, the preferred first-line treatment for patients with good performance status and without significant comorbidities involves the combination of an ICI with another ICI (e.g., an anti–PD-1 with anti–CTLA-4 monoclonal antibody) or with a VEGFR TKI. These combination therapies may be followed by VEGFR TKI monotherapy upon disease progression. Currently, publicly funded options in Canada include up to 3 lines of therapy, although treatment options are limited beyond the second line.[18]

Despite the availability of a broad range of systemic treatment options for advanced RCC, there is limited information on the current utilization patterns and the duration of these treatments in Canada.[19] Therefore, the aim of this study is to characterize the recent (2017 to 2022) utilization of systemic treatments for advanced RCC in 3 Canadian provinces (Ontario, Alberta, and British Columbia) among patients who start on publicly funded first-line treatment. Specifically, we will determine the sequence of treatment as well as mean duration and dose at each line of therapy. Together, the results of this study may contribute to a clearer understanding of how advanced RCC is treated in Canadian provinces and may be useful for future economic analyses and resource planning for the health care system.

Main Take-Aways

RCC is the most common type of kidney cancer and is often detected in advanced stages. Treatments for advanced RCC have evolved substantially in the past decade, especially with the use of targeted therapies and ICIs. However, there is limited information on how these treatments are used in the real-world setting in Canada.

Policy Issue

The utilization of systemic treatments for advanced RCC in the real-world setting in Canada (including sequence of treatments, treatment duration, and mean treatment dose) is not well understood.

Policy Question

How are drugs approved for the treatment of 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 Canada. The findings could be used to determine potential areas of drug funding pressures and inform system resource planning. It could also prompt the development of additional projects to address clinical and economic questions impacting the treatment of advanced RCC.

Research Questions

The following research questions will guide our study:

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 for this cohort?

Objectives

The objectives of this study are to use administrative health care data in Ontario, Alberta, and British Columbia to:

- quantify the number of patients who received targeted systemic therapy for advanced RCC by type and year
- describe the treatment duration for each treatment by estimating restricted mean survival time
- describe the most observed treatment sequences within the funding algorithm
- describe baseline clinical and demographic characteristics of the patient population treated for advanced RCC.

Methods

Population and Setting

The population of interest in this study was adult patients who initiated first-line systemic therapy for advanced RCC through the public drug program in Ontario, Alberta, and British Columbia.

Study Design

We used a retrospective population-based cohort design to conduct this study. We included patients who started publicly funded first-line treatment for advanced RCC (sunitinib, pazopanib, combination pembrolizumab and axitinib, or combination ipilimumab and nivolumab) between January 1, 2017, and

December 31, 2021, in Alberta and British Columbia, and between January 1, 2017, and December 31, 2022, in Ontario. The accrual period in Ontario was longer than that of Alberta and British Columbia, as more recent data were available in the Ontario cancer registry. After entering the cohort on the start date of publicly funded first-line therapy, patients were followed until the first diagnosis of an additional non-RCC cancer, end of the observation window (December 31, 2023, in all provinces), or death. Figures 1 and 2 display the study design diagrams for each province.

Figure 1: Study Design Diagram for Ontario

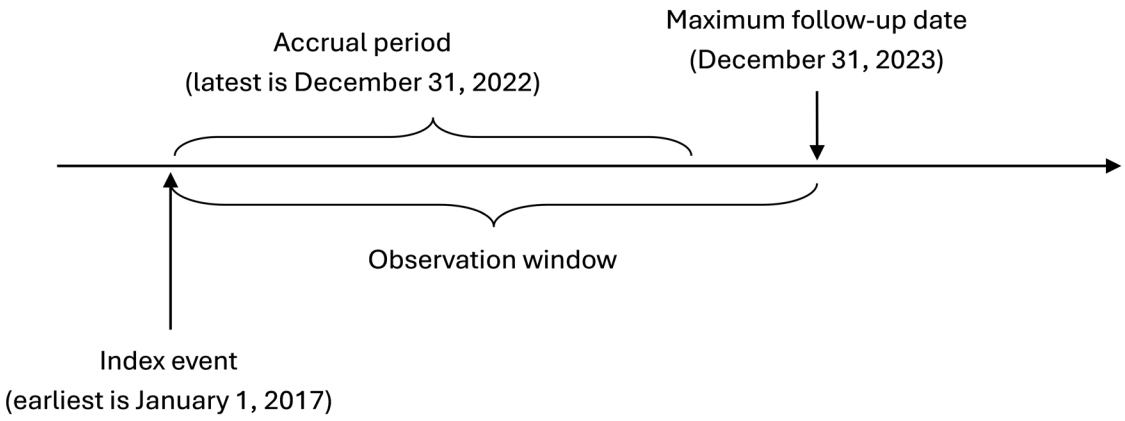
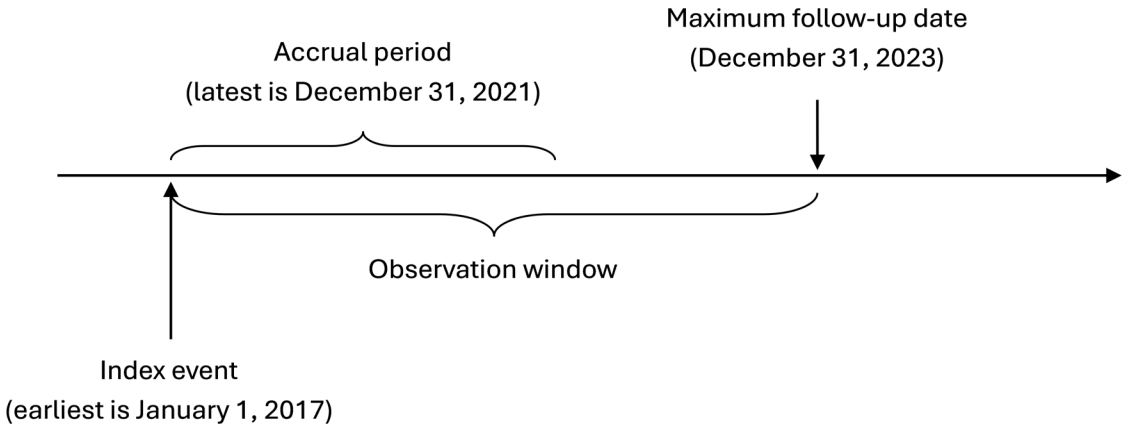


Figure 2: Study Design Diagram for Alberta and British Columbia



Eligibility Criteria

We initially started with patients who received publicly funded systemic therapy for advanced RCC (sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, nivolumab, cabozantinib, combination pembrolizumab and axitinib, or combination nivolumab and ipilimumab) during the accrual period, and had a diagnosis of RCC (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] site:

C64.9, C65.9) recorded before initial treatment. This list of treatments includes all publicly funded systemic treatments at any line of treatment for advanced RCC. Subsequently, we defined our cohort by identifying patients who started treatment on publicly funded first-line treatment (i.e., sunitinib, pazopanib, combination pembrolizumab and axitinib, or combination ipilimumab and nivolumab). We defined the first dispensing date or reimbursement record of the first-line treatment as a patient's index date and the most recent RCC diagnosis before the index date was defined as their index RCC diagnosis.

Then, we excluded patients based on the following criteria:

- Diagnosis of another primary cancer that is not RCC in the 5 years before index RCC diagnosis.
- Diagnosis of a new primary cancer between their index RCC diagnosis and index date.
- Index RCC had a histology code unrelated to RCC (refer to Appendix 2).
- Index treatment was not publicly funded for a first-line indication, they initiated their index treatment before public funding date of the drug, or index treatment was funded via private insurance (Appendix 2).
- Receipt of other systemic therapy between index RCC diagnosis and index date.
- Receipt of first-line treatment as part of a clinical trial.
- Aged less than 18 years at diagnosis.
- Missing or invalid values for a personal identification number, age, sex, and death date (i.e., death before index date).
- Nonresidents of the province of interest at index date.

Data Sources

We used population-based administrative data in all Canadian Cancer Real-world Evaluation (CCRE) Platform sites (Ontario, Alberta, and British Columbia) to define the study cohort, obtain clinical and demographic characteristics, and define longitudinal drug utilization, and mortality outcomes. Data sources included provincial cancer registries, systemic therapy dispensing records and/or claims, and other records of health services utilization, summarized in Appendix 2. The Ontario patient cohort consisted of those who received systemic therapy funded by the Ontario Drug Benefit provincial drug insurance program (individuals aged 65 years and older, those who live in long-term care facilities or receive home care, and those who have high medication costs relative to their income), as well as patients who received systemic therapy through a Regional Cancer Centre or an outpatient clinic in Ontario that receives funding through the Systemic Therapy – Quality Based Program and/or the New Drug Funding Program. British Columbia and Alberta provide universal public coverage for systemic therapy drugs on their formularies. Dispensing records in those provinces include all publicly funded systemic therapy, regardless of route of administration (IV versus oral or take home), location of care, or patient age.

The CCRE Platform's access to data in Ontario is governed under section 45 of the province's *Personal Health Information Protection Act* and is not subject to additional review by an ethics review board. Alberta's data access is governed under the province's *Health Information Act*. The Alberta site of the CCRE Platform

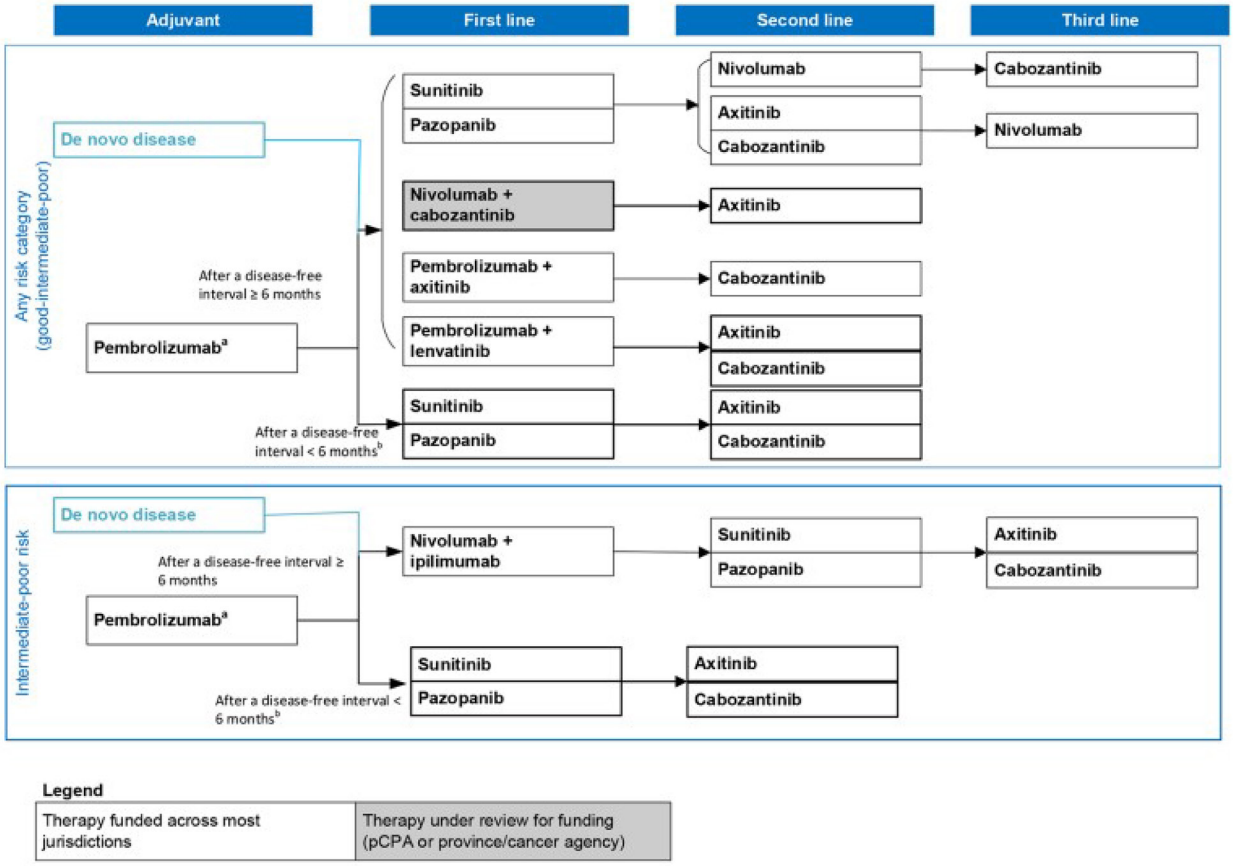
was approved by the Health Research Ethics Board of Alberta – Cancer Control. Data access was approved by the Alberta Data Stewards. The British Columbia site of the CCRE Platform was approved by the University of British Columbia – BC Cancer Research Ethics Board. Data access was approved by the BC Cancer Data Stewards. Based on privacy policies to protect patient confidentiality set by each province, we only reported values greater than 5 in Ontario and British Columbia, and values greater than 9 in Alberta. In situations where a suppressed value is a part of a categorical variable, we reported a range for a second category to avoid back calculation of the suppressed value.

