

## Real-world evaluation of access-driven Canadian treatment sequences in progressive prostate cancer (REACTIVATE)

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### ABSTRACT

**INTRODUCTION:** The results of the phase 3 ALSYMPCA trial showed that Radium-223 (Ra-223) improves overall survival (OS) and delays onset of first symptomatic skeletal event vs. placebo in patients with metastatic castration-resistant prostate cancer (mCRPC). The purpose of the REACTIVATE study was to inform the optimal placement of Ra-223 in the treatment sequence by evaluating clinical outcomes and healthcare resource utilization using real-world data from multiple Canadian provinces.

**METHODS:** This retrospective cohort study analyzed patient outcomes according to Ra-223 placement using administrative databases of four Canadian provinces, encompassing 4301 patients with mCRPC who received at least two lines of life-prolonging therapy (LPT) for mCRPC. Outcomes included OS, event-free survival (EFS), and healthcare resource utilization. Each province was analyzed separately.

**RESULTS:** OS, measured from the start of second-line LPT, differed between provinces: those in Ontario receiving second-line Ra-223 had a longer OS vs. those receiving it in third-line or later (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66–0.95). There was no difference between lines of therapy in patients in British Columbia (HR 1.165, 95% CI, 0.894–1.518,  $p=0.2576$ ), and OS was numerically worse but not statistically significant in patients receiving Ra-223 in second-line in Quebec (HR 1.44, 95% CI, 0.93–2.24). Other outcomes also varied across provinces, with second-line use of Ra-223 being associated with longer EFS and reduced healthcare utilization vs. third-line use in Ontario but not in Quebec.

**CONCLUSIONS:** Significant heterogeneity exists in the management and outcomes of mCRPC between provinces, particularly regarding the placement of Ra-223 in the treatment sequence.

### INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in males in North America and the second leading cause of death in Canadian males.<sup>1,2</sup> Worldwide, it is the second most diagnosed cancer in men,<sup>3</sup> with the global burden expected to almost double by 2040 due to an aging population.<sup>4</sup>

For many years, docetaxel was the mainstay of metastatic castration-resistant prostate cancer (mCRPC) treatment; more recently, additional therapies that prolong overall survival (OS) have been developed. These therapies are grouped based on their therapeutic targets: androgen receptor axis targeted (ARAT) therapy (e.g., abiraterone acetate, enzalutamide); immunotherapy (e.g., sipuleucel-T, pembrolizumab for microsatellite instability-high mPC); cytotoxic chemotherapy (e.g., docetaxel, cabazitaxel); poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., niraparib, olaparib); and radiopharmaceuticals (e.g., radium-223 [Ra-223], Lutetium-177 [Lu-177]).

Abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, and Ra-223 are non-biomarker-dependent life-prolonging therapies (LPTs) approved for mCRPC in parts of Canada as of December 2022.<sup>5-8</sup> However, limited evidence exists on the optimal sequencing of these treatments, especially for the optimal placement of Ra-223.<sup>9</sup> Common mechanisms of resistance are anticipated to attenuate the improvement in OS when active drugs of the same class are used sequentially; for example, there is cross-resistance between ARAT

KEY MESSAGES

- Multiple real-world studies support the use of Ra-223 after abiraterone or enzalutamide, with observational studies demonstrating that late sequencing of Ra-223 led to lower completion rates and shorter survival.
- This large, retrospective cohort study focused on Ra-223 use and identified differences in survival outcomes and healthcare resource utilization among patients from AB, BC, ON, and QC who were prescribed at least two lines of LPT.
- Significant heterogeneity exists in the management and outcomes of mCRPC between provinces, particularly regarding the placement of Ra-223 in the treatment sequence.

Data collection

Canada has a federalized, publicly funded, universally available healthcare system in which each province makes its own decisions with regards to drug reimbursement, creating differential patterns of access to various mCRPC LPTs across provinces (Table 1).<sup>19</sup> PARP inhibitors were not included as LPTs as they were not approved in Canada for use at the time of the study design and data collection. Data were drawn from registries across four Canadian provinces (Alberta, British Columbia, Ontario, and Quebec), including the Alberta Cancer Registry (ACR), British Columbia Cancer Registry (BCCR), the Institute for Clinical Evaluative Sciences (ICES), and the Régie de l'assurance maladie du Québec (RAMQ).

