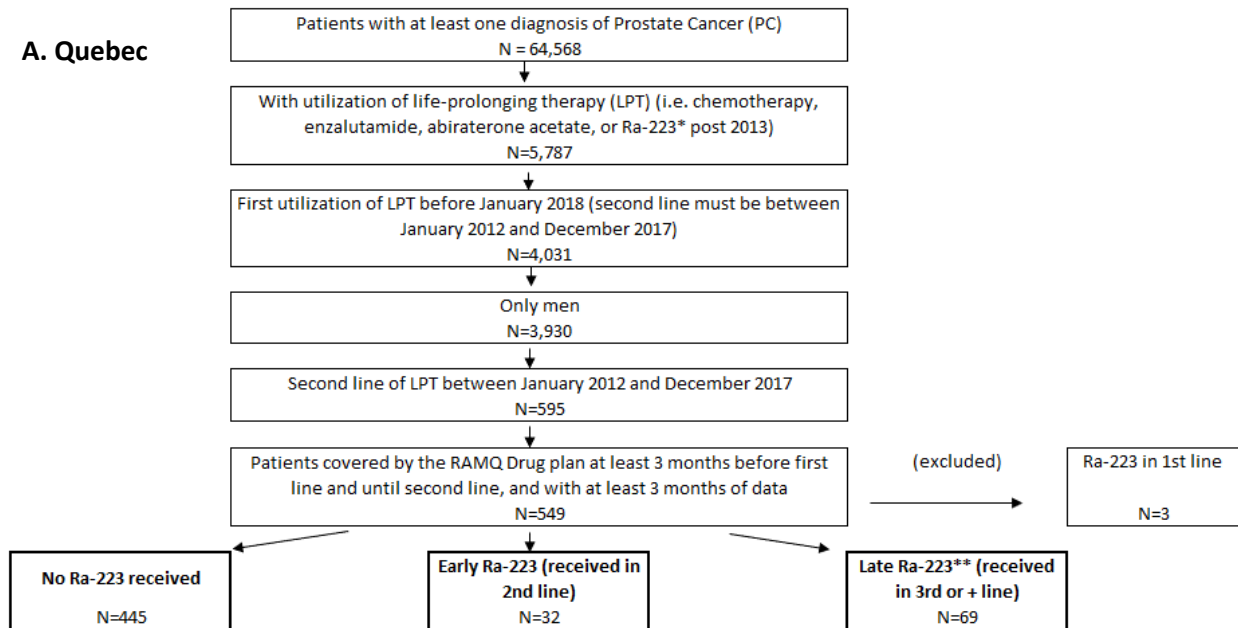


**APPENDIX**

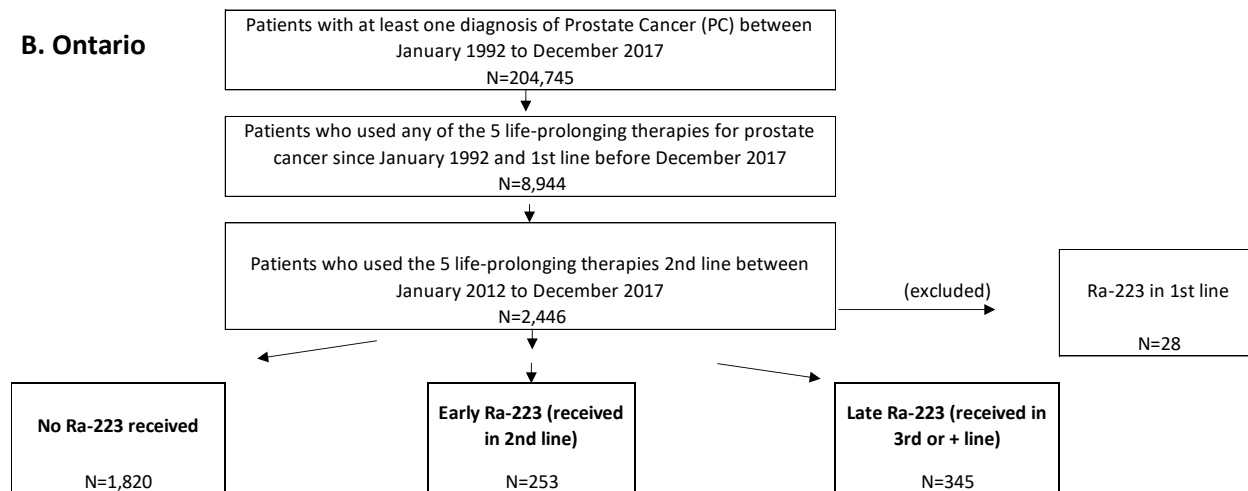
**Supplementary Figure 1.** Flowchart of patient selection per province.



\* Unlike other provinces, in QC, use of Ra-223 was identified by using billing codes used for the administration of Ra-223. To increase certainty about the use of the billing code to mean administration of Ra-223 over another reason for using that billing code, some rules were applied:

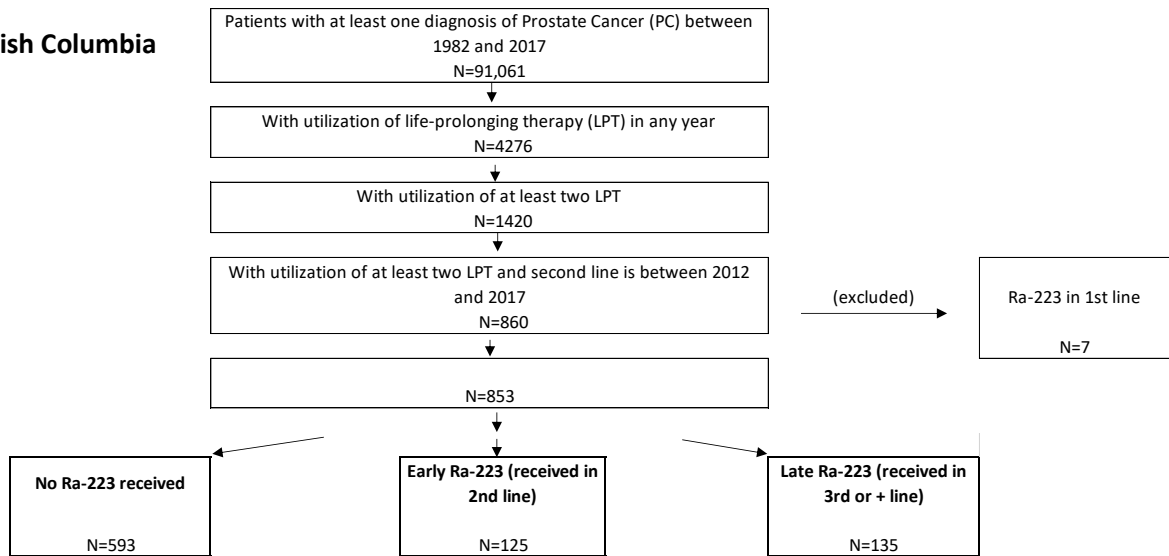
- Exclude patients with any thyroid cancer or hyperthyroidism diagnosis before the first procedural code (3 patients, no patient with any thyroid cancer or hyperthyroidism diagnosis after the first procedural code and not before);
- Only one code used within 4 weeks - 1 day (27 days);
- For patients with more than 1 codes: subsequent cycles were used within 28-35 days