Key Study Measures

Outcomes of Interest

The outcomes of interest in this study were the utilization, duration, and dose of systemic therapy for advanced RCC, by drug or combination, line of therapy, and treatment sequence among patients who started first-line systemic therapy via public funding. Drugs and sequences of interest were limited to the CDA-AMC provisional funding algorithm for RCC (Figure 3).[18] First-line therapies of interest were publicly funded sunitinib, pazopanib, combination nivolumab plus ipilimumab, and combination pembrolizumab plus axitinib. Second-line therapies included nivolumab monotherapy, axitinib monotherapy, cabozantinib, sunitinib, and pazopanib. Third-line therapies included cabozantinib, nivolumab, and axitinib. Use of second-line and third-line therapies that are not listed in the CDA-AMC provisional funding algorithm in Figure 3 (including clinical trials) or use of a funded drug in an unfunded sequence (i.e., sunitinib in third line) were included in an 'other' category in the utilization analysis. However, we did not calculate the dose and duration of these therapies. Use of pembrolizumab for adjuvant treatment of RCC as well as first-line pembrolizumab plus lenvatinib were not analyzed because of its recent introduction in clinical practice. Due to limitations in the availability of dose data in Alberta, we calculated dose for patients in Ontario and British Columbia only.

Figure 3: Provisional Funding Algorithm Diagram for Renal Cell Carcinoma (As of February 2024)



pCPA = pan-Canadian Pharmaceutical Alliance.

Note: The provisional funding algorithm (except for the adjuvant setting) applies to all renal cell carcinoma histologies.

Drug funding status have changed since the publication of this provisional funding algorithm. Although first-line nivolumab plus cabozantinib, as well as first-line pembrolizumab plus lenvatinib, are now both funded across most jurisdictions, these treatments were not publicly funded at the time of conducting this study.

[a] Clear cell–renal cell carcinoma at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

[b] Patients who experience disease progression less than 6 months from completion of adjuvant pembrolizumab do not qualify for any further immunotherapy in the metastatic setting.

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

Baseline Characteristics of Interest

We included the following baseline characteristics: age, sex, year of index RCC diagnosis, time between index RCC diagnosis and initial systemic treatment, stage at diagnosis, tumour histology, and prior partial or radical nephrectomy. In Ontario and Alberta, we also reported on neighbourhood income quintile, residential rurality, and Charlson Comorbidity Index score (calculated using a 2-year look back). Such data were not available in British Columbia.

Analyses

We conducted a descriptive analysis of baseline characteristics using frequency distributions for categorical or indicator variables (count and percent of total) and mean, standard deviation, median, and interquartile range for continuous variables.

Line of therapy was assigned in sequence. We identified the start of a new line of therapy using changes in drug or treatment policy name from dispensing records. The first dispensing date of the new drug or policy was defined as the start date of the next line of therapy. However, switching between sunitinib and pazopanib was not considered as commencement of a new line of therapy, after consultation with clinical advisors who suggested that such switches are likely due to intolerance. In such cases, the line of therapy encompassed both sunitinib and pazopanib treatments and was categorized based on the drug used the longest.

Total utilization, defined as number of unique users by year and treatment was summarized using stacked bar charts, by province and line of therapy.

We summarized the frequency of each sequence of interest using patient counts by province. Frequency was calculated by treatment and line of therapy, conditional on previous therapy, to correspond to treatment pathways on the provisional funding algorithm. To account for censoring of patients who did not have complete observations, we calculated weighted frequencies for second-line and third-line therapies using inverse-probability-of-censoring weights. The probability of censoring at the end of each line of therapy (i.e., before the start of the next line of therapy) was calculated using the Kaplan-Meier method. Patients who died or who were observed to start a fourth line of therapy were considered complete observations. Patients were censored if they had not reached fourth-line therapy and were alive at the end of follow-up (December 31, 2023) or at the point of diagnosis if they were diagnosed with a new primary cancer (unrelated to RCC) during the follow-up period. We observed heterogeneity in censoring rates by first-line therapy, with recently funded therapies having higher rates of censoring. We stratified the inverse probability weighting by first-line therapy to account for this difference.

Duration of therapy was calculated as the time, in months (defined as a period of 30 days) between first treatment record and end of therapy. The end date for each line of therapy was defined as the last dispensing date or treatment record, plus the treatment's cycle length. For patients who were not observed to start a subsequent line of therapy or who die, we used a 30-day look-forward window following the end of treatment to define treatment completion. Patients who had at least 30 days of observation after the treatment end date were considered to have completed the line of therapy. Patients who had less than 30 days of observation between end of treatment and end of follow-up were censored. For these patients, treatment may have continued beyond the end of the follow-up period. Calculating mean treatment duration using only the observed treatment time, without accounting for this potential ongoing treatment, would underestimate treatment duration. To account for this right censoring, we estimated restricted mean treatment duration as the area under the Kaplan-Meier curve, up to 30 months. The 30-month time horizon was selected as the longest possible follow-up available in all provinces, based on preliminary analysis. Restricted mean duration was calculated by treatment and line of therapy; however, we combined treatment pathways where necessary to achieve sufficient sample size. We conducted meta-analysis of restricted

mean estimates using the generic inverse variance method with random effects to pool the results across 3 provinces. Higgins and Thompson's I^2 heterogeneity measure was used to determine the degree of heterogeneity.

Dose analysis was conducted in British Columbia and Ontario. Total dose was calculated as the sum of all dispensed amounts, by drug, between first treatment record and end of therapy. Where dose information was incomplete in British Columbia, we used dose, dispensed amount and/or cycle length from each province's systemic therapy protocols to impute the missing values. In Ontario, we calculated doses for all publicly funded treatments. Total dose was divided by the total treatment duration as previously mentioned, to provide a dose per month (30-day interval; dose per week was also calculated, refer to Appendix 1). We calculated mean dose and standard error, by drug and line of therapy, weighted by treatment to duration in each province. We determined the appropriateness of calculating an aggregate mean dose between Ontario and British Columbia by conducting pooled or Welch-Satterthwaite t tests (based on the folded F test of variance equivalence) and reported a weighted mean dose between the 2 provinces. We calculated the accompanying standard error using the following formula, where *w* is the sum of weights (total person-time on treatment) in each province:

$$SE_{overall} = \sqrt{\left(\frac{w_{ON}}{w_{ON}+w_{BC}}\right)^2 SE_{ON}^2 + \left(\frac{w_{BC}}{w_{ON}+w_{BC}}\right)^2 SE_{BC}^2}$$

All analyses in Ontario and British Columbia were completed using SAS Enterprise Guide version 7.12 and SAS 9.4, respectively, (SAS Institute, Cary, North Carolina, US). All analyses in Alberta were carried out in R version 4.2.2 (R Core Team, 2022).

Main Take-Aways

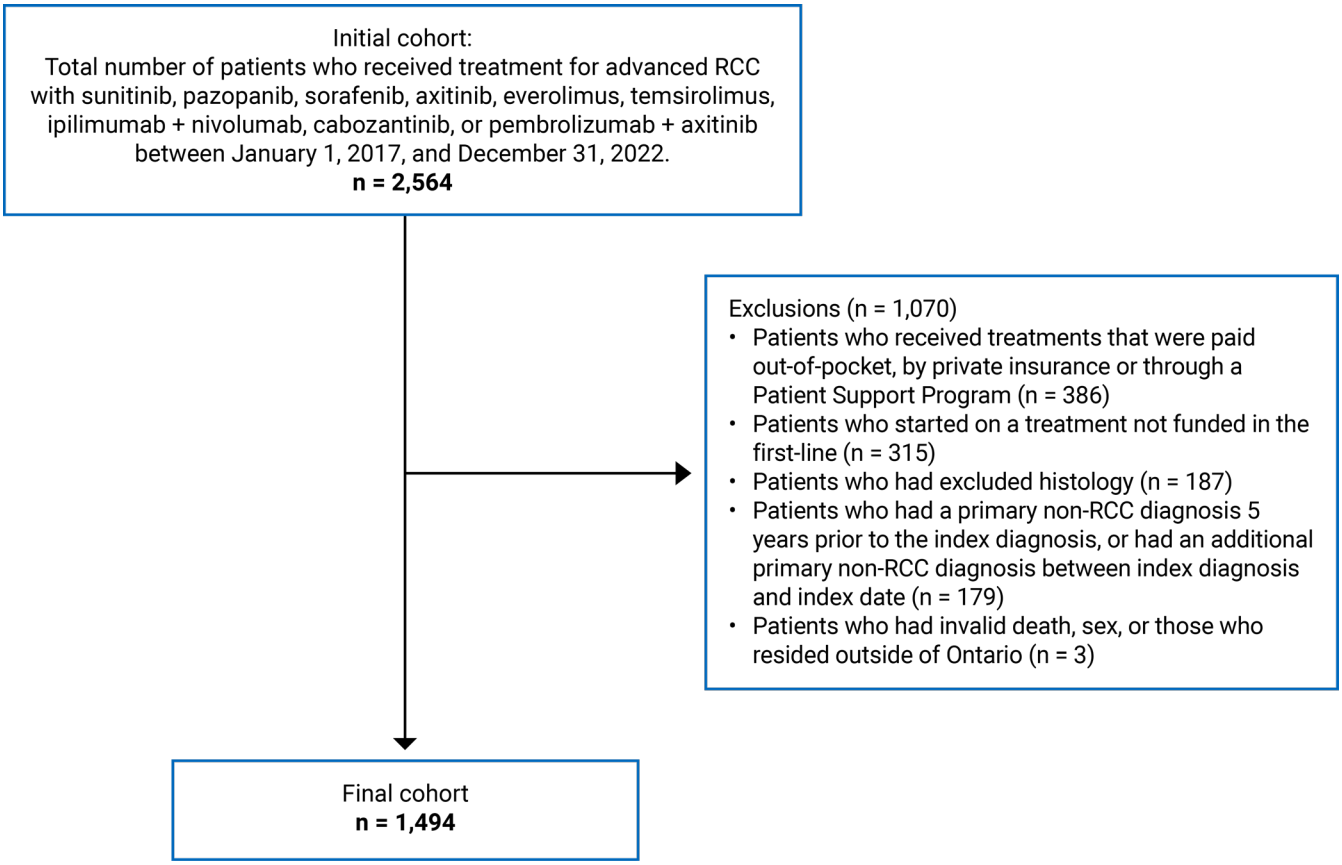
We conducted this study to analyze the use of systemic treatments for advanced RCC in 3 Canadian provinces (Ontario, Alberta, and British Columbia) between 2017 and 2022. We focused on characterizing patients who started publicly funded first-line treatments and examined treatment sequences, duration, dosages, and trends in use across 3 lines of therapy. Understanding these patterns can help enhance clinical guidelines and resource planning.