Data sources

BRITISH COLUMBIA

Data on demographic, tumor, and treatment characteristics as well as diagnoses, including primary malignancies besides mCRPC, and outcomes were obtained from the British Columbia Cancer Registry (BCCR). In the registry, details of all radiation therapy delivered since 1984 have been prospectively recorded by trained data abstractors based on information specified on prescription sheets using a pre-specified data dictionary. The data are periodically audited for quality assurance. The database includes detailed data on the treated anatomic site, treatment intent, technique, dose, and fractionation. The database cutoff was July 31, 2019.

agents (e.g., abiraterone acetate and enzalutamide). Therefore, it is crucial for clinicians to consider therapeutic options with a unique mechanism of action.<sup>10</sup>

The phase 3 ALSYMPCA trial showed that Ra-223 improved OS, delayed onset of the first symptomatic skeletal event, and had a favorable safety profile compared with placebo in patients with mCRPC; however, no patients with prior ARAT therapy were included.<sup>11</sup> Multiple real-world studies support the use of Ra-223 after abiraterone or enzalutamide.<sup>12-16</sup> Observational studies demonstrated that later placement of Ra-223 in the treatment sequence led to lower completion rates and shorter survival after Ra-223 initiation.<sup>15,17,18</sup> The purpose of our study was to describe the placement of Ra-223, and associated outcomes, in the treatment sequence for mCRPC by evaluating clinical outcomes and healthcare resource utilization using real-world data from multiple provinces throughout Canada.

METHODS

We conducted a retrospective cohort study using data from administrative databases of patients with mCRPC in four Canadian provinces: Alberta, British Columbia, Ontario, and Quebec. Challenges in transferring patient level data across provinces precluded pooling of individual level data from the four provinces. A standardized approach to extract and analyze data within each province was adopted to enhance comparability.

**Table 1. Funding requirements for life-prolonging systemic mCRPC therapy among the four Canadian provinces queried in this study**

Life-prolonging treatment	Alberta	British Columbia	Ontario	Quebec
<b>Ra-223</b>	Not funded	Pre- and post-docetaxel	Pre- and post-docetaxel	Post-docetaxel, or in docetaxel ineligible patients
<b>Docetaxel</b>	No restriction	No restriction	No restriction	No restriction
<b>Cabazitaxel</b>	Post-docetaxel	Post-docetaxel (if no ARAT therapy used)	Post-docetaxel	Post-docetaxel
<b>ARAT therapy (abiraterone acetate or enzalutamide)</b>	Both may be used if sequenced with chemotherapy in between	Only 1 may be used Not funded if cabazitaxel used	Both may be used if sequenced with chemotherapy in between	Only 1 may be used

ARAT: androgen receptor axis targeted; mCRPC: metastatic castration-resistant prostate cancer.

**ALBERTA**

The Alberta Cancer Registry (ACR) covers the province's entire population. All patients have access to a single-payer, universal healthcare system. The ACR prospectively collects information on patient demographics, tumor characteristics, primary treatment, and treatment facility from all individuals who resided in the province at the time of their initial, confirmed cancer diagnosis. Because cancer is a reportable disease in the province, case ascertainment is complete and accurate in the ACR within 12 months of diagnosis. Additional data for the study can be pulled from Discharge Abstract Data, National Ambulatory Care Reporting System, provincial physician billing claims data, Pharmaceutical Information Network data, and Vital Statistics Data. The database cutoff was July 31, 2019.

**QUEBEC**

The administrative database for Quebec is the Régie de l'assurance maladie du Québec (RAMQ), a provincial governmental board that administers public healthcare insurance programs. All Quebec residents are eligible for the public healthcare insurance plan, which covers medical visits and procedures. These databases contain data regarding beneficiary demographic information, inpatient and outpatient medical services rendered, and drugs dispensed in the community setting. Diagnoses in the databases are classified according to the International Classification of Diseases, 9<sup>th</sup> and 10<sup>th</sup> revisions. The database cutoff was May 31, 2020.

**ONTARIO**

The Institute for Clinical Evaluative Sciences (ICES) Data Repository consists of record-level, coded, linkable health data sets. It encompasses much of the publicly funded administrative health service records for the Ontario population eligible for universal health coverage since 1986 and is capable of integrating research-specific data, registries, and surveys.

Attributes of the data in the repository include individual level data, longitudinal data (most health records extend back to 1991), population-based data (all people eligible for healthcare in Ontario), most publicly funded health services, some related services other than healthcare, and coded de-identified data. These data are all linkable to provide information about continuity of care.

The data from the registry originates from physician claims submitted to the Ontario Health Insurance Plan, medical drug claims submitted to the Ontario Drug Benefit Program, discharge summaries of hospital stays

and emergency department visits, special registry collections such as the Ontario Cancer Registry (Cancer Care Ontario), derived chronic condition cohorts developed at ICES using linked data algorithms, detailed clinical data extracted from electronic medical records or through ICES primary data collection projects, and population and demographic data used to characterize study subjects, determine rates of various conditions, infer ecological variables, and characterize deaths. The database cutoff was August 31, 2019.

**Sampling**

Ra-223 received a notice of compliance from Health Canada in December 2013.<sup>20</sup> We collected data from patients treated for mCRPC from January 1, 2012 to December 31, 2017 according to prespecified variables, if available, from the time of prostate cancer diagnosis until death or end of followup. The index date was the date of initiation of the second LPT for mCRPC.