\*\*Patients have to be covered until the Ra-223 by the RAMQ Drug Plan

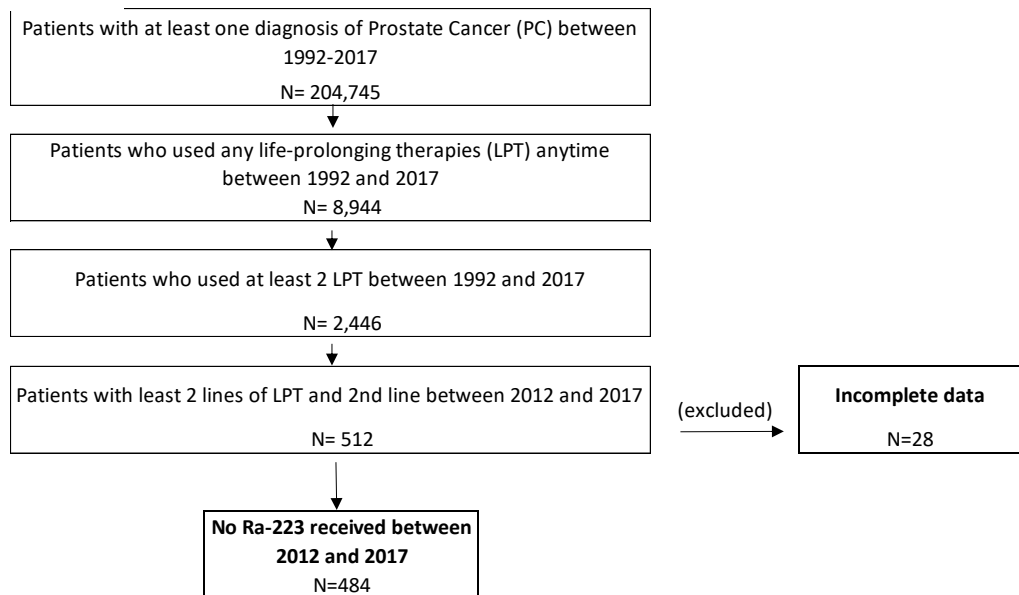


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**C. British Columbia**



**D. Alberta**



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<b>Supplementary Table 1. Baseline characteristics in the No Ra-223 cohort</b>					
<b>Patient characteristics: No Ra-223 cohort</b>					
Variable	<b>AB (n=484)</b>	<b>BC (n=593)</b>	<b>QC (n=445)</b>	<b>ON (n=1820)</b>	<b>p</b>
Age (years): mean (SD)	69.9 (9.2)	72.0 (9.1)	73.3 (8.1)	71.7 (8.8)	<0.001
No. of Ra-223 cycles used during study period: mean (SD)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
No. of lines of LPT used during study period: mean (SD)	2.7 (0.9)	2.2 (0.5)	2.3 (0.5)	2.5 (0.8)	<0.001
Use of bone health agents (within +/-90 days of first-line LPT): n (%)					<0.001
No	434 (89.7)		156 (35.1)	922 (50.7)	
Yes	50 (10.3)		289 (64.9)	898 (49.3)	
No. of lines of LPT used during study period					<0.001
Only 2 lines	248 (51.2)	468 (78.9)	331 (74.4)	1131 (62.1)	
3 lines	151 (31.2)	117 (19.7)	102 (22.9)	512 (28.1)	
4 lines	68 (14.1)	4-8*	11 (2.5)	136 (7.5)	
5 lines	12 (2.5)	1-5*	1 (0.2)	35-39*	
6+ lines	5 (1)	0 (0.0)	0 (0.0)	2-6*	
First-line LPT: n (%)					<0.001
Abiraterone acetate	165 (34.1)	176 (29.7)	147 (33.0)	552 (30.3)	
Docetaxel	249 (51.4)	284 (47.9)	260 (58.4) <sup>†</sup>	1025 (56.3)	
Enzalutamide	69 (14.3)	122 (20.6)	37 (8.3)	243 (13.4)	
Cabazitaxel	1 (0.2)	4-8*		0 (0.0)	
LPTs (irrespective of sequence): n (%)					<0.001

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Abiraterone acetate	420 (86.8)	482 (81.3)	373 (83.8)	1441 (79.2)	
Docetaxel	425 (87.8)	473 (79.8)	410 (92.1) <sup>†</sup>	1657 (91.0)	
Enzalutamide	262 (54.1)	287 (48.4)	138 (31.0)	893 (49.1)	
Cabazitaxel	138 (28.5)	36 (6.1)		291 (16.0)	
Gleason score at PC diagnosis: n (%)					0.134
6-7		29 (4.9)		123 (6.8)	
8-10		206 (34.7)		574 (31.5)	
Unknown		358 (60.4)		1123 (61.7)	
De novo metastatic disease (%)					<0.001
No	216 (44.6)	94 (15.9)		373 (20.5)	
Yes	246 (50.8)	176 (29.7)		532 (29.2)	
Unknown	22 (4.5)	323 (54.5)		915 (50.3)	
Days from initial ADT to initiation of first-line LPT: mean +/-SD		1573.9 (1452.3)	1206.7 (623.0)	835.2 (1351.7)	<0.001
Previous treatment with RP, brachytherapy, EBRT, or cryotherapy: n (%)					<0.001
No	227 (46.9)	315 (53.1)		1,124 (61.8)	
Yes	257 (53.1)	278 (46.9)		696 (38.2)	
Proportion of patients who were previously treated with RP, brachytherapy, EBRT, or cryotherapy: n (%)					<0.001
RP	68 (26.5)	83 (29.9)		429 (61.6)	
Brachytherapy	3 (1.2)	16 (5.8)		37 (5.3)	
EBRT	212 (82.4)	228 (82.0)		326 (46.8)	

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Cryotherapy	18 (7.0)			77 (11.1)	
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\*Due to low numbers and to maintain patient anonymity, only a range can be provided.