Results

Population Characteristics

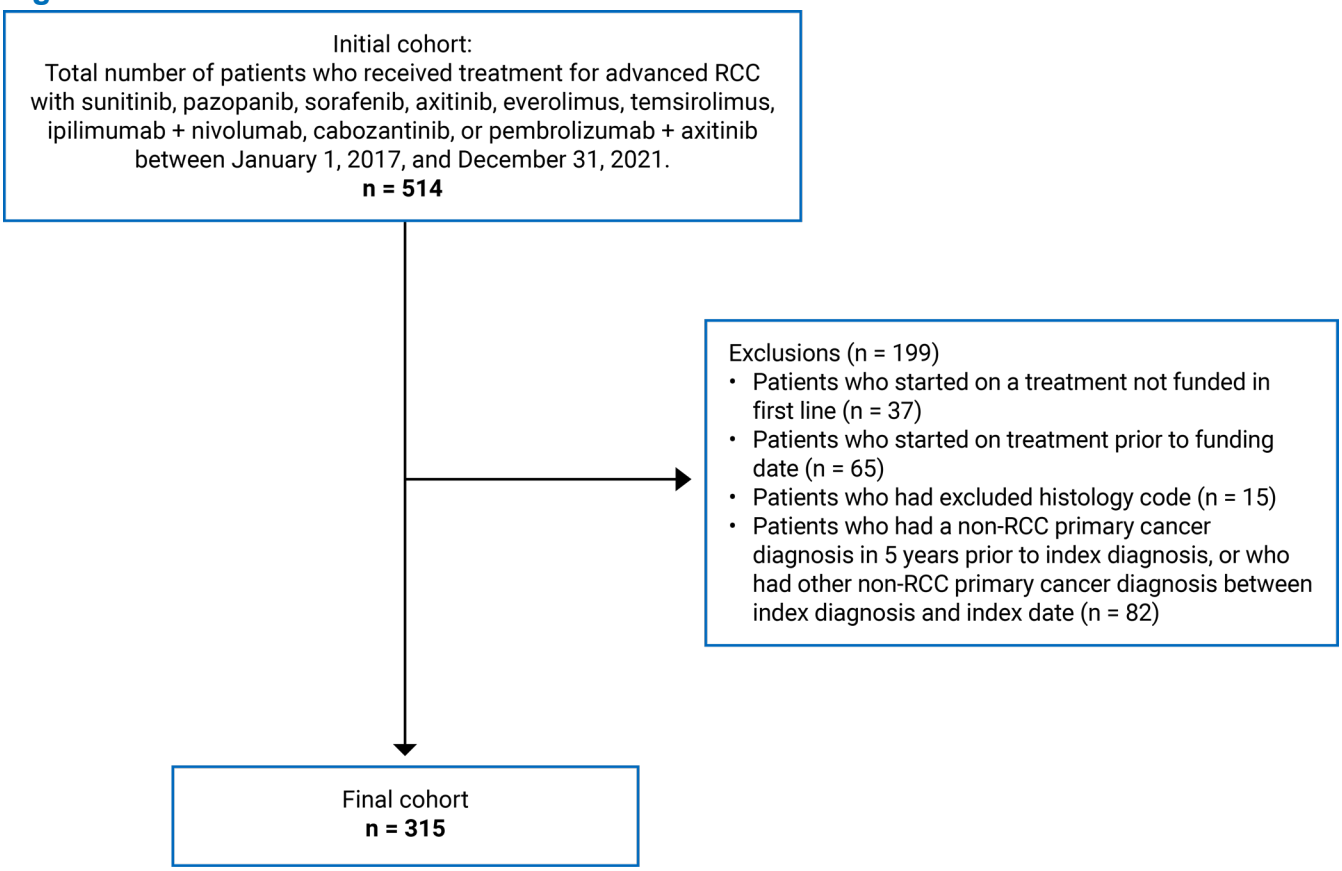
After applying exclusion criteria, we identified 1,494 patients in Ontario (Figure 4), 315 patients in Alberta (Figure 5), and 415 patients in British Columbia (Figure 6) who had a diagnosis of RCC and initiated publicly funded first-line systemic therapy during the accrual period. Combined, we included 2,224 patients in the study cohort.

Figure 4: Cohort Creation and Exclusion Criteria for Ontario



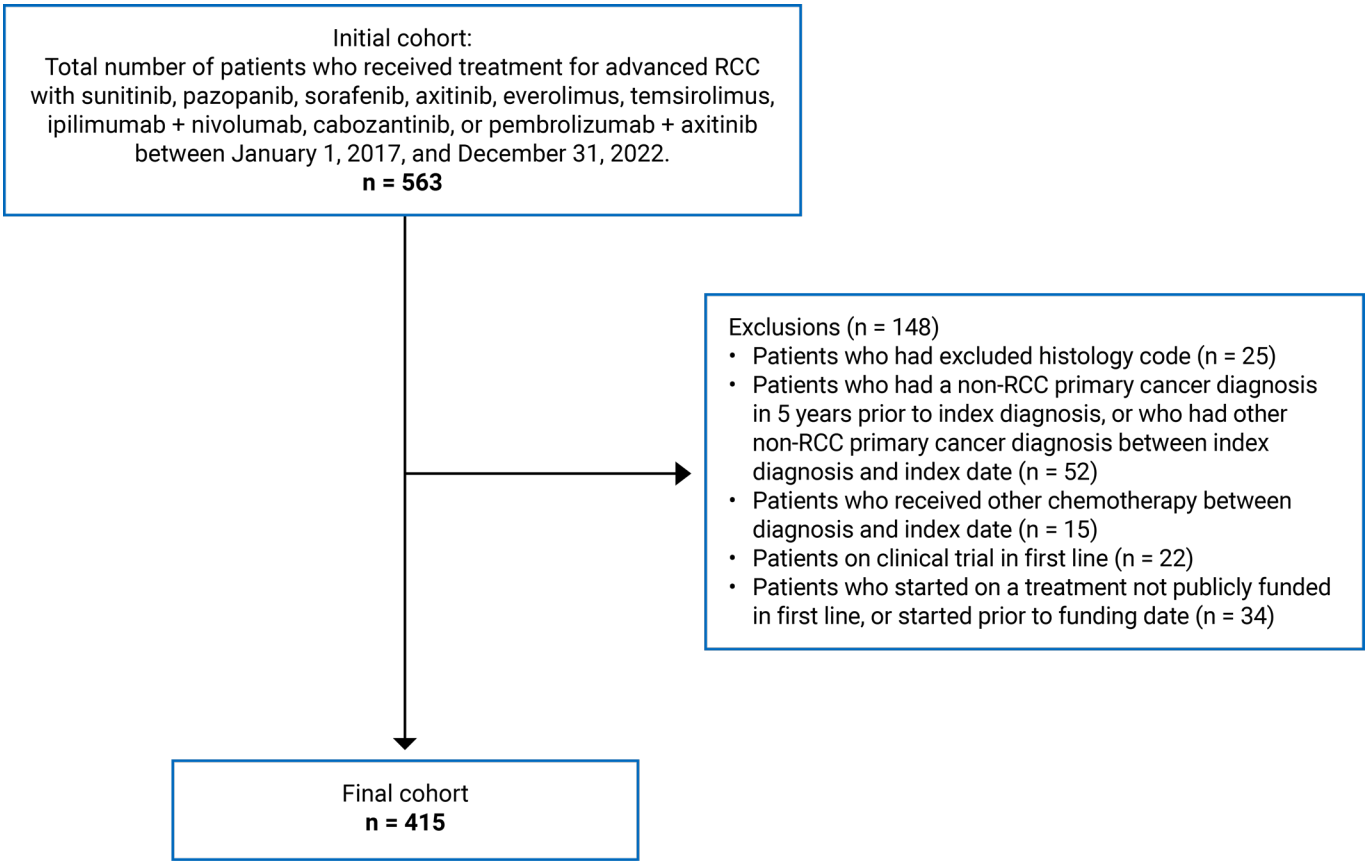
RCC = renal cell carcinoma.

Figure 5: Cohort Creation and Exclusion Criteria for Alberta



RCC = renal cell carcinoma.

Figure 6: Cohort Creation and Exclusion Criteria for British Columbia



RCC = renal cell carcinoma.

The study cohort at initiation of first-line treatment consisted mostly of males (72.3%, n = 1,607; females: 27.7%, n = 617) with a mean age of 67.0 years (standard deviation = 10.6 years) (Table 1). In general, cohort characteristics were consistent across provinces. Patients were evenly distributed across neighbourhood income quintiles, and approximately 80% of patients (n = 1,445) resided in urban areas. Stage data were unavailable for approximately one-half of the British Columbia and Ontario cohorts, but of those with data available, stage IV disease was most common (n = 823; 37.0%). More than 70% of patients (n = 1,588) were diagnosed with clear cell histology, and 57% of patients (n = 1,265) had a prior nephrectomy. Patients in the Ontario cohort were observed to have a longer time between RCC diagnosis and index date than patients in British Columbia and Alberta (more than 1,000 days in Ontario, versus 600 to 750 days in British Columbia and Alberta). Additionally, fewer patients in the British Columbia cohort were diagnosed with stage III disease when compared to the Alberta and Ontario cohorts (7.4% of nonmissing stage in British Columbia versus 27% to 30% in Ontario and Alberta).