**Eligibility**

All patients who had received at least two lines of LPT for mCRPC (i.e., docetaxel, cabazitaxel, enzalutamide, abiraterone acetate, or Ra-223) that were approved for use in Canada were considered if the second-line of LPT was initiated between January 1, 2012, and December 31, 2017. Olaparib and Lu-177 were not approved in Canada at the time of the study.

The cohorts were defined as: no Ra-223 received, Ra-223 received in second-line (2L), and Ra-223 received in third-line or later (3L+). This excluded patients who used Ra-223 in first-line. Such use is rare in Canada as Ra-223 is typically initiated in patients who show symptoms, as per the Health Canada indication and the Canadian Urology Association guidelines.<sup>21</sup>

**Cohort size**

A sample of 1380 patients (460 per cohort) was required to provide a statistical power of 90% to detect a hazard ratio (HR) of 0.7 for the hazard of death between any two cohorts, with a two-sided level of significance set at  $\alpha=0.05$ . These computations assumed a 1:1:1 allocation ratio and 336 events in each pairwise comparison. The estimates of HR and survival probabilities in the control and Ra-223 cohorts were drawn from the ALSYMPCA trial (54% and 65% respectively).<sup>11</sup> We would have required 513 participants for a HR as small as 0.88 or 10506 participants for a HR as large as 0.53 (derived from the 95% confidence intervals [CIs] of the HRs in the ALSYMPCA trial). The computations were calculated using the *power* command in STATA

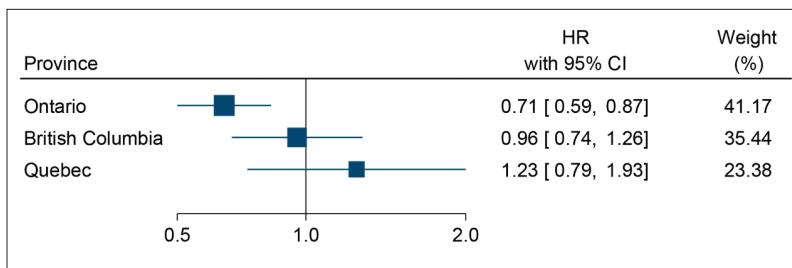
(StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). These estimations were valid for parallel cohort comparisons in which the participants had equal weights, which was not the case in this study. Power to detect a difference in this study depended on the number of participants and events, completeness of data, and the statistical approaches used.

### Data management and analysis

Each site analyzed their own data according to a standardized and mutually agreed upon analytical plan.

At the provincial level, each data set was verified for consistency and errors by checking for outliers, improbable dates, and missing data. All modifications to the data were documented and reported alongside the results. The cutoff dates varied for each province and are detailed in the data sources.

We used descriptive statistics to characterize mCRPC patient cohorts included in the datasets. Continuous data were described using means (standard deviation [SD]) or medians (quartile 1; quartile 2). Categorical data were described using counts (percent).