†In Quebec, docetaxel and cabazitaxel are grouped together as “chemotherapy” because specific hospital medications are not available in the database. The procedural codes used for physicians’ fees were used to identify these treatments (i.e. administration of chemotherapy). ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; LPT: life-prolonging therapy; RP: radical prostatectomy; SD: standard deviation.

<b>Supplementary Table 2. Baseline characteristics in the 2L Ra-223 cohort</b>				
<b>Patient Characteristics: 2L Ra-223 cohort</b>				
<b>Variables</b>	<b>BC (n=125)</b>	<b>QC (n=32)</b>	<b>ON (n=253)</b>	<b>p</b>
Age (years): mean (SD)	74.7 (8.02)	74.4 (9.0)	74.5 (9.3)	0.974
No. of Ra-223 cycles used during study period: mean (SD)	4.6 (1.8)	3.3 (1.9)	4.5 (1.7)	0.001
No. of lines of LPT used during study period: mean (SD)	2.2 (0.4)	2.3 (0.7)	2.7 (0.9)	<0.001
Use of bone health agents (within +/- 90 days of first-line LPT): n (%)				0.091
No		10 (31.2)	119 (47.0)	
Yes		22 (68.8)	134 (53.0)	
No. of lines of LPT used during study period: n (%)				<0.001
Only 2 lines	99 (79.2)	26 (81.2)	138 (54.5)	
3 lines	21-25*	4 (12.5)	64 (25.3)	
4 lines	1-5*	1 (3.1)	42 (16.6)	
5 lines	0 (0.0)	1 (3.1)	4-8*	
6+ lines	0 (0.0)	0 (0.0)	1-5*	
First-line of LPT: n (%)				0.004
Abiraterone acetate	54 (43.2)	19 (59.4)	129 (51.0)	
Docetaxel	10-14*	5 (15.6)†	42 (16.6)	
Enzalutamide	56 (44.8)	5 (15.6)	82 (32.4)	
Cabazitaxel	1-5*		0 (0.0)	0.001

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LPTs (irrespective of sequence): n (%)				
Abiraterone acetate	55 (44.0)	23 (71.9)	155 (61.3)	
Docetaxel	35-39*	11 (34.4) <sup>†</sup>	121 (47.8)	
Enzalutamide	56 (44.8)	6 (18.8)	106 (41.9)	
Cabazitaxel	0 (0.0)		22 (8.7)	
Gleason score at PC diagnosis: n (%)				0.719
6-7	7 (5.6)		26 (10.3%)	
8-10	49 (39.2)		82 (32.4%)	
Unknown	69 (55.2)		145 (57.3%)	
De novo metastatic disease: n (%)				0.727
No	24 (19.2)		64 (25.3)	
Yes	44 (35.2)		66 (26.1)	
Unknown	57 (45.6)		123 (48.6)	
Days from initial ADT to initiation of first-line LPT: mean +/-SD	1692.5 (1493.8)	1522.2 (609.3)	841.6 (1511.7)	<0.001
Previous treatment with RP, brachytherapy, EBRT, or cryotherapy: n (%)				<0.001
No	68 (54.4)		158 (62.5)	
Yes	57 (45.6)		95 (37.5)	
Proportion of patients with previous local treatment: n (%)				<0.001
RP	18 (31.6)		58 (61.1)	
Brachytherapy	1-5*		1-5*	
EBRT	46 (80.7)		44 (46.3)	
Cryotherapy			9 (9.5)	

\*Due to low numbers and to maintain patient anonymity, only a range can be provided.

<sup>†</sup>In Quebec, docetaxel and cabazitaxel are grouped together as “chemotherapy” because specific hospital medications are not available in the database. The procedural codes used for physicians’ fees were used to identify these treatments (i.e. administration of chemotherapy). ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; LPT: life-prolonging therapy; RP: radical prostatectomy; SD: standard deviation.

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<b>Supplementary Table 3. Baseline characteristics in 3<sup>rd</sup> line or later Ra-223 use cohort</b>				
<b>Patient Characteristics: 3L+ Ra223</b>				
<b>Variables</b>	<b>BC (n=135)</b>	<b>QC (n=69)</b>	<b>ON (n=345)</b>	<b>P</b>
Age (years): mean (SD)	70.3 (8.1)	71.0 (6.6)	69.8 (8.4)	0.95
No. of Ra-223 cycles used during study period: mean (SD)	4.5 (1.9)	3.6 (1.8)	4.1 (1.8)	0.003
No. of lines of LPT used during study period: mean (SD)	3.4 (0.6)	3.5 (0.7)	3.8 (0.9)	<0.001
Use of bone health agents (within +/- 90 days of first-line LPT): n (%)				0.006
No		23 (33.3)	178 (51.6)	
Yes		46 (66.7)	167 (48.4)	
No. of lines of LPT used during study period: n (%)				<0.001
Only 2 lines	0 (0.0)	0 (0.0)	0 (0.0)	
3 lines	89 (65.9)	42 (60.9)	151 (43.8)	
4 lines	39 (28.9)	22 (31.9)	128 (37.1)	
5 lines	4-8*	4 (5.8)	51 (14.8)	
6+ lines	1-5*	1 (1.4)	15 (4.3)	
First line of life-prolonging therapy: n (%)				<0.001
Abiraterone acetate	52 (38.5)	22 (31.9)	133 (38.6)	
Docetaxel	37 (27.4)	42 (60.9) <sup>†</sup>	165 (47.8)	
Enzalutamide	43 (31.9)	5 (7.2)	47 (13.6)	
Cabazitaxel	1-8*		0 (0.0)	
Combo LPT	1-5*	0 (0.0)		
LPTs (irrespective of sequence): n (%)				<0.001
Abiraterone acetate	106 (78.5)	54 (78.3)	272 (78.8)	
Docetaxel	105 (77.8)	68 (98.6) <sup>†</sup>	310 (89.9)	
Enzalutamide	90 (66.7)	21 (30.4)	220 (63.8)	
Cabazitaxel	4 (3.0)		76 (22.0)	
Gleason score at PC diagnosis: n (%)				0.028
6-7	14 (10.4)		27 (7.8)	
8-10	63 (46.7)		129 (37.4)	
Unknown	58 (43.0)		189 (54.8)	
De novo metastatic disease: n (%)				0.176
0	29 (21.5)		78 (22.6)	

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1	56 (41.5)		113 (32.8)	
Unknown	50 (37.0)		154 (44.6)	
Days from initial ADT to initiation of first line of life-prolonging therapy: mean +/-SD	1380 (1357.4)	1310.4 (592.6)	822.7 (1368.3)	<0.001
Previous treatment with RP, brachytherapy, EBRT, or cryotherapy: n (%)				<0.001
No	71 (52.6)		204 (59.1)	
Yes	64 (47.4)		141 (40.9)	
Proportion of patients who were previously treated with local therapy: n (%)				<0.001
RP	28 (43.8)		99 (70.2)	
Brachytherapy	1-5*		1-5*	
EBRT	47 (73.4)		68 (48.2)	
Cryotherapy			10 (7.1)	

\*Due to low numbers and to maintain patient anonymity, only a range can be provided.