Table 1: Cohort Characteristics on Index Date for Patients Who Received First-Line Treatment for Advanced RCC (Full Cohort)

Baseline characteristics	Total n = 2,224	Ontario n = 1,494	Alberta n = 315	British Columbia n = 415
Age, mean (SD)	67.0 (10.6)	67.6 (10.4)	65.1 (10.6)	66.3 (11.3)
Sex, N (%)				
Female	617 (27.7)	442 (29.6)	76 (24.1)	99 (23.9)
Male	1,607 (72.3)	1,052 (70.4)	239 (75.9)	316 (76.1)
Income quintile, N (%)[a]				
1	357 (19.7)	293 (19.6)	64 (20.3)	NA
2	349 (19.3)	284 (19.0)	65 (20.6)	NA
3	358 to 370 (19.7 to 20.5)	310 to 314 (20.7 to 21.0)	48 to 56 (15.2 to 17.8)	NA
4	384 (21.2)	316 (21.2)	68 (21.6)	NA
5	347 (19.2)	286 (19.1)	61 (19.4)	NA
Missing	2 to 14	< 6	< 10	NA
Urban residence, N (%)[a]				
Rural	359 to 363 (19.6 to 20.1)	310 to 314 (20.5 to 21.0)	49 (15.6)	NA
Urban	1,445 (79.9)	1,179 (78.9)	266 (84.4)	NA
Missing	< 6	< 6	0 (0)	NA
Charlson Comorbidity Index score, N (%)[a]				
0	823 (45.5)	664 (44.4)	159 (50.5)	NA
1	342 (18.9)	249 (16.7)	93 (29.5)	NA
2+	491 to 499 (27.1 to 27.6)	437 (29.3)	54 to 62 (17.1 to 20.0)	NA
No records	145 to 153 (8.0 to 8.5)	144 (9.6)	< 10	NA
Year of RCC diagnosis, N (%)				
2011 and earlier	234 (10.5)	184 (12.3)	29 (9.2)	21 (5.1)
2012	32 to 40 (1.4 to 1.8)	23 (1.5)	< 10	8 (1.9)
2013	53 to 61 (2.4 to 2.7)	44 (3.0)	< 10	8 (1.9)
2014	74 (3.3)	45 (3.0)	17 (5.4)	12 (2.9)
2015	111 (5.0)	70 (4.7)	21 (6.7)	20 (4.8)
2016	153 (6.9)	84 (5.6)	42 (13.3)	27 (6.5)
2017	306 (13.8)	161 (10.8)	57 (18.1)	88 (21.2)

Baseline characteristics	Total n = 2,224	Ontario n = 1,494	Alberta n = 315	British Columbia n = 415
2018	251 (11.3)	138 (9.2)	42 (13.3)	71 (17.1)
2019	311 (14.0)	218 (14.6)	35 (11.1)	58 (13.4)
2020	268 (12.1)	174 (11.7)	31 (9.8)	63 (15.2)
2021	282 (12.7)	212 (14.2)	31 (9.8)	39 (9.4)
2022[b]	141 (9.4)[b]	141 (9.4)	NA	NA
Stage at diagnosis, N (%)				
I to III	472 to 480 (21.2 to 21.6)	285 (19.1)	142 to 150 (45.0 to 47.6)	45 (10.8)
IV	823 (37.0)	489 (32.7)	164 (52.1)	170 (41.0)
Missing	921 to 929 (41.4 to 41.8)	720 (48.2)	< 10	200 (48.2)
Tumour histology, N (%)				
Clear cell	1,588 (71.4)	1,062 (71.1)	235 (74.6)	291 (70.1)
Papillary	126 to 134 (5.7 to 6.0)	90 (6.0)	12 to 20 (3.8 to 6.3)	24 (5.8)
Chromophobe	27 to 35 (1.2 to 1.6)	16 (1.1)	< 10	10 (2.4)
Other	475 (21.4)	326 (21.8)	59 (18.7)	90 (21.7)
Prior nephrectomy, N (%)	1,265 (56.9)	848 (56.8)	178 (56.5)	239 (57.6)
Time in days from diagnosis to index treatment, mean (SD)	953.2 (1,620.6)	1,094.4 (1,854.5)	753.4 (1,118.8)	596.7 (952.0)
Index year, N (%)				
2017	364 (16.4)	201 (13.5)	79 (25.1)	84 (20.2)
2018	314 (14.1)	176 (11.8)	64 (20.3)	74 (17.8)
2019	393 (17.7)	250 (16.7)	66 (21.0)	77 (18.6)
2020	321 (14.4)	203 (13.6)	38 (12.1)	80 (19.3)
2021	525 (23.6)	357 (23.9)	68 (21.6)	100 (24.1)
2022	307 (20.6)	307 (20.6)	NA	NA
Index treatment, N (%)				
Axitinib + pembrolizumab	366 (16.5)	283 (18.9)	28 (8.9)	55 (13.3)
Ipilimumab + nivolumab	768 (34.5)	574 (38.4)	72 (22.9)	122 (29.4)
Pazopanib	418 (18.8)	241 (16.1)	95 (30.2)	82 (19.8)
Sunitinib	672 (30.2)	396 (26.5)	120 (38.1)	156 (37.6)

NA = not applicable; RCC = renal cell carcinoma; SD = standard deviation.

Note: Some values are reported as a range to avoid back calculation of small cell values suppressed for confidentiality.

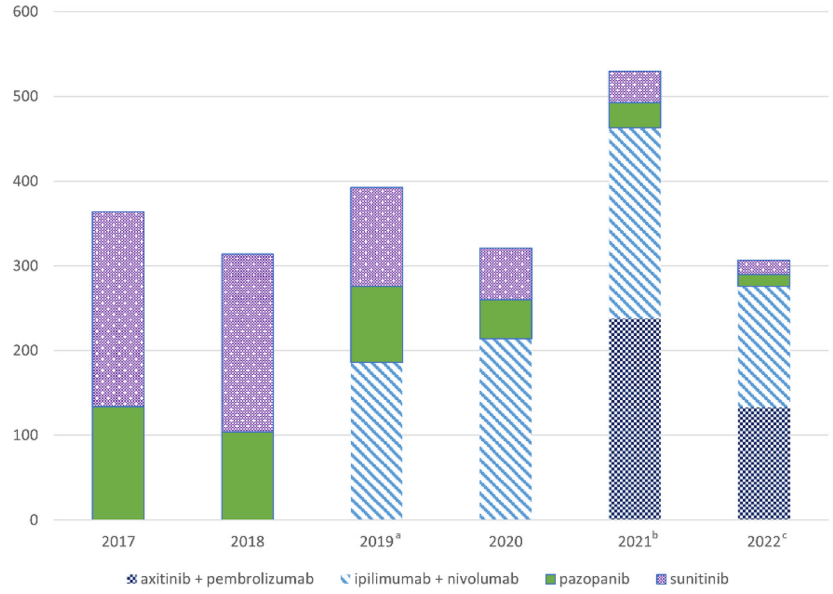
[a]Denominator for Ontario and Alberta (i.e., total): N = 1,809.

[b]Denominator for Ontario only (i.e., total): N = 1,494.

Main Take-Aways

This study presents data from Ontario, Alberta, and British Columbia. We identified a total of 2,224 patients who received publicly funded first-line systemic treatment for advanced RCC. On average, patients were 67 years of age at the start of first-line therapy and the majority of patients were male.

Figure 7: Bar Chart of Treatment Exposure in First Line for All Sites by Year

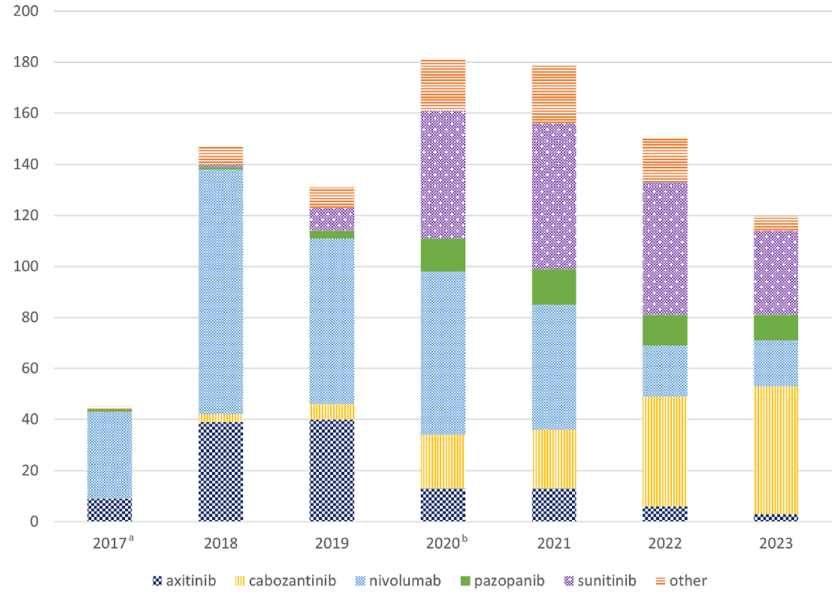


[a]Ipilimumab + nivolumab funding dates: May 2019 (Ontario, British Columbia), July 2019 (Alberta).

[b]Axitinib + pembrolizumab funding dates: February 2021 (Alberta), March 2021 (Ontario, British Columbia).

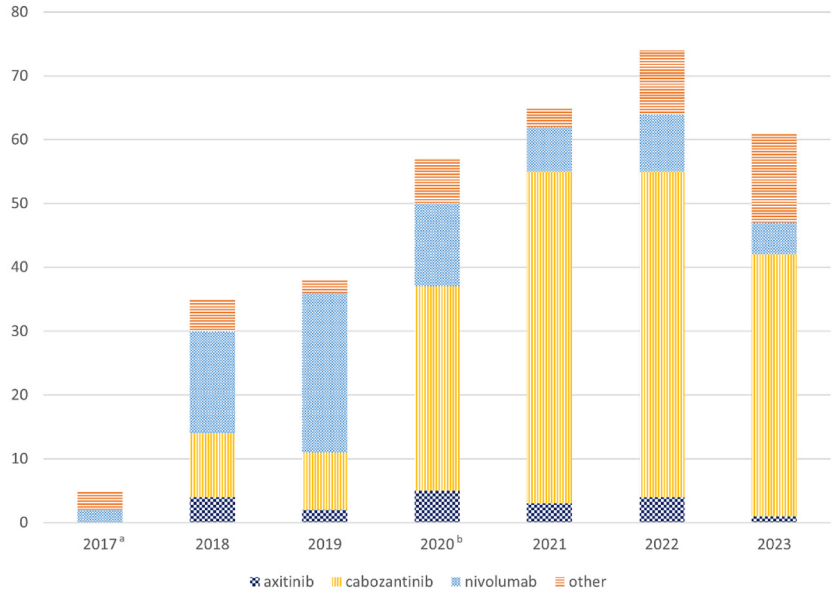
[c]Only Ontario contributed data for 2022.

Figure 8: Bar Chart of Treatment Exposure in Second Line for All Sites by Year



[a]Nivolumab funding dates: March 2017 (British Columbia, Ontario), April 2017 (Alberta).
[b]Cabozantinib funding dates: January 2020 (British Columbia), April 2020 (Alberta), May 2020 (Ontario).

Figure 9: Bar Chart of Treatment Exposure in Third Line Across All Sites by Year



[a]Nivolumab funding dates: March 2017 (British Columbia, Ontario), April 2017 (Alberta).
[b]Cabozantinib funding dates: January 2020 (British Columbia), April 2020 (Alberta), May 2020 (Ontario).

Main Take-Aways

The introduction of combination therapies like ipilimumab plus nivolumab in 2019 and axitinib plus pembrolizumab in 2021 changed the use of first-line treatments, leading to less reliance on sunitinib and pazopanib. The average duration of first-line treatment ranged from 11 to 13 months, while second-line and third-line therapies were generally shorter, ranging from 6 to 8 months. Additionally, combination therapies typically involved lower monthly doses compared to when these therapies were used alone (monotherapy), indicating a trend toward tailored treatment plans. The most common first-line therapy in Alberta and British Columbia was sunitinib (largely driven by utilization before combination therapies became publicly funded) while the most common first-line therapy in Ontario was combination ipilimumab plus nivolumab. The most common sequence that includes 2 lines of treatment for all provinces was nivolumab monotherapy after first-line treatment with sunitinib or pazopanib.

Utilization

Figure 7 illustrates the change in utilization of publicly funded first-line therapies over time, for all provinces combined. Use of sunitinib and pazopanib decreased following the introduction of publicly funded combination ipilimumab and nivolumab in 2019 and again following the introduction of combination axitinib and pembrolizumab in 2021. The distribution of subsequent-line therapies also changed over the study period, with increasing use of cabozantinib over time and decreasing use of nivolumab monotherapy in both second-line and third-line treatment (Figures 8 and 9).