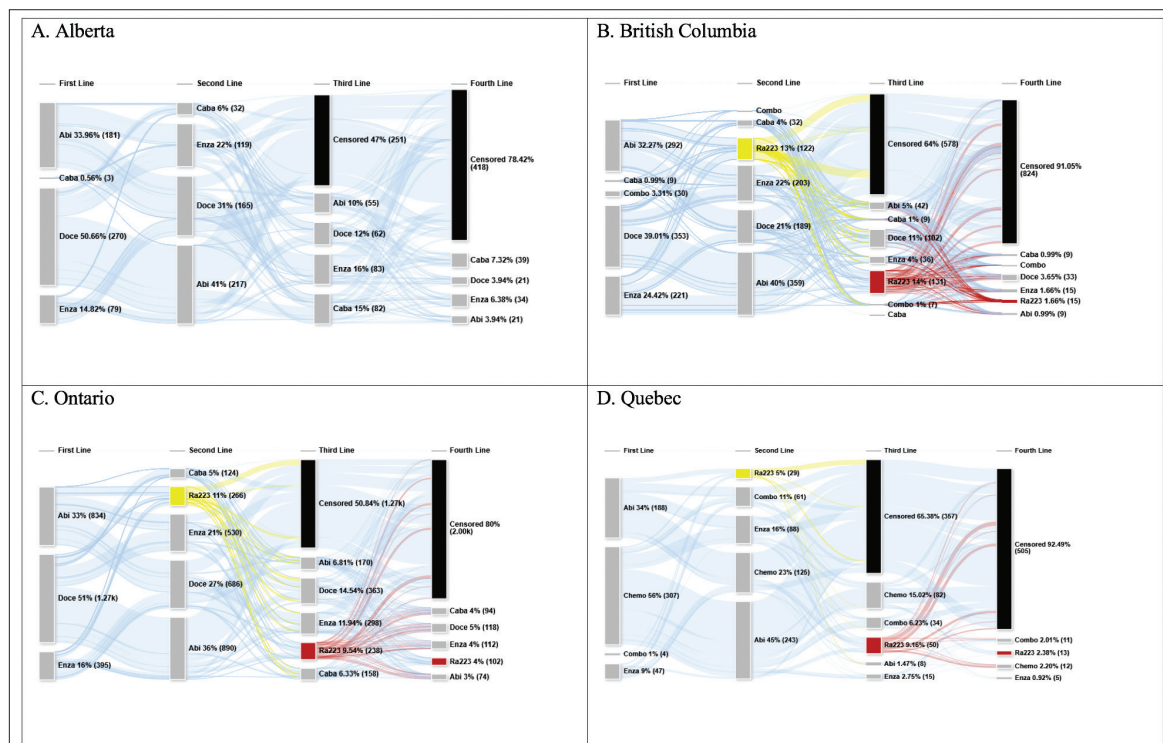


**Figure 1.** Event-free survival in patients prescribed Ra-223 in second-line vs. third-line or later. CI: confidence interval; HR: hazard ratio.

### Measures of effect

To determine the role of Ra-223 placement on OS, we used counting process data and Cox's proportional hazards models to adjust for the dynamic relationship between duration of each sequence, time-varying confounders, and outcomes. This approach allowed us to account for immortal time bias and time-varying covariates.<sup>22</sup>

Counting process was an alternative style of data input. Multiple rows of data were created for each patient, and each row corresponded to a period during which all covariates remained constant. Changes in exposure (artificial censoring), outcomes, and covariates were captured as a new period or row of data. Monthly



**Figure 2.** Sankey diagram of treatment patterns of life-prolonging therapy.

**Table 2. Baseline patient characteristics in provincial cohorts**

Variable	Alberta (n=484)	British Columbia (n=853)	Ontario (n=2418)	Quebec (n=546)
Age (years), mean (SD)	69.9 (9.2)	72.1 (8.1)	71.7 (8.9)	73.1 (8.0)
No. of Ra-223 cycles used, mean (SD)	-	4.6 (1.8)	4.3 (1.7)	3.5 (1.8)
No. of lines of LPTs, mean (SD)	2.7 (0.9)	2.4 (0.6)	2.7 (0.9)	2.4 (0.7)
Use of bone health agents, n (%)				
No	434 (89.7)	-	1219 (50.4)	189 (34.6)
Yes	50 (10.3)	-	1199 (49.6)	357 (65.4)
No. of lines of LPTs, n (%)				
Only 2 lines	248 (51.2)	567 (66.5)	1269 (52.5)	357 (65.4)
3 lines	151 (31.2)	231 (27.1)	727 (30.1)	148 (27.1)
4 lines	68 (14.1)	46 (5.4)	306 (12.7)	34 (6.2)
5 lines	12 (2.5)	4-8*	94 (3.9)	6 (1.1)
6+ lines	5 (1)	1-5*	22 (0.9)	1 (0.2)
First-line of LPTs for mCRPC, n (%)				
Abiraterone acetate	165 (34.1)	282 (33.1)	814 (33.7)	188 (34.4)
Docetaxel	249 (51.4)	333 (39.0)	1232 (51.0)	307 (56.2) <sup>†</sup>
Enzalutamide	69 (14.3)	221 (25.9)	372 (15.4)	47 (8.6)
Cabazitaxel	1 (0.2)	12 (1.4)	0 (0)	-
Life-prolonging therapies (regardless of lines), n (%)				
Abiraterone acetate	420 (86.8)	643 (75.4)	1868 (77.3)	450 (82.4)
Docetaxel	425 (87.8)	614 (72)	2088 (86.4)	489 (89.6) <sup>†</sup>
Enzalutamide	262 (54.1)	433 (50.8)	1219 (50.4)	165 (30.2)
Cabazitaxel	138 (28.5)	43 (5.0)	389 (16.1)	-
Gleason score at prostate cancer diagnosis date, n (%)				
6-7		50 (5.9)	176 (7.3)	-
8-10		318 (37.3)	785 (32.5)	-
Unknown		485 (56.9)	1457 (60.3)	-
De novo metastatic disease, n (%)				
No	216 (44.6)	147 (17.2)	515 (21.3)	-
Yes	246 (50.8)	276 (32.4)	711 (29.4)	-
Unknown	22 (4.5)	430 (50.4)	1192 (49.3)	-

\*Due to low numbers, to maintain patient anonymity, only a range can be provided. <sup>†</sup>In Quebec, chemotherapy received cannot be differentiated by type of chemotherapy, so numbers include all chemotherapy regimens, not solely docetaxel. - means variable not available. ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; LPT: life-prolonging therapy; mCRPC: metastatic castration-resistant prostate cancer; RP: radical prostatectomy; SD: standard deviation.

observations for each subject were created from the date of diagnosis. Each observation was matched to the most recent date of time-dependent covariates: prostate-specific antigen (PSA), alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BSAP), Eastern Cooperative Oncology Group (ECOG) score, and lactate dehydrogenase (LDH), when available.