†In Quebec, docetaxel and cabazitaxel are grouped together as “chemotherapy” because specific hospital medications are not available in the database. The procedural codes used for physicians’ fees were used to identify these treatments (i.e. administration of chemotherapy). ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; LPT: life-prolonging therapy; RP: radical prostatectomy; SD: standard deviation

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<b>Supplementary Table 4. Treatment sequences</b>						
	<b>Second-line Ra-223</b>			<b>Third-line Ra-223 or later</b>		
	<b>ON (N=253)</b>	<b>BC (N=125)</b>	<b>QC (N=32)</b>	<b>ON (N=345)</b>	<b>BC (N=135)</b>	<b>QC (N=69)</b>
<b>Number of lines of LPT: n (%)</b>						
2 lines	138 (54.5)	99 (79.2)	26 (81.2)	0 (0.0)	0 (0.0)	0 (0.0)
3 lines	64 (25.3)	23 (18.4)	4 (12.5)	151 (43.8)	89 (65.9)	42 (60.9)
4 lines	42 (16.6)	3 (2.4)	1 (3.1)	128 (37.1)	39 (28.9)	22 (31.9)
5 lines	6 (2.4)	0 (0.0)	1 (3.1)	51 (14.8)	6 (4.4)	4 (5.8)
6 lines	3 (1.2)	0 (0.0)	0 (0.0)	15 (4.3)	3 (2.2)	1 (1.4)
<b>First-line LPT: n (%)</b>						
Abiraterone acetate	129 (51.0)	54 (43.2)	19 (59.4)	133 (38.6)	52 (38.5)	22 (31.9)
Enzalutamide	82 (32.4)	56 (44.8)	5 (15.6)	47 (13.6)	43 (31.9)	5 (7.2)
Docetaxel	42 (16.6)	12 (9.6)	5 (15.6)	165 (47.8)	37 (27.4)	42 (60.9)
Cabazitaxel	0 (0.0)	3 (2.4)		0 (0.0)	3 (2.2)	
<b>LPT received irrespective of sequence: n (%)</b>						
Abiraterone acetate	155 (61.3)	55 (44.0)	23 (71.9)	272 (78.8)	106 (78.5)	54 (78.3)

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Enzalutamide	106 (41.9)	56 (44.8)	6 (18.8)	220 (63.8)	90 (66.7)	21 (30.4)
Docetaxel	121 (47.8)	37 (29.6)	11 (34.4)*	310 (89.9)	105 (77.8)	68 (98.6)*
Cabazitaxel	22 (8.7)	0 (0.0)	--	76 (22.0)	4 (3.0)	--

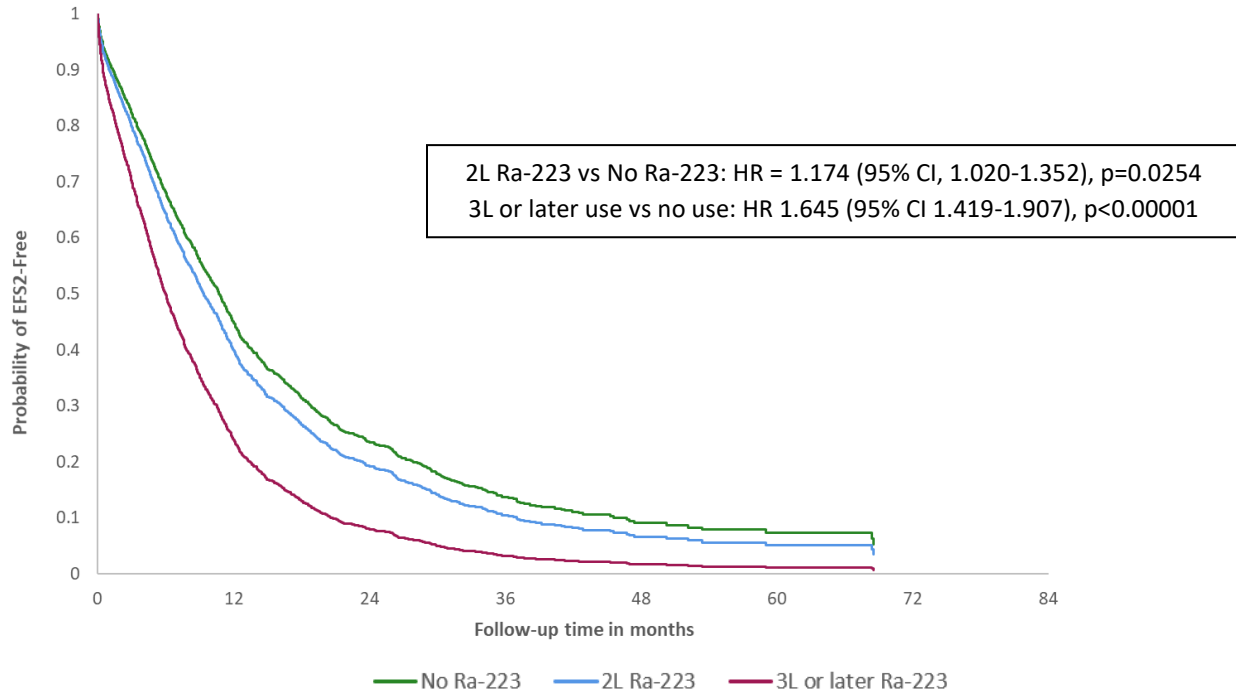
\*In Quebec, chemotherapy received cannot be differentiated by type of chemotherapy, so numbers include all chemotherapy regimens, not solely docetaxel. LPT: life-prolonging therapy.