The distribution of therapies for advanced RCC, conditional on prior lines of treatment, are summarized in Table 2 and Figures 10-13. Sunitinib was the most common first-line therapy in British Columbia and Alberta between 2017 and 2021, used by approximately 38% of patients in both provinces. In Ontario, where the cohort accrual period included an extra year to 2022, the combination of ipilimumab and nivolumab was most frequently used (38.4%). The most common sequence that includes 2 lines of treatment for all provinces was nivolumab monotherapy after first-line sunitinib or pazopanib. The number of patients in the cohort who received third-line treatment was very small and there were no common treatment patterns between provinces in this setting. In Alberta, the most common sequence that included third-line treatment was sunitinib or pazopanib followed by nivolumab and flowing to cabozantinib. In Ontario, the most common sequence was combination ipilimumab and nivolumab, followed by sunitinib or pazopanib, and finally cabozantinib. In British Columbia, the most common sequence was sunitinib or pazopanib followed by second-line axitinib or cabozantinib, followed by third-line nivolumab. In Ontario, there were 576 patients (39%) who received 2 lines of therapy and 164 patients (11%) who received 3 lines of therapy. In Alberta, there were 136 patients (43%) who received 2 lines of therapy and 49 patients (16%) who received 3 lines of therapy. In British Columbia, there were 156 to 160 patients (38% to 39%) who received at least 2 lines of therapy and 45 to 49 patients (11% to 12%) who received 3 lines of therapy. When the option was available (after first-line pazopanib or sunitinib), there was a notable preference to switch to a different drug class (i.e., nivolumab) upon progression. Overall, in all 3 jurisdictions combined, just more than one-half of

patients (51.7%) treated with combination nivolumab and ipilimumab received second-line therapy; a similar proportion (53%) received subsequent therapy after first-line TKI monotherapy and slightly fewer (42.6%) received cabozantinib after first-line pembrolizumab plus axitinib. Weighting with inverse-probability-of-censoring weights particularly increases the frequency of sequences following combination nivolumab and ipilimumab, and combination pembrolizumab and axitinib, which were approved during the observation period and subject to higher censoring.

Table 2: Treatment Frequency by Sequence and Line

Node	Sequence to node	Crude incident users, n				Weighted incident users (IPCW), n			
		All	ON	BC	AB	All	ON	BC	AB
A	**SUN**	672	396	156	120	672	396	156	120
B	**PAZ**	418	241	82	95	418	241	82	95
C	**PEM + AXI**	366	283	55	28	366	283	55	28
D	**NIV + IPI**	768	574	122	72	768	574	122	72
E	SUN or PAZ → **NIV**	339	222	52	65	397	257	57	83
F	SUN or PAZ → **AXI**	112	41	46	25	131	48	51	32
G	SUN or PAZ → **CAB**	35 to 45[a]	27	8	< 10	50	31	9	10
H	PEM + AXI → **CAB**	88 to 98[a]	75	13	< 10	151 to 161[a]	131	20	< 10
I	NIV + IPI → **SUN**	233	177	36	20	329	259	44	26
J	NIV + IPI → **PAZ**	34 to 50[a]	34	< 6	< 10	68	50	6	12
K	SUN or PAZ → NIV → **CAB**	88	59	8	21	126	81	11	34
L	SUN or PAZ → AXI or CAB → **NIV**	68	27	27	14	95	37	35	23
M	NIV + IPI → SUN or PAZ → **CAB**	81 to 91[a]	73	8	< 10	162	136	11	15
N	NIV + IPI → SUN or PAZ→ **AXI**	3 to 22[a]	< 6	< 6	< 10	9 to 25[a]	9	< 6	< 10

AB = Alberta; AXI = axitinib; BC = British Columbia; CAB = cabozantinib; IPCW = inverse-probability-of-censoring weighting; NA = not applicable; NIV = nivolumab; NIV + IPI = nivolumab with ipilimumab; ON = Ontario; PAZ = pazopanib; PEM + AXI = pembrolizumab with axitinib; SUN = sunitinib; SD = standard deviation.

[a]Some values are reported as a range to avoid back calculation of small cell values suppressed for confidentiality.

Duration of Therapy

Pooled restricted mean treatment duration across all 3 provinces for first-line therapies ranged from approximately 10 months for pazopanib and combination nivolumab and ipilimumab to 13 months for combination pembrolizumab and axitinib (Table 3). Duration of therapy in second-line and third-line therapies was generally shorter, ranging from just over 6.5 months for second-line sunitinib or pazopanib to 10 months for second-line cabozantinib or nivolumab and 6 months for third-line nivolumab to 8 months for third-line cabozantinib. The magnitude and order of treatment durations were generally consistent across provinces,

and we observed considerable heterogeneity in 2 models in the meta-analysis (sequences G and H and L; refer to Appendix 1 for full model results).

Dose

Dose per month (30-day interval) is summarized in Table 3; dose expressed as a weekly rate is presented in Appendix 1. Doses recommended per product monograph are summarized in Appendix 2. The mean dose for combination therapies is generally lower than for the same drugs used a monotherapy. For example, the overall mean dose for nivolumab in combination with ipilimumab was 395 mg per 30 days, while the overall mean dose for nivolumab monotherapy was 440 mg; the maximum dose according to treatment protocols is 120 mg per week, or 480 mg per 30 days.[20,21] For axitinib, the overall mean monotherapy dose was 283 mg per 30 days, or 9.4 mg/day, and while in combination with pembrolizumab the overall mean dose was 174 mg per 30 days, or 5.8 mg/day.

Table 3: Treatment Duration and Dose by Sequence and Line

Node	Sequence to node	Restricted mean (SE) treatment duration, months[a]				Mean (SE) dose, mg per 30 days			
		All	ON	BC	AB	Drug	All	ON	BC
A	**SUN**	10.7 (0.4)	10.7 (0.5)	10.4 (0.8)	11.3 (0.9)	SUN	747 (12)[b]	668 (14)	953 (22)
B	**PAZ**	9.9 (0.5)	9.9 (0.6)	9.1 (1.1)	10.3 (0.9)	PAZ	14,845 (390)	15,049 (459)	14,062 (671)
C	**PEM + AXI**	13.0 (1.0)	12.7 (0.5)	15.3 (1.5)	10.8 (1.7)	AXI	169 (5)	168 (6)	173 (13)
						PEM	174 (4)	178 (5)	161 (9)
D	**NIV + IPI**	9.8 (0.6)	10.3 (0.4)	8.6 (0.8)	10.4 (1.1)	IPI	25 (1)	24 (1)	27 (3)
						NIV	395 (4)	398 (4)	376 (9)
E	SUN or PAZ → **NIV**	8.0 (0.5)	8.0 (0.6)	7.6 (1.3)	8.6 (1.2)	NIV	440 (6)	441 (7)	436 (13)
F	SUN or PAZ → **AXI**	6.9 (0.7)	6.9 (1.1)	7.0 (1.1)	6.8 (1.4)	AXI	283 (51)	245 (14)	328 (109)
G and H	SUN or PAZ → **CAB** *and* PEM + AXI → **CAB**	7.9 (1.6)	7.8 (0.7)	11.8 (2.1)	5.4 (1.1)	CAB	1,043 (39)	1,024 (44)	1,135 (73)
I and J	NIV + IPI →**SUN** *and* NIV + IPI → **PAZ**	6.6 (0.4)	6.5 (0.5)	7.4 (1.3)	6.8 (1.3)	SUN	804 (27)[b]	734 (34)	993 (35)
						PAZ	NA[c]	16,103 (1,545)	NA[c]

Node	Sequence to node	Restricted mean (SE) treatment duration, months[a]				Mean (SE) dose, mg per 30 days			
		All	ON	BC	AB	Drug	All	ON	BC
K and M	SUN or PAZ → NIV → **CAB** *and* NIV + IPI → SUN or PAZ → **CAB**	8.4 (0.6)	8.8 (0.7)	7.8 (1.8)	7.3 (1.4)	CAB	1,026 (40)	1,007 (44)	1,159 (85)
L	SUN or PAZ → AXI or CAB → **NIV**	6.2 (1.9)	5.6 (1.7)	10.4 (2.0)	3.7 (0.7)	NIV	414 (16)	441 (35)	404 (18)

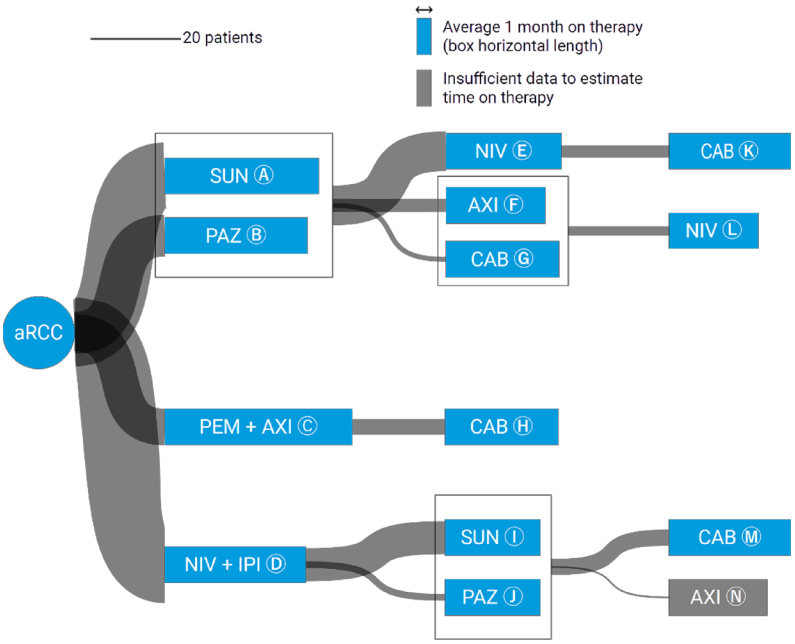
AB = Alberta; AXI = axitinib; BC = British Columbia; CAB = cabozantinib; NA = not applicable; NIV = nivolumab; NIV + IPI = nivolumab with ipilimumab; ON = Ontario; PAZ = pazopanib; PEM + AXI = pembrolizumab with axitinib; SUN = sunitinib; SE = standard error.

[a]Restricted to 30 months; month defined as a 30-day interval.

[b]There is a statistically significant difference ($P < 0.05$) in the mean dose between Ontario and British Columbia for this treatment sequence and therefore the calculation for a pooled mean dose may not be appropriate.

[c]Insufficient sample size.

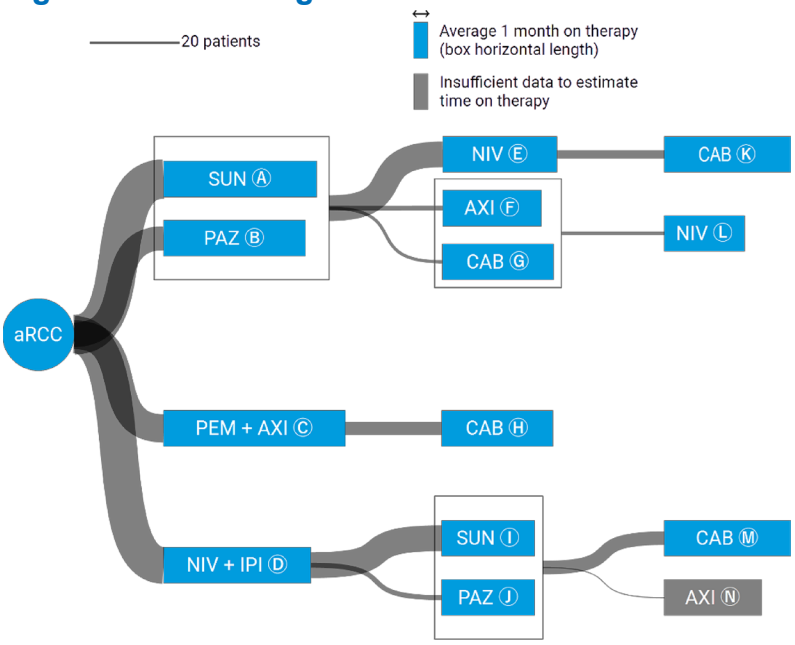
Figure 10: Flow Diagram for Treatment Duration and Weighted Incident Frequency Across All Sites



aRCC = advanced renal cell carcinoma; AXI = axitinib; CAB = cabozantinib; IPCW = inverse-probability-of-censoring weighting; NIV = nivolumab; NIV + IPI = nivolumab with ipilimumab; PAZ = pazopanib; PEM + AXI = pembrolizumab with axitinib; RCC = renal cell carcinoma; SUN = sunitinib.