Person-time ended at death, dataset closure, outcome event, ordinary censoring, or artificial censoring. This allowed us to incorporate patient data from multiple regimens or sequences and to improve statistical efficiency.<sup>23</sup>

Covariate availability varied by province. When available, we included the following covariates in the model: age (years), use of bone health agents (yes/no), prior systemic treatments (yes/no), duration of response to androgen deprivation therapy (ADT) (weeks), cancer grade at initial prostate cancer diagnosis (Gleason score; 6-7 and 8-10), standardized pain score (0-4), and comorbidities (Charlson Comorbidity Index; 0-1, 2-3, 4-6, and 7+), PSA and hemoglobin (Hb) (in 10 unit increments), and tumor, node, and metastasis (TNM) staging (ordinal). Covariates were entered into the model in a block using the forced entry approach, i.e., all chosen covariates were entered into the regression model simultaneously. HRs and 95% CIs were reported. We set a type I error rate of  $\alpha=0.05$  to test the null hypothesis that differences in Ra-223 sequencing were not associated with OS. Survival curves were plotted for time-to-event outcomes using the Kaplan-Meier function. Similar analyses were conducted for event-free survival (EFS) and use of palliative external beam radiation therapy (EBRT). EFS measured time from the start of second-line LPT to the start of fourth-line LPT or death. We used the Bonferroni-Holm method to adjust the type I error rate for secondary outcomes.<sup>24</sup> OS was measured from the start of second-line LPT and as a surrogate for disease progression.

The incidences of EBRT, hospitalizations, and emergency room visits were computed and presented as incidence rate per 100-person-year, with 95% CIs. The time from completion of Ra-223 therapy to initiation of the next LPT was reported as a median with quartiles.

Exploratory endpoints (ALP and PSA based on Ra-223 sequencing) were reported as percentage change from date of first Ra-223 cycle to the third cycle.

Our primary analytical approach was a complete case analysis. Complete cases would be defined as: all records with complete baseline, covariate, and outcome (or censoring) data. Variables that were collected poorly or inconsistently across study sites were excluded.

## Meta-analyses of pooled data

We planned to pool sufficiently similar data (in terms of methodology and clinical characteristics), but substantial heterogeneity precluded these analyses.

## RESULTS

A total of 4301 patients diagnosed with mCRPC who received at least two lines of LPT with the second-line starting between January 1, 2012, and December 31, 2017 were identified throughout Alberta, British Columbia, Ontario, and Quebec (Table 2). Of these patients, 959 (22.3%) received Ra-223 in second-line or later (260 from British Columbia, 598 from Ontario, and 101 from Quebec). Out of the 4301 patients included, 3859 (89.7%) had died at time of analysis. Median followup ranged from 12–14.8 months (interquartile range [IQR] 6.1–26.8).

### Treatment sequence

Of the patients receiving Ra-223, 410 received it in second-line and 549 received it in third-line or later. Patients receiving Ra-223 in second-line received a mean (SD) 2.2 (0.4), 2.3 (0.7), and 2.7 (0.9) lines of LPT in British Columbia, Quebec, and Ontario, respectively. Patients receiving Ra-223 in third-line or later received 3.4 (0.6), 3.5 (0.7), and 3.8 (0.9) lines of LPT in British Columbia, Quebec, and Ontario, respectively. Of the patients that did not receive Ra-223, the mean (SD) lines of LPT received was 2.7 (0.9), 2.2 (0.5), 2.3 (0.5), and 2.5 (0.8) in Alberta, British Columbia, Quebec, and Ontario, respectively. Docetaxel was used in 80–90% of patients that did not receive Ra-223, in 28–48% of patients receiving Ra-223 in second-line, and in 78–99% of patients receiving Ra-223 in third-line or later (Appendix available at [cuaj.ca](http://cuaj.ca)).

### Overall survival

OS was measured from the start of second-line LPT (Figure 3). Patients in Ontario who received Ra-223 in second-line had longer OS than patients who received Ra-223 in third-line or later (HR 0.79, 95% CI 0.66–0.95). In British Columbia, there was no difference in OS when Ra-223 was used in second-line vs. third-line or later (HR 1.165, 95% CI 0.894–1.518,  $p=0.2576$ ). In British Columbia, of the patients receiving Ra-223 in second-line, 79.2% ( $n=99$ ) received only two lines of LPT. Notably, of the patients receiving Ra-223 in second-line, 97.6% had died during the followup period. In Quebec, the frequency of Ra-223 used in second-line ( $n=32$ ) was low; OS was statistically similar for those receiving Ra-223 earlier compared to those