<b>Supplementary Table 5. Event-free survival</b>							
	<b>ON</b>		<b>BC</b>		<b>QC</b>		<b>AB</b>
	<b>Second-line Ra-223, N=253 N (%)</b>	<b>Second-line Ra-223, N=345 N (%)</b>	<b>Second-line Ra-223, N=125 N (%)</b>	<b>Second-line Ra-223, N=135 N (%)</b>	<b>Second-line Ra-223, N=32 N (%)</b>	<b>Second-line Ra-223, N=69 N (%)</b>	<b>No Ra-223 (all patients), N=484</b>
Reached EFS	226 (89.3)	324 (93.9)	122 (97.6)	129 (95.6)	32 (100)	61 (88.4)	445 (91.9%)
Death	175 (77.4%)	130 (40.1%)	121 (99.2%)	83 (64.3%)	30 (93.8)	34 (55.7)	360 (74.4%)
Started Fourth-line LPT	51 (22.6%)	194 (59.9%)	1 (0.8%)	46 (35.7%)	2 (6.2)	27 (44.3)	85 (17.6%)

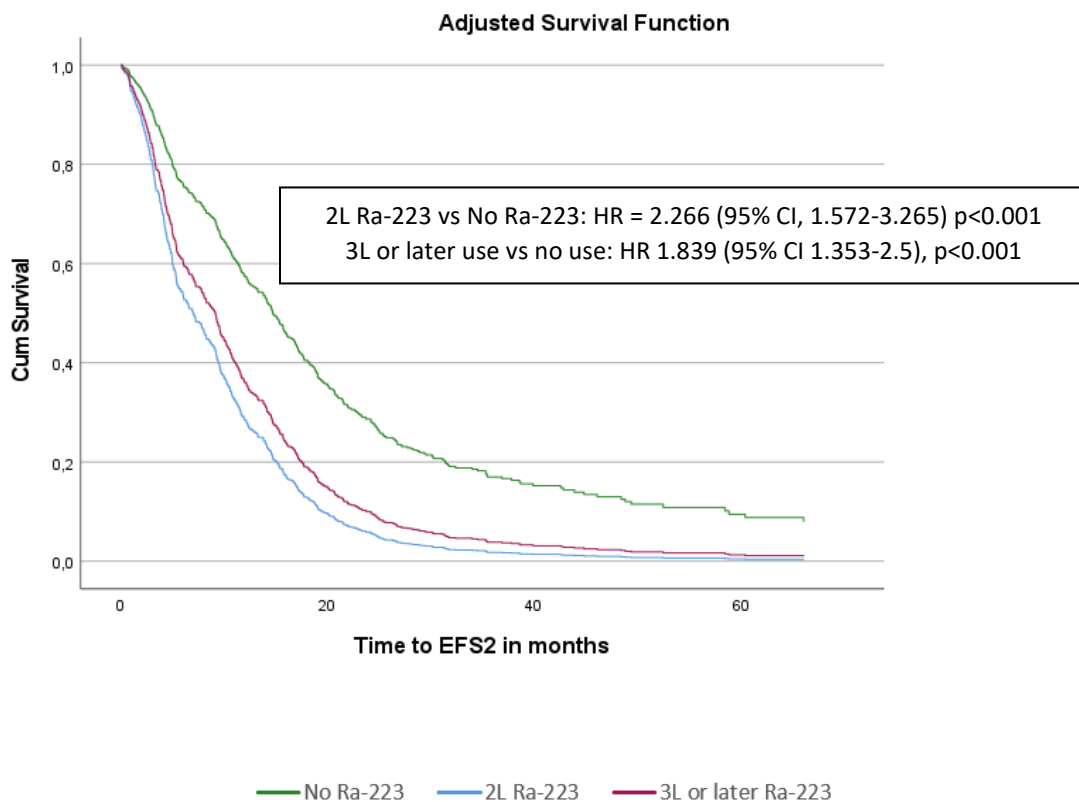
EFS: event-free survival; LPT: life-prolonging therapy