Note: Patient counts were taken from Table 2 (IPCW); time on therapy was taken from Table 3. For intervals, the midpoint was used.

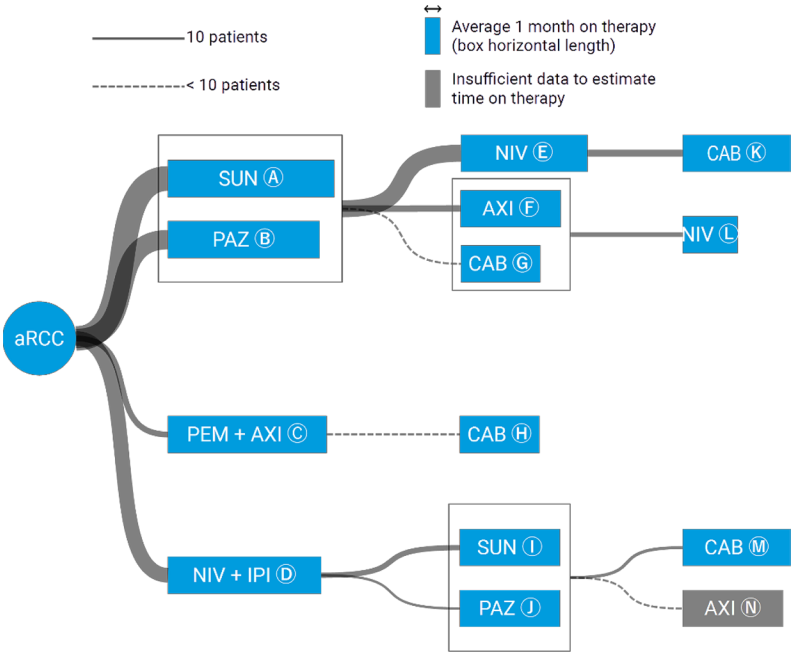
Figure 11: Flow Diagram for Treatment Duration and Weighted Incident Frequency in Ontario



aRCC = advanced renal cell carcinoma; AXI = axitinib; CAB = cabozantinib; IPCW = inverse-probability-of-censoring weighting; NIV = nivolumab; NIV + IPI = nivolumab with ipilimumab; PAZ = pazopanib; PEM + AXI = pembrolizumab with axitinib; RCC = renal cell carcinoma; SUN = sunitinib.

Note: Patient counts were taken from Table 2 (IPCW); time on therapy was taken from Table 3. For intervals, the midpoint was used.

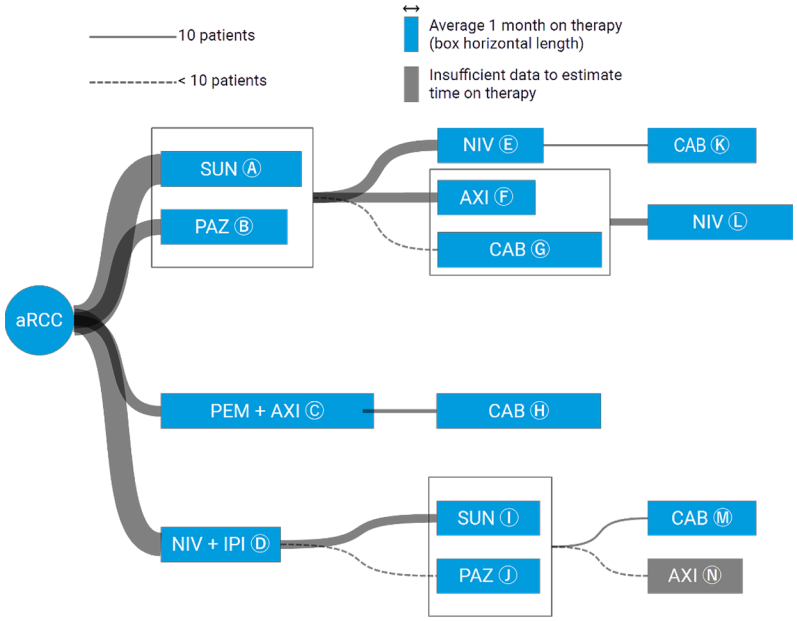
Figure 12: Flow Diagram for Treatment Duration and Weighted Incident Frequency in Alberta



aRCC = advanced renal cell carcinoma; AXI = axitinib; CAB = cabozantinib; IPCW = inverse-probability-of-censoring weighting; NIV = nivolumab; NIV + IPI = nivolumab with ipilimumab; PAZ = pazopanib; PEM + AXI = pembrolizumab with axitinib; RCC = renal cell carcinoma; SUN = sunitinib.

Note: Patient counts were taken from Table 2 (IPCW); time on therapy was taken from Table 3. For intervals, the midpoint was used.

Figure 13: Flow Diagram for Treatment Duration and Weighted Incident Frequency in British Columbia



aRCC = advanced renal cell carcinoma; AXI = axitinib; CAB = cabozantinib; IPCW = inverse-probability-of-censoring weighting; NIV = nivolumab; NIV+IPI = nivolumab with ipilimumab; PAZ = pazopanib; PEM+AXI = pembrolizumab with axitinib; RCC = renal cell carcinoma; SUN = sunitinib

Note: Patient counts were taken from Table 2 (IPCW); time on therapy was taken from Table 3. For intervals, the midpoint was used.

Interpretation

We found that treatment patterns for patients with advanced RCC changed rapidly since 2017 in Ontario, Alberta, and British Columbia. In 2017 and 2018, sunitinib and pazopanib dominated first-line treatments, but by 2021, these treatments only accounted for approximately 13% of all first-line treatments. This is largely due to the approval of public funding for combination nivolumab and ipilimumab in 2019 and combination pembrolizumab and axitinib in 2021.This switch from first-line sunitinib or pazopanib to first-line ICI-based therapies is supported by the pivotal clinical trials for combination pembrolizumab and axitinib and combination ipilimumab and nivolumab, where the use of both combination therapies showed superior efficacy compared to sunitinib alone.[15,22] Our results are consistent with those from a report from Cardenas et al. describing real-world metastatic RCC treatment patterns between 2011 and 2021 among patients in the Canadian Kidney Cancer Information System, a registry of patients with kidney cancer across Canada.[19] The authors observed a substantial decrease in first-line sunitinib and pazopanib use from approximately 90% of all first-line therapies between 2011 and 2017, to 35% of first-line therapies in 2021.

Treatment patterns in the second and third lines also changed considerably following widespread uptake of ICI combination therapies in the first-line treatment setting. Nivolumab monotherapy was the most frequently used second-line and third-line treatment before 2020. From 2020 onwards, nivolumab monotherapy was displaced using VEGFR TKI's (axitinib, cabozantinib, pazopanib, and sunitinib) in the second line and cabozantinib in third line. These trends also broadly mirror the observations described by Cardenas

et al., who reported relative increases in the use of second-line sunitinib and cabozantinib, and third-line cabozantinib in more recent years.

Although we focused on patients who received publicly funded first-line therapies for advanced RCC, we did not restrict subsequent lines of therapy to publicly funded treatments. Therefore, among the patients who started treatment for advanced RCC on publicly funded therapies, we identified some individuals who initiated second-line or third-line treatment using therapies before they were funded by the provincial drug programs. This is evidenced by the observed use of second-line and third-line cabozantinib in 2018 and 2019 before its 2020 approval for public funding. These treatments occurring in 2018 and 2019 were likely funded via clinical trials or patient support programs (PSPs). Cardenas et al. included treatments funded by all payers in their study and therefore observed similar trends in drug use before public funding approvals.[19]

We observed a decrease in incident patient numbers in 2020 for publicly funded first-line treatment. This is likely due to the introduction of PSP-funded combination pembrolizumab and axitinib in 2020 before its public funding, which led to fewer patients receiving publicly funded therapies in that year. In 2021, combination pembrolizumab and axitinib was publicly funded and the number of incident first-line treatments returned to its expected baseline. Although access to many medications decreased during the COVID-19 pandemic due to drug shortages, systemic treatments for cancer were prioritized and therefore experienced minimal disruptions.[23] Conversely, there were delays for patients with cancer seeking and being able to access care. Challenges around health human resources and capacity led to delays in diagnosis and treatment of cancer.[24] Thus, we hypothesized that the decrease in first-line patient volume in 2020 might in part be due to fewer diagnoses during the pandemic but might also represent a decreased demand from patients who were publicly insured acquiring these treatments through alternative programs.

Our analysis of treatment duration showed that restricted mean duration on treatment decreased as patients progressed to second-line and third-line therapies. In Ontario and British Columbia, we found that mean doses of oral drugs of interest, of those that had fixed dosing in the real world, were lower than the recommended doses available in product monographs.[21,25-30] The dosing of several of our treatments of interest are dependent on a patients' weight, and in recent years, there has been a push toward reassessing the use of a drug's full dose for many oncology drugs to balance potential effectiveness and adverse events.[31] Therefore, it is not unexpected that the mean doses observed in our study were slightly lower in the real world than product monograph recommendations.

Strengths and Limitations

The main strength of this study is that we used a population-based cohort in Ontario, Alberta, and British Columbia. Our data in Alberta and British Columbia captured all publicly funded treatments for advanced RCC in these provinces, and therefore the cohorts were less likely to be subject to selection bias. This suggests that our study cohort is likely generalizable to patients with advanced RCC undergoing systemic treatment through publicly funded programs in other provinces in Canada.

However, we limited the patient population by excluding patients who received treatments via PSPs, private payment, off label, or clinical trials in the first line. This study design provided us with a cohort of patients who started treatment via publicly funded means, consistent with the CDA-AMC provisional funding algorithm. However, this approach may underestimate utilization from the perspective of the public payer. Further, some of the excluded patients may have received publicly funded second-line or third-line therapy following the start of public funding of these treatments. Conversely, inclusion of patients exposed to nonfunded regimens in the second-line setting and beyond may overestimate the impact on the payer.

Two important variables often used to describe RCC, IMDC score, and cancer stage, were limited in availability in the administrative databases accessed by CCRE Platform sites. IMDC score as well as the components required to calculate this score were unavailable to all CCRE Platform sites, and cancer stage at diagnosis data were available in all 3 provinces, though British Columbia and Ontario had missing stage data for close to one-half of the patients included in the study. Therefore, we were unable to report treatment utilization in the context of these risk criteria and stage. While this information could provide additional context for treatment and allow for assessment of concordance between clinical practice and evidence-based treatment guidelines, the primary objective of this study was to describe the utilization patterns in publicly funded first line as well as the subsequent sequence and duration of treatments among individuals with advanced RCC. Therefore, the lack of IMDC score and complete stage data did not hinder our ability to achieve the primary objectives of this study.