**Table 2 (cont'd). Baseline patient characteristics in provincial cohorts**

Variable	Alberta (n=484)	British Columbia (n=853)	Ontario (n=2418)	Quebec (n=546)
Months from initial ADT to initiation of first-line of life-prolonging therapy, mean (SD)	–	51.2 (48.2)	27.8 (45.7)	41.3 (20.7)
Previous treatment of RP, brachytherapy, EBRT, or cryotherapy, n (%)				
No	227 (46.9)	454 (53.2)	1486 (61.5)	–
Yes	257 (53.1)	399 (46.8)	932 (38.5)	–
Among patients who had any previous treatment of RP, brachytherapy, EBRT, or cryotherapy, n (%)				
Previous treatment of RP	68 (26.5)	129 (32.3)	586 (62.9)	–
Previous treatment of brachytherapy	3 (1.2)	23 (5.8)	44 (4.7)	–
Previous treatment of EBRT	212 (82.4)	321 (80.5)	438 (47.0)	–
Previous treatment of cryotherapy	18 (7.0)	–	96 (10.3)	–

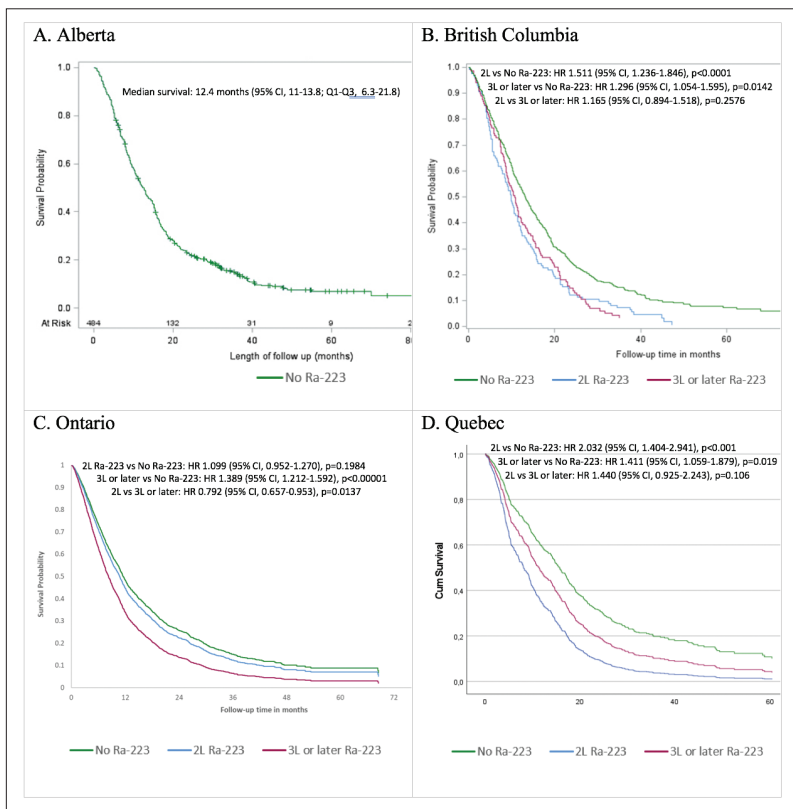
\*Due to low numbers, to maintain patient anonymity, only a range can be provided. †In Quebec, chemotherapy received cannot be differentiated by type of chemotherapy, so numbers include all chemotherapy regimens, not solely docetaxel. – means variable not available. ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; LPT: life-prolonging therapy; mCRPC: metastatic castration-resistant prostate cancer; RP: radical prostatectomy; SD: standard deviation.

receiving Ra-223 in third-line or later (HR 1.44, 95% CI 0.93–2.24). In Ontario, British Columbia, and Quebec, patients who had not yet received Ra-223 at the time of analysis reported the longest OS. In Alberta, no patients received Ra-223, and the median OS from the start of second-line LPT was 12.4 months (95% CI 11–13.8). Note that not all patients had died at time of analysis, and these data may be subject to change over time as some patients who had not yet received Ra-223 might receive it in the future.

### EFS

In Ontario, patients receiving Ra-223 in second-line had a longer time to EFS compared to patients receiving Ra-223 in third-line or later (HR 0.71, 95% CI 0.59–0.87). These results were similar in British Columbia (HR 0.96, 95% CI 0.74–1.26) and in Quebec (HR 1.23, 95% CI 0.79–1.93) (Figure 1). The median time to EFS in Alberta (no Ra-223 use) was 11 months.

Most patients in each province had reached the start of fourth-line LPT or death (range 88.4–100%) at the time of data cut-off. Notably, in Ontario, more patients receiving Ra-223 in second-line received a fourth-line LPT compared to the other provinces.



**Figure 3.** Overall survival curves adjusted for all variables in Cox model analysis. 2L: second-line; 3L: third-line; CI: confidence interval; HR: hazard ratio.

### Healthcare resource utilization

Time to first palliative EBRT after second LPT for mCRPC was measured for patients in Ontario and British Columbia, while time to first hospitalization and time to first emergency department visit were measured for those in Ontario and Quebec. For all endpoints, the index date was start of second-line LPT. Time to first palliative EBRT was longer in patients receiving Ra-223 in second-line compared to those receiving Ra-223 in third-line or later in both Ontario and British Columbia. In Ontario, patients receiving Ra-223 in second-line also had a longer time to first hospitalization (HR 0.61, 95% CI 0.48–0.77) and emergency department visit (HR 0.78, 95% CI 0.61–1.00). Patients in Quebec receiving Ra-223 in second-line had a statistically similar time to first hospitalization (HR 1.89, 95% CI 1.07–3.34) and time to first emergency department visit (HR 1.83, 95% CI 0.93–3.58) between the two groups.