**Supplementary Figure 3. Adjusted survival curves of EFS-2, adjusted for all variables in Cox model analysis**

**a. Adjusted EFS-2 for Ontario**

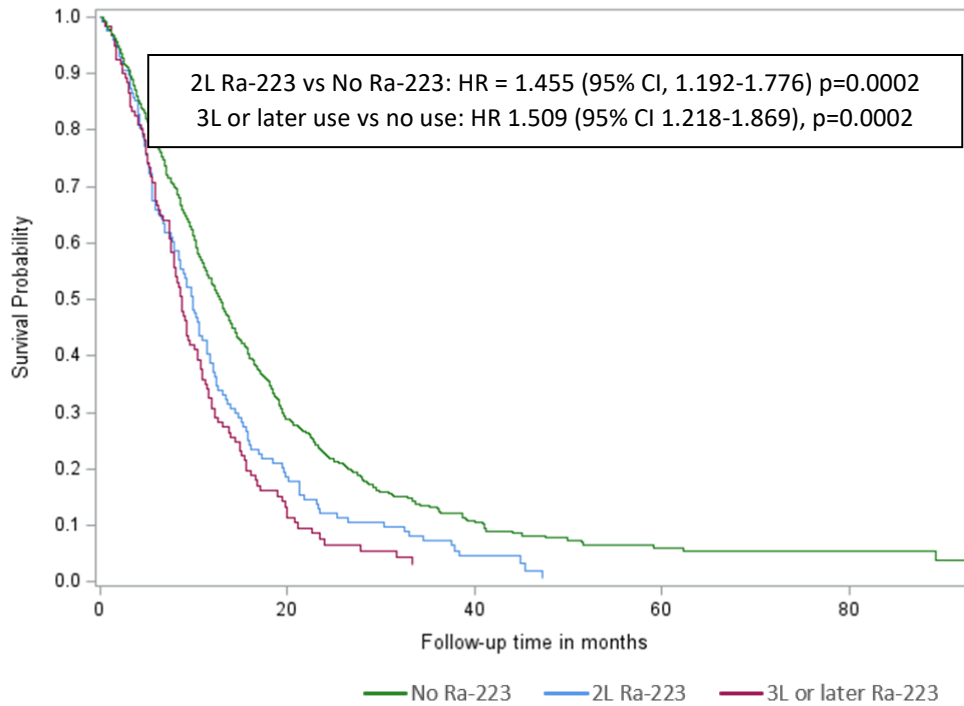


**b. Adjusted EFS-2 for Quebec**

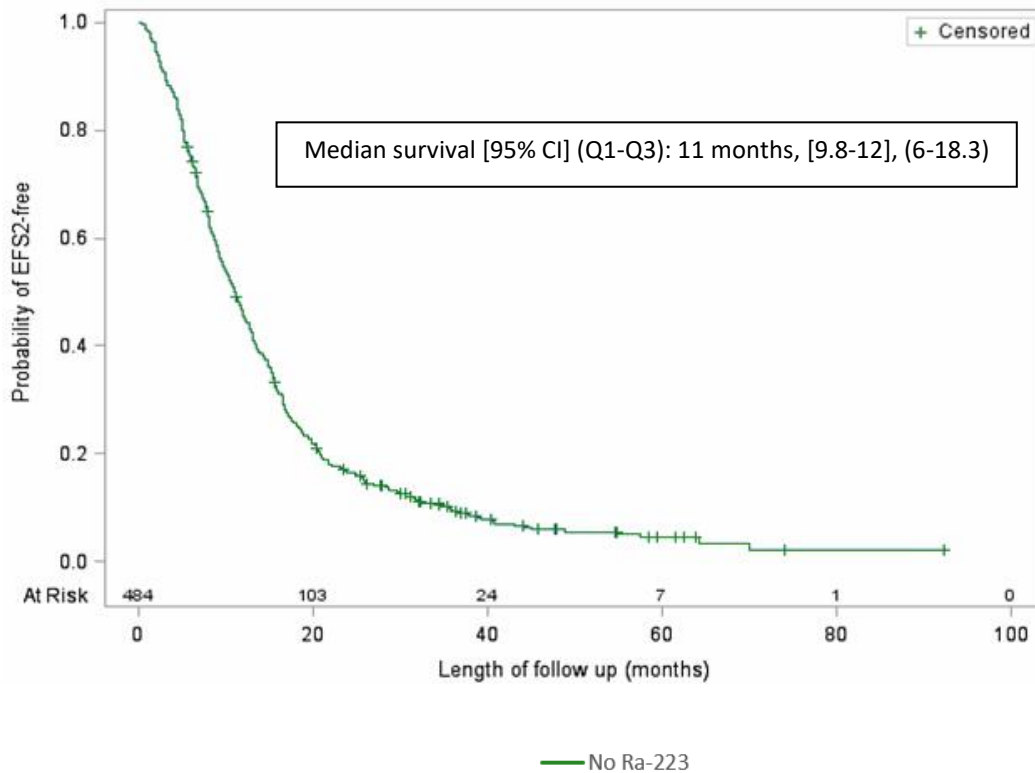


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**c. Adjusted EFS-2 for British Columbia**



**d. EFS-2 for Alberta**



**HEALTHCARE RESOURCE UTILIZATION (EBRT, HOSPITALIZATION, ER VISITS)**

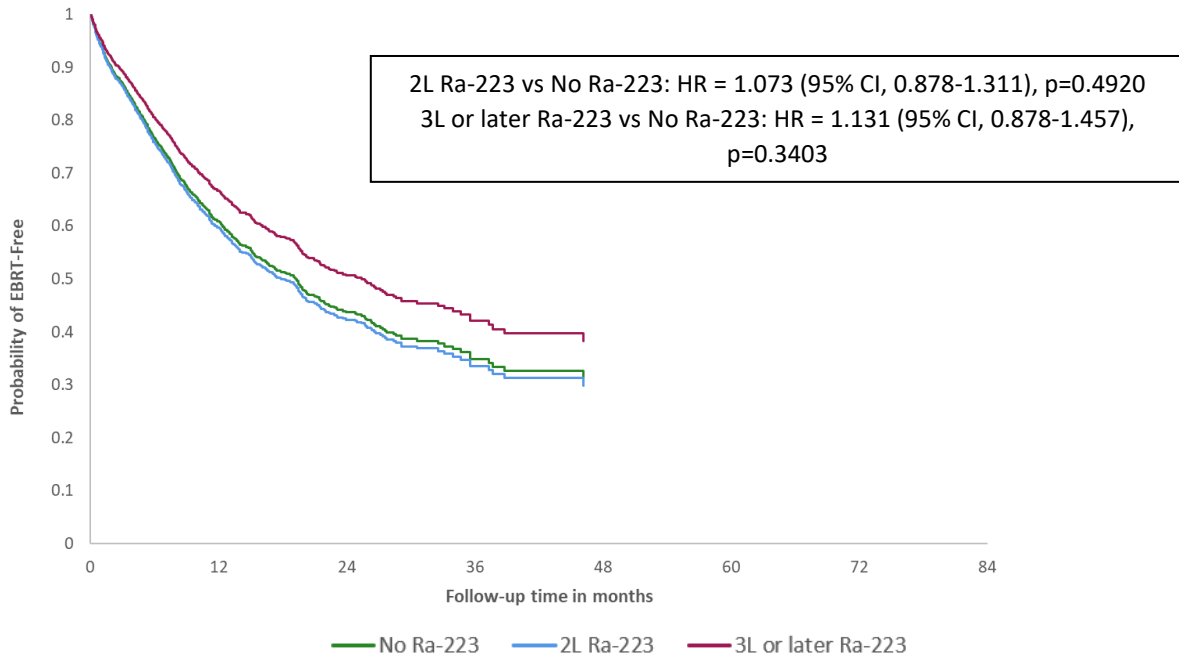
<b>Supplementary Table 6: Use of EBRT (Ontario, British Columbia, and Alberta only)</b>							
	<b>Ontario</b>			<b>British Columbia</b>			<b>Alberta</b>
	<b>No Ra-223 N=1820</b>	<b>2L Ra-223 N=253</b>	<b>3L+ Ra-223 N=345</b>	<b>No Ra-223 N=593</b>	<b>2L Ra-223 N=125</b>	<b>3L+ Ra-223 N=125</b>	<b>No Ra-223 N=484</b>
Received EBRT following initiation of second-line treatment: n (%)	766 (42.1%)	110 (43.5%)	211 (61.2%)	325 (54.8%)	69 (55.2%)	115 (85.2%)	289 (59.7%)
Number of EBRT treatments after second-line LPT: n (%)							
0	1,054 (57.9%)	143 (56.5%)	134 (38.8%)	268 (45.2%)	56 (44.8%)	20 (14.8%)	195 (40.3 %)
1	461 (25.3%)	71 (28.1%)	103 (29.9%)	171 (28.8%)	35 (28.0%)	37 (27.4%)	97 (20 %)
2	208 (11.4%)	28 (11.1%)	60 (17.4%)	86 (14.5%)	23 (18.4%)	37 (27.4%)	77 (15.9 %)
3+	97 (5.3%)	11 (4.3%)	48 (13.9%)	68 (11.5%)	11 (8.8%)	30 (22.2%)	115 (23.8 %)
Median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	1 (0 - 2)	1 (0 - 2)	2 (1 - 2)	1 (0 - 2)

EBRT: external beam radiation therapy; IQR: interquartile range; LPT: life=prolonging therapy.