The estimates of treatment duration provide valuable insight into the real-world utilization patterns of these therapies, but they should not be compared directly across regimens or used as a proxy for treatment effectiveness. The patient characteristics are not balanced across treatments, clinical outcomes were not captured, and reasons for discontinuation are not known. This study was not designed to estimate the effectiveness or comparative effectiveness of these therapies.

Conclusions and Implications for Decision or Policy-Making

Main Take-Aways

There is a broad range of publicly funded treatment options for patients with advanced RCC. The findings from this study identify some current trends in the utilization of advanced RCC treatments, such as the substantial uptake of VEGFR TKI therapies. They reflect the evolution of a rapidly changing treatment landscape and can be used for resource planning and to identify pressure points in the system regarding drug funding for advanced RCC.

There is currently a broad range of publicly funded systemic treatment options available to patients with advanced RCC in Canada, and additional treatments continue to undergo trials and approvals. However, it remains unclear how treatment patterns have evolved over time across multiple lines of therapy for this disease site. Canadian provinces that fund these treatments want to better understand resource allocation

such as patient volumes, duration of treatment, and dose in the real world. We found that the use of combination ICI and VEGFR TKI treatments in the first line have increased substantially since their approval for public funding. Sequencing patterns indicate that, when given the choice, prescribers will more often select a drug of a different class for the next line of therapy. Duration of treatment decreases as patients progress onto subsequent lines of treatment and mean doses in the real world is typically lower than that recommended in product monographs for oral drugs with fixed dosing.

The findings from this study can be used by funders to monitor how patients progress along the lines of treatment in funding algorithms of each jurisdiction. Understanding these treatment trajectories and how they change after the introduction of new therapies may provide support for increasing drug budgets and aid in the estimation of financial impacts of current regimens and new therapies in the future. These results may also support conversations between funders and clinicians when new therapies become available on the market. However, it is important to note that our findings reflect the real-world use of these treatments within the framework of each jurisdiction's funding algorithm and therefore may not be reflective of the treatment sequences of jurisdictions with different funding criteria or regulatory indications.

Finally, these findings may prompt further clinical and economic questions to be explored, particularly as we continue to see the treatment landscape of advanced RCC shift, expand, and become more complex.[10,18] In the past few years, additional TKI ICI combination treatments have emerged for the first line such as nivolumab in combination with cabozantinib,[17] and lenvatinib in combination with pembrolizumab.[16] Furthermore, there is emerging work on biomarker testing[32] and additional shifts in treatment in later lines of therapy that will cause a ripple effect now and into the future.

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Authors and Contributors

Authors

Reka E Pataky contributed to the development of the proposal and study protocol, acquired data and conducted the analysis for the British Columbia arm of the study, contributed to the presentation of results, drafting of the report, and the critical review of the final report.

Qi Guan contributed to the study design, analysis, interpretation of analysis, and the drafting of the report.

Mariet Mathew Stephen was responsible for analyzing data and created Alberta site-specific reports in accordance with the study protocol, participated in reviewing various versions of the study protocol and report.

Nicola Bai contributed to data analysis and report drafting.

Katharina Forster supported the drafting and review of the proposal and protocol, contributed to the review and interpretation of data, and participated in writing and reviewing the report.

Winson Y Cheung contributed to conception and design, acquisition of data, analysis and interpretation, and reviewed the report to ensure accuracy and reliability of its content.

Samara Strub contributed to conception, drafting key messages, and revising the report for content and consistency.

Safiya Karim contributed to the analysis and interpretation of study results, review of key messages and conclusion, and the review of sequencing of drugs.

Steven Yip contributed to conception and design, acquisition of data, and analysis and interpretation of the study results, and to the drafting and reviewing of the report.

Mina Tadrous contributed to conception and design, acquisition of data, and analysis and interpretation of the study results, and to the drafting and reviewing of the report.

Stuart Peacock worked directly with the British Columbia researchers and contributed to all aspects of study design, executing, and writing.

Kelvin KW Chan contributed to the conception, design, analysis, and interpretation of the study; revising of the report; and the overall supervision of this Post-Market Drug Evaluation query as the senior responsible author.

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The CCRE Platform would like to acknowledge the following individuals:

Scott Gavura reviewed draft and final reports, Christie Farrer reviewed a draft report, and Jessica Arias and Caroline Muñoz reviewed a draft report.

Conflicts of Interest

Safiya Karim disclosed the following:

Travel Funding or Payment

Pfizer – Gastric Cancer 2023

Bayer – Prostate Cancer 2023

Ipsen – hepatocellular cancer 2023

Speaking Engagement

Bayer – Prostate Cancer 2023

Amgen – Colorectal Cancer 2022

Educational Lectures

EMD-Serano – Immunotherapy 2023

Steven Yip disclosed the following:

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Pfizer, Novartis, AstraZeneca, Merck, Bayer, Janssen Astellas – Prostate Cancer

Speaking Engagements

Pfizer, Novartis, AstraZeneca, Merck, Bayer, Janssen Astellas – Prostate Cancer

BMS, Roche, Ipsen

Educational Lectures

Pfizer, Novartis, AstraZeneca, Merck, Bayer, Janssen Astellas – Prostate Cancer

Writing Articles or Editorials

Pfizer, Novartis, AstraZeneca, Merck, Bayer, Janssen Astellas – Prostate Cancer

Other - Consulting

Oncohelp

Participation in Developing Scientific Advice:

Pfizer, Novartis-AAA – 2024

AstraZeneca, Merck – 2023

Bayer – 2023

BMS – 2023

Roche – 2023

Ipsen − 2024

Janssen Astellas – 2023

Mina Tadrous disclosed the following:

Other – Consulting Fees

Health Canada – Drug Shortages

Payment as Advisor or Consultant

Green Shield Canada – Data Analytics

Jessica Arias disclosed the following:

Involvement With Projects or Scientific Advice

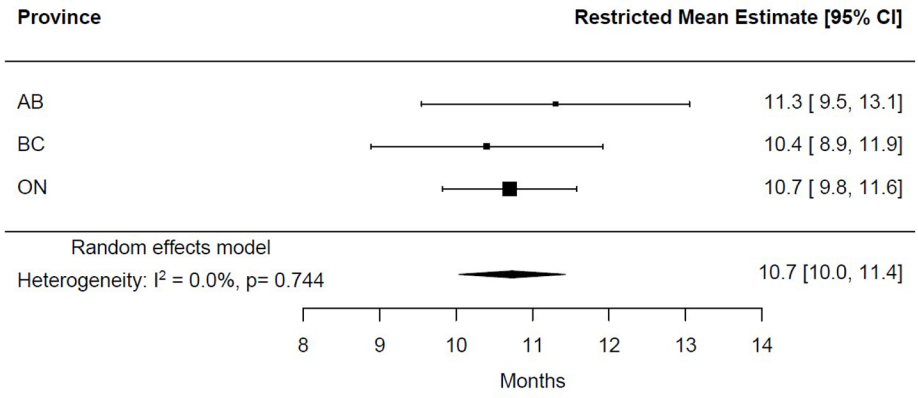
CADTH Working Group for Time Limited Recommendations – represented Ontario's cancer agency and provided advice on relevant documents and communications.

No other conflicts of interest were declared.

Appendix 1: Additional Results

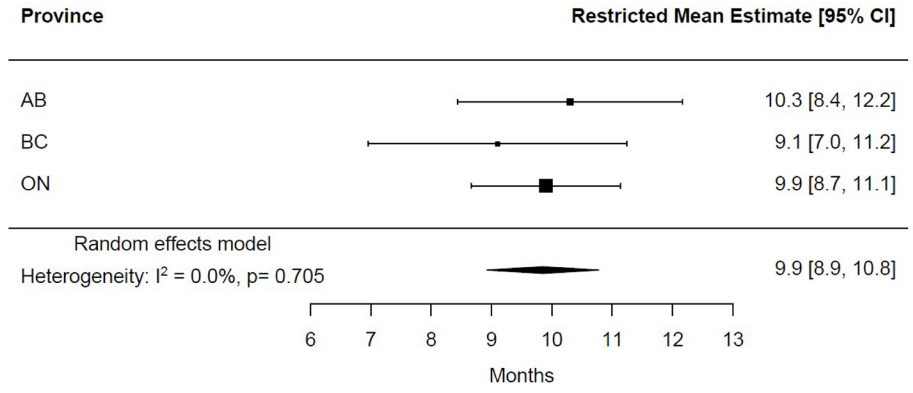
Please note that this appendix has not been copy-edited.

Figure 14: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for First-Line Sunitinib (Sequence A)



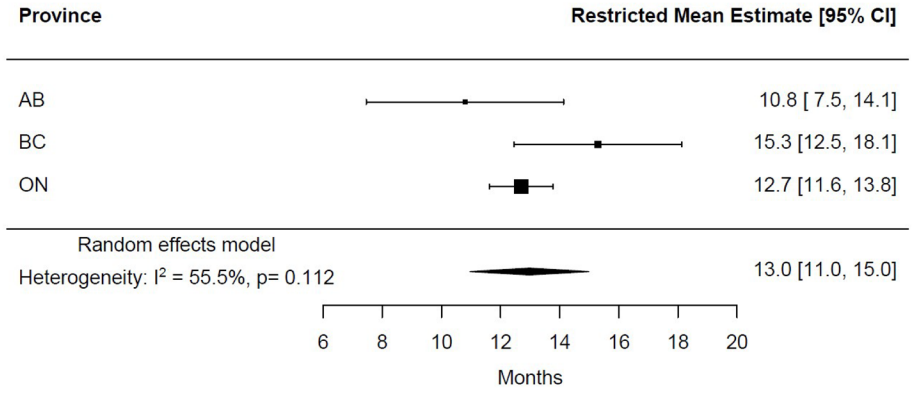
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 15: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for First-Line Pazopanib (Sequence B)



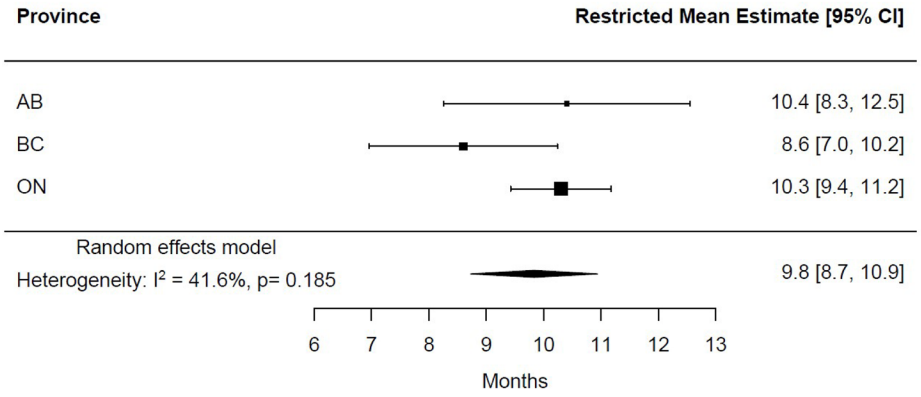
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 16: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for First-Line Pembrolizumab With Axitinib (Sequence C)