### Time from Ra-223 completion to next LPT

For patients who completed six cycles of Ra-223 and received a subsequent LPT, there were no statistical differences or consistent trends across provinces

regarding median time to subsequent therapy, which ranged from 0.9–3.4 months across the cohorts. Of the patients completing Ra-223, the number receiving subsequent therapy was generally low and ranged from 20.8–60.8%.

### Changes in PSA and ALP for patients on Ra-223

PSA data was available for Ontario and British Columbia, while ALP data was available for British Columbia only. Similar to the ALSYMPCA trial, a decline PSA of  $\geq 25\%$  from cycle 1 to cycle 3 was infrequently observed (11.9% in Ontario and 18.9% in British Columbia), while the majority of patients had a decline in ALP of  $\geq 25\%$  from cycle 1 to cycle 3 (70.4% in British Columbia). There were no differences observed in PSA or ALP variations from cycle 1 to cycle 3 of Ra-223 due to differential Ra-223 sequencing (2L vs. 3L+).

### DISCUSSION

To our knowledge, this is one of the few Canadian studies to date to review the treatment patterns of patients with mCRPC across multiple provinces, with a focus on Ra-223 placement in treatment sequencing. Our study has identified significant heterogeneity in the management of mCRPC between provinces. Some of the variation observed may be due to differences in the available data sources obtained from specific provinces; however, differences in funding and healthcare delivery may also play a role.

For patients who received at least two LPTs for mCRPC, docetaxel (the current standard-of-care for mCRPC in Quebec) was the most commonly used first-line treatment for mCRPC at the time of this analysis (2012–2017), followed by ARATs, such as abiraterone/prednisone and enzalutamide (Figure 2). These data are consistent with other real-world studies from this period.<sup>25</sup> Nevertheless, in 2022, most patients with mCRPC were likely to receive ARAT in first-line. Our study shows that only approximately 50% of patients who receive a first-line LPT receive a second-line LPT, and only about one-third receive a third-line LPT. Given this finding, the choice of first-line therapy likely affects subsequent treatment patterns, quality of life, and survival outcomes associated with mCRPC. Future studies to assess both combination and sequential regimens are needed to address this question.

Our study revealed that there are substantial differences in primary and secondary outcomes among provinces in terms of second-line vs. third-line or later use of Ra-223. Though we do not identify a cause

for such differences, these data describe prescribing behaviors across Canada.

In Ontario, OS and other secondary outcomes are more favorable with the second-line use of Ra-223. In contrast, no statistically significant differences were found in survival outcomes between the use of Ra-223 in second-line, third-line, or later in British Columbia and Quebec. This inconsistency could be explained by the heterogeneity of funding criteria for LPTs across Canada.

In Quebec, Ra-223 is often prescribed in third-line or later, or for patients who are ineligible for docetaxel. In all provinces, Ra-223 use would intuitively be higher in patients deemed ineligible for chemotherapy due to performance status or comorbidities. Given that such patients would be anticipated to have a worse prognosis generally, this may be a source of unaccounted-for bias in our analyses. Survival outcomes did not favor second-line use of Ra-223 numerically, possibly because patients with comorbidities or those who are frail and unable to receive subsequent treatment are selected for second-line use of Ra-223.

In British Columbia, approximately 80% of patients who received Ra-223 did not receive further systemic LPT for mCRPC, and 97.6% had died by the end of the followup period, indicating that Ra-223 was often their final therapeutic option. This aligns with the eligibility criteria for Ra-223 in British Columbia, which at the time mandated that patients must have bone pain on assessment and have been considered for all other LPT options. In practice, case-by-case “exceptional” funding decisions were often made to use Ra-223 in an earlier line when requested, which may explain the lack of differences in outcome between second-line and third-line cohorts.

Since the time of the study, the eligibility criteria for Ra-223 funding in British Columbia has been updated to be more inclusive.<sup>26</sup> Lastly, in Ontario, the sequencing of Ra-223 is less restricted by funding, allowing physicians to make clinical decisions regarding Ra-223 placement in treatment sequencing, irrespective of factors that might affect funding in other provinces, although there are restrictions in the sequencing of other agents.<sup>26</sup>

No data exist that define how funding availability for cancer treatment may affect therapeutic sequencing. The Pan-Canadian Oncology Drug Review (pCODR) provides a clinical and pharmacoeconomic assessment of new drugs at the request of provincial cancer agencies, pharmaceutical companies, or other relevant stakeholders. Despite mechanisms to ensure timely, equitable recommendations based on clinical evidence and

cost-effectiveness, the adoption of pCODR recommendations is heterogeneous across the country.<sup>19,27</sup> Some provinces may decide against listing a new cancer drug for a variety of reasons or may adopt restrictive inclusion criteria. Accessibility can directly impact patient outcomes, given the disparities among the three provinces, British Columbia, Ontario, and Quebec, regarding Ra-223 use.