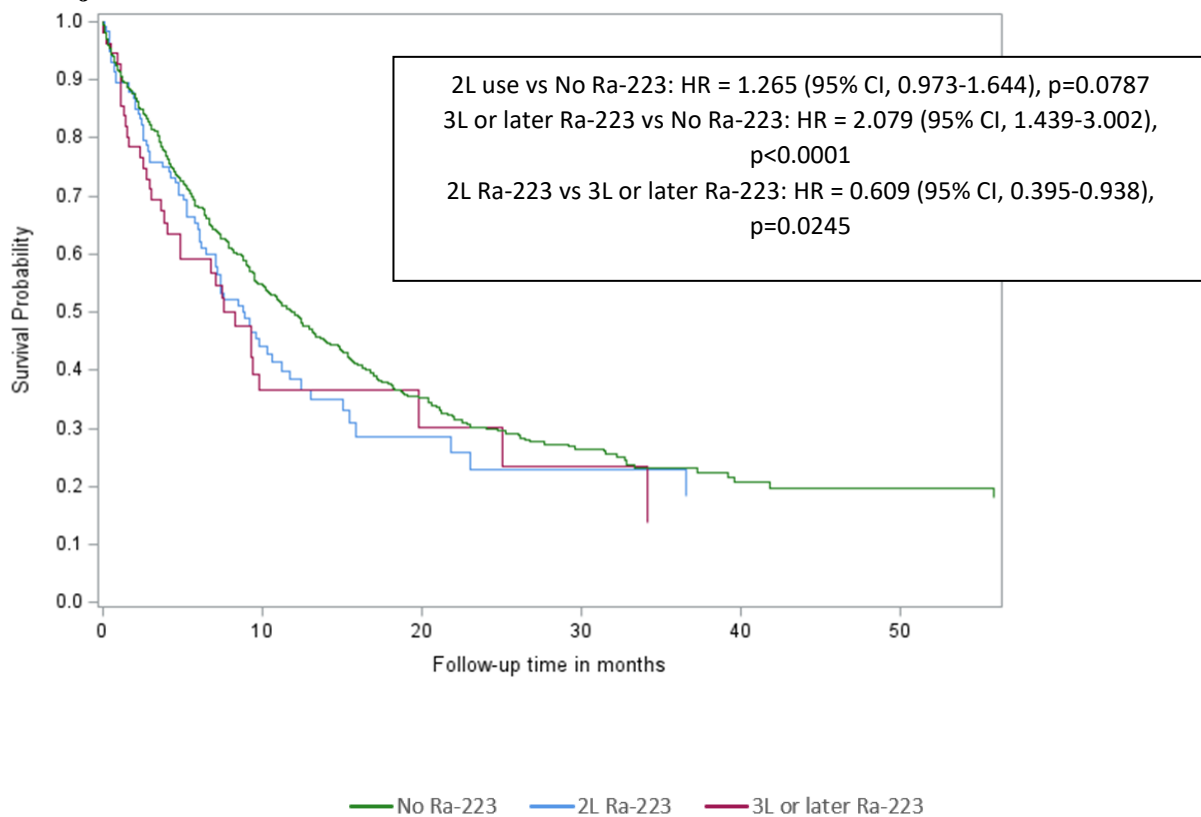
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**Supplementary Figure 4.** Survival curves for patients treated with palliative EBRT, adjusted for all variables in Cox model analysis