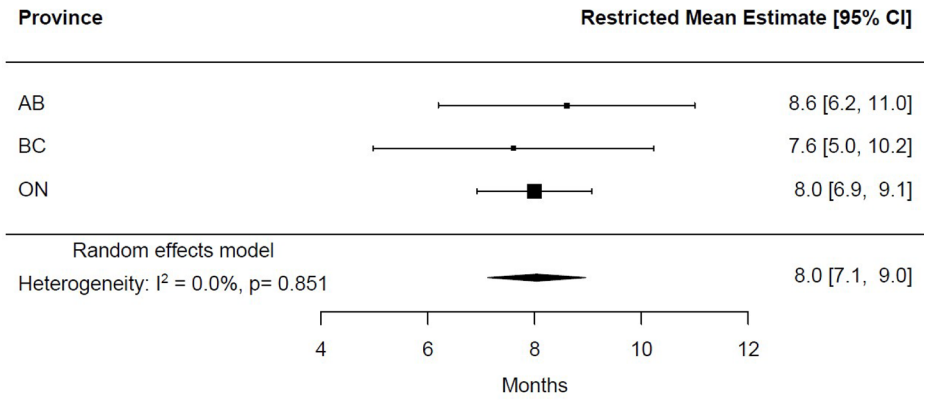
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 17: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for First-Line Nivolumab With Ipilimumab (Sequence D)



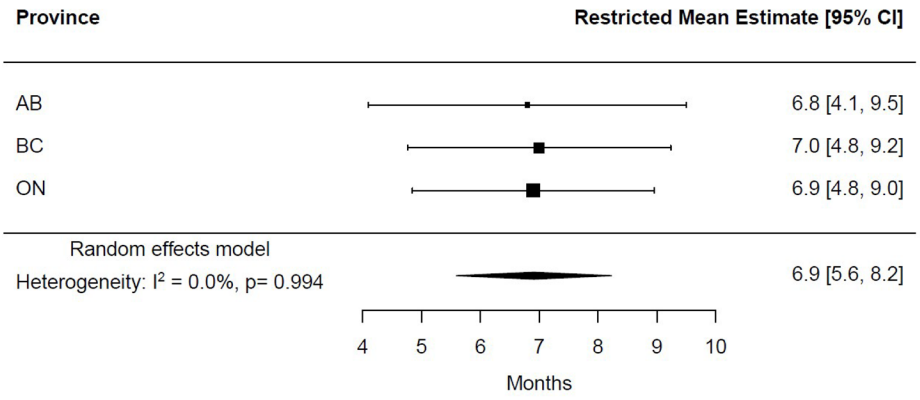
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 18: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Second-Line Nivolumab (Sequence E)



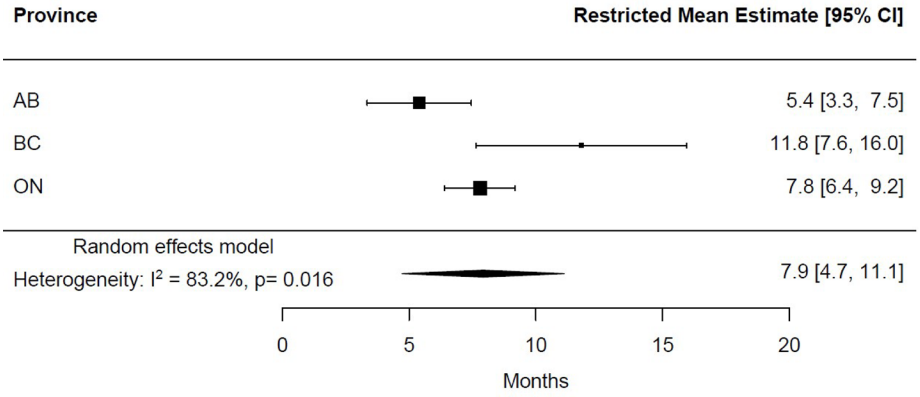
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 19: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Second-Line Axitinib (Sequence F)



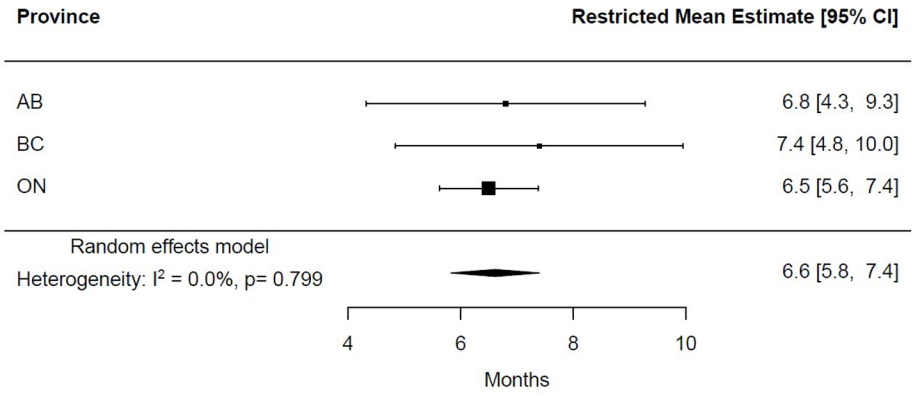
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 20: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Second-Line Cabozantinib (Sequences G and H)



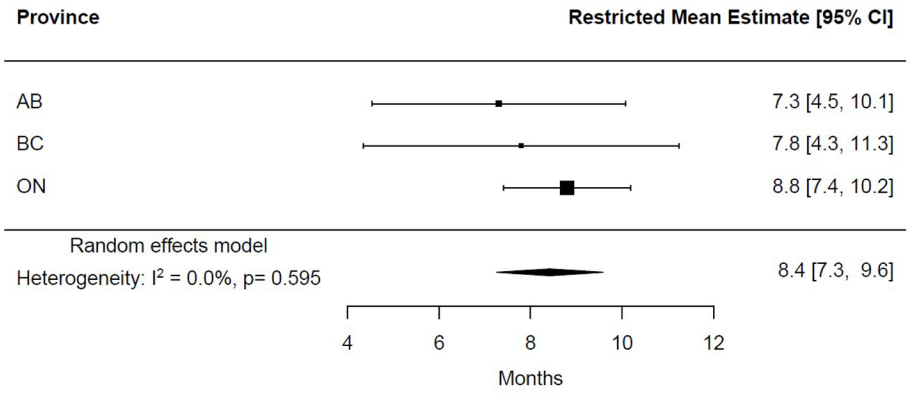
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 21: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Second-Line Sunitinib or Pazopanib (Sequences I and J)



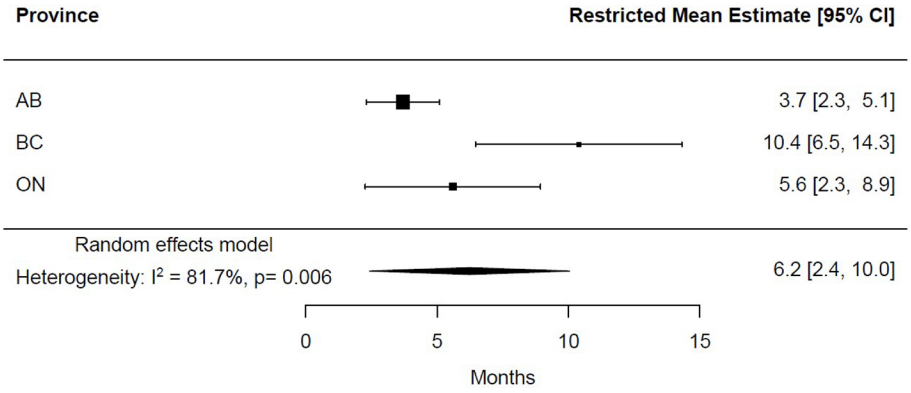
AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 22: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Third-Line Cabozantinib (Sequences K and M)



AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Figure 23: Forest Plot of Meta-Analysis of Restricted Mean Treatment Duration Estimates Across All CCRE Platform Sites for Third-Line Nivolumab (Sequence L)



AB = Alberta; BC = British Columbia; CCRE = Canadian Cancer Real-world Evaluation; CI = confidence interval; ON = Ontario.

Table 4: Mean Weekly Dose

Node	Sequence to node	Mean (SE) dose, mg per week			
		Drug	All	ON	BC
A	**SUN**	SUN	204 (4)[a]	156 (3)	222 (5)
B	**PAZ**	PAZ	3,363 (108)	3,511 (107)	3,281 (157)
C	**PEM + AXI**	AXI	40 (2)	39 (1)	40 (3)
		PEM	39 (1)	41 (1)	37 (2)
D	**NIV + IPI**	IPI	6 (0.4)	6 (0.3)	6 (0.7)
		NIV	89 (1)	91 (1)	88 (2)
E	SUN or PAZ →**NIV**	NIV	102 (2)	101 (2)	102 (3)

Node	Sequence to node	Mean (SE) dose, mg per week			
		Drug	All	ON	BC
F	SUN or PAZ →**AXI**	AXI	74 (22)	57 (3)	76 (25)
G and H	SUN or PAZ →**CAB** and PEM + AXI →**CAB**	CAB	254 (11)	239 (10)	265 (17)
I and J	NIV + IPI →**SUN** and NIV + IPI →**PAZ**	SUN	215 (6)[a]	171 (8)	232 (8)
		PAZ	NA[b]	3,757 (360)	NA[b]
K and M	SUN or PAZ →NIV →**CAB** and NIV + IPI →SUN or PAZ → **CAB**	CAB	253 (11)	235 (10)	271 (20)
L	SUN or PAZ →AXI or CAB →**NIV**	NIV	95 (4)	101 (8)	94 (4)

AXI = axitinib; BC = British Columbia; CAB = cabozantinib; NA = not applicable; NIV = nivolumab; NIV+IPI = nivolumab with ipilimumab; ON = Ontario; PAZ = pazopanib; PEM+AXI = pembrolizumab with axitinib; SUN = sunitinib; SE = standard error.

[a]There is a statistically significant difference ($P < 0.05$) in the mean dose between Ontario and British Columbia for this treatment sequence and therefore the calculation for a pooled mean dose may not be appropriate.

[b]Insufficient sample size.

Appendix 2: Additional and Supporting Information

Please note that this appendix has not been copy-edited.

Table 5: 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

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 6: 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 hospital settings in Ontario • **OCR:** records of cancer diagnoses • **RPDB:** demographics data
Clinical and demographic characteristics	• **CIHI-DAD: a**ll 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**

Province and data type	Data sources
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 BC 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.

Table 7: Summary of Funding Dates by Province

Drug or drug combination	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	Sep 2011
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 8: Summary of Drug Dosing

Drug or drug combination	Cycle length	Dosing[a]
Sunitinib	42 days	50 mg/day on a schedule of 4 weeks on treatment followed by 2 weeks off
Sorafenib	28 days	800 mg daily dose
Everolimus	28 days	10 mg/day
Temsirolimus	28 days	25 mg/week
Pazopanib	28 days	800 mg/day
Pembrolizumab with axitinib	21 days	Axitinib: 10 mg/day Pembrolizumab: 2 mg/kg up to a maximum of 200mg per 3 weeks
Nivolumab with ipilimumab	21 days	Ipilimumab: 1 mg/kg, per cycle Nivolumab: 3 mg/kg up to a maximum of 240 mg per 2 weeks, or 6 mg/kg up to 480 mg per 4 weeks
Nivolumab (single agent)	14 or 28 days	3 mg/kg up to a maximum of 240 mg per 2 weeks, or 6 mg/kg up to 480 mg per 4 weeks
Axitinib (single agent)	28 days	10 mg/day (up to 20 mg/day)
Cabozantinib	28 days	60 mg/day

[a]Dosing is presented without adjustment for toxicity or impaired organ function. For recommended dose adjustments, consult the product monograph.

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

This work was conducted by the Canadian Cancer Real-world Evaluation (CCRE) Platform team through the Post-Market Drug Evaluation CoLab Network. It was supported by Canada's Drug Agency (CDA-AMC) and its Post-Market Drug Evaluation Program through funding provided by Health Canada.

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.