We found that patients who had not yet received Ra-223 at the time of analysis survived longer, as calculated from the index date. If an analysis were to be repeated after all patients in the cohort had died, this finding may or may not persist. Immortal time bias, significant selection bias, duration of response to initial lines of therapy, and other confounders may play a role in determining patient survival. Regardless of the sequence, patients who never received Ra-223 had a median OS from the time of second-line LPT initiation of 1–1.5 years across all provinces compared to <1 year for those who received Ra-223. Ra-223 is often offered to patients with reported pain or symptomatic disease; in some provinces, exclusively.

This is consistent with the inclusion criteria of the ALSYMPCA trial, where patients were required to have symptomatic disease with regular use of analgesic medication or treatment with EBRT for cancer-related bone pain within 12 weeks prior to randomization. The manifestation of pain may represent a higher burden of disease, as well as more aggressive biology compared with patients who respond to ARATs and remain asymptomatic throughout.

Because Ra-223 is not regularly used as first-line therapy in any province, many patients are not exposed to Ra-223, especially if the use of ARAT or another therapy is prolonged due to a strong patient response and such patients may have died before utilizing another therapy. In Ontario and British Columbia, use of docetaxel as first-line therapy occurred in more than 50% of patients who never received Ra-223, and in significantly fewer patients who did.

Lastly, we note that treatment patterns changed between 2012 and 2017 (data not shown). For example, Ra-223 was more frequently used in an earlier line from 2015 to 2017, while the frequency of patients receiving at least two LPTs remained consistent, suggesting that Ra-223 use increased over time. Thus, patients who were not previously candidates for second-line treatment may have become eligible for sequential therapy once Ra-223 was approved and were recorded in the cohort as they received Ra-223 as a later-line therapy. For patients in the early years of the

“With an OS benefit, a tolerable safety profile, and an ability to alleviate pain and SREs, Ra-223 is an important tool in mCRPC treatment.”

cohort, the majority could only have received Ra-223 in later lines of therapy due to the earlier approvals and funding of other mCRPC agents in Canada (e.g., notice of compliance from Health Canada was issued in 2005 for docetaxel, 2015 for abiraterone, 2013 for enzalutamide, and 2011 for cabazitaxel).

### Limitations

Our study is limited by several factors. We examined survival outcomes measured from the start of second-line LPT as an index date. With immortal time bias, participants who are diagnosed with mCRPC but only initiate treatment later may have a period of “immortal time” during which their outcomes cannot be measured because the exposure has not yet occurred, and which they must survive to receive treatment. We chose the index date to reduce immortal time bias and to ensure that only patients with sufficient data to assess sequencing would be included; however, there may still be some immortal time bias and other time-related biases.

Eligibility criteria for the index date may have affected cohort selection, in which age, comorbidities, and first-line LPT were only included for patients who have survived. This process can select for patients with relatively favorable outcomes and responsiveness to first-line treatments and exclude patients with aggressive disease.

Our results were also significantly affected by confounders innate to the multicenter, retrospective database, including selection bias, differences in cohort characteristics, access to treatments, and varying inclusion criteria for LPT use. Although survival differences were noted, potential confounders render it difficult to associate the use of a specific LPT with a given outcome.

We used multivariate time-varying Cox model to adjust for several potential prognostic factors, such as comorbidities, age, and use of bone health agents before the first-line LPT. It is possible that some patients, particularly those in Alberta, could have sought and received LPTs in other provinces or outside Canada (especially Ra-223) that we were not able to capture in the study. Clinical experience, however, is that this is

rare in all four provinces. Due to administrative restrictions, we were unable to merge the data from the four provinces, precluding formal statistical comparisons, as such differences across provinces may be due to chance.

Lastly, there were limitations in being able to capture the data for use of bone-modifying agents or pain medications, hospitalizations, or surgery for fractures accurately.

### CONCLUSIONS

In conclusion, Ra-223 is prescribed for mCRPC to varying degrees across Canada. Many patients never receive subsequent therapy after initial LPT for mCRPC, and identifying optimal treatment sequencing for these patients is important. With an OS benefit comparable to other LPTs, a tolerable safety profile, and an ability to alleviate pain and skeletal-related events, Ra-223 is an important cornerstone in the treatment of mCRPC.<sup>8</sup> Earlier initiation of Ra-223 may improve patient outcomes in select patients, and predictive biomarkers (e.g., measures of DNA repair defects) may guide sequencing of novel targeted therapies. With the emergence of more therapeutic options for prostate cancer, including olaparib and Lu-177, further studies are needed to identify optimal LPT sequencing and individualize treatment for patients with mCRPC, with tumor-specific genomic factors likely to inform personalized approaches in the future.

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