**a. Adjusted time to EBRT for Ontario**

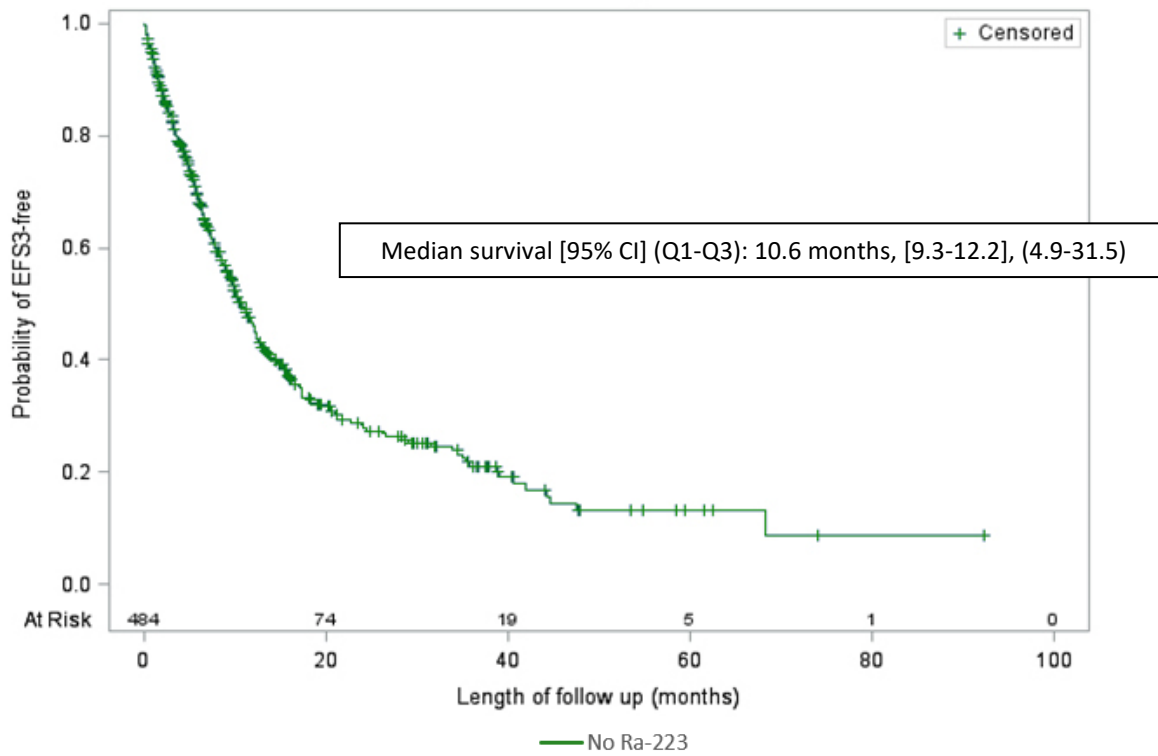


**b. Adjusted time to EBRT for British Columbia**

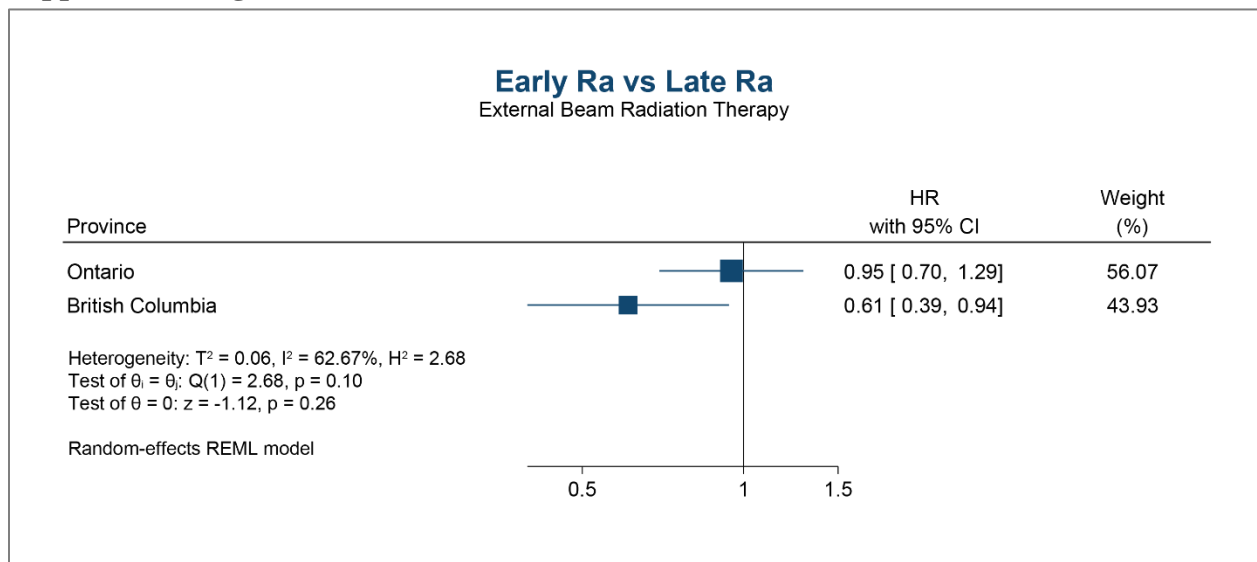


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**c. Time to EBRT for Alberta**



**Supplemental Figure 5.** Use of EBRT in Ontario and British Columbia

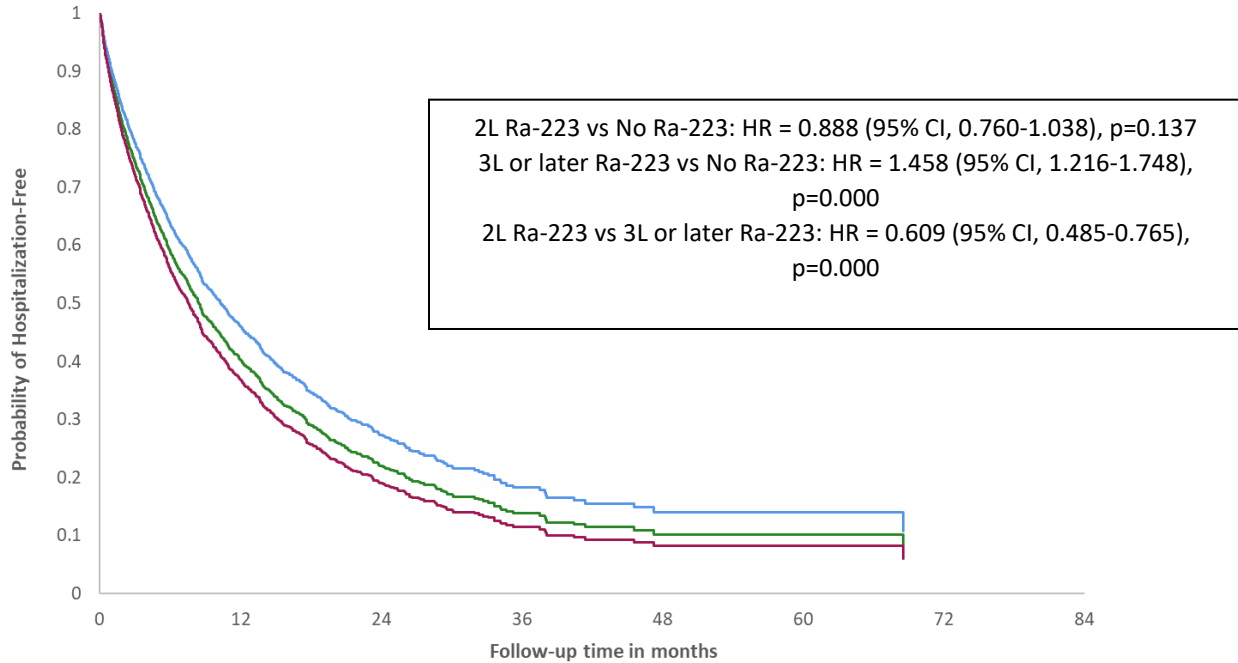


<b>Supplementary Table 7. Hospitalizations in Ontario and Quebec only</b>								
	<b>Ontario</b>				<b>Quebec</b>			
	<b>No Ra-223 (N=1820)</b>	<b>2L Ra-223 (N=253)</b>	<b>3L+ Ra-223 (N=345)</b>	<b>Total (N=2418)</b>	<b>No Ra-223 (N=445)</b>	<b>2L Ra-223 (N=32)</b>	<b>3L+ Ra-223 (N=69)</b>	<b>Total (N=546)</b>
Hospitalization after the initiation of second-line LPT: n (%)	1,450 (79.7%)	180 (71.1%)	277 (80.3%)	1,907 (78.9%)	374 (84.0)	26 (81.2)	56 (81.2)	456 (83.5)
Number of hospitalizations after second-line LPT: n (%)								
0	370 (20.3%)	73 (28.9%)	68 (19.7%)	511 (21.1%)	71 (16.0)	6 (18.8)	13 (18.8)	90 (16.5)
1	656 (36.0%)	90 (35.6%)	95 (27.5%)	841 (34.8%)	120 (27.0)	8 (25.0)	13 (18.8)	141 (25.8)
2	392 (21.5%)	41 (16.2%)	82 (23.8%)	515 (21.3%)	91 (20.4)	7 (21.9)	10 (14.5)	108 (19.8)
3	217 (11.9%)	23 (9.1%)	38 (11.0%)	278 (11.5%)	74 (16.6)	6 (18.8)	12 (17.4)	92 (16.8)
4	86 (4.7%)	11 (4.3%)	33 (9.6%)	130 (5.4%)	30 (6.7)	1 (3.1)	2 (2.9)	33 (6.0)
5+	99 (5.4%)	15 (5.9%)	29 (8.4%)	143 (5.9%)	59 (13.3)	4 (12.5)	19 (27.5)	82 (15.0)
Median (IQR)	176 (57-399)	229 (114-428)	423 (199-681)	210 (72-456)	2.0 (1.0 - 3.0)	2.0 (1.0 - 3.0)	2.0 (1.0 - 5.0)	2.0 (1.0 - 3.0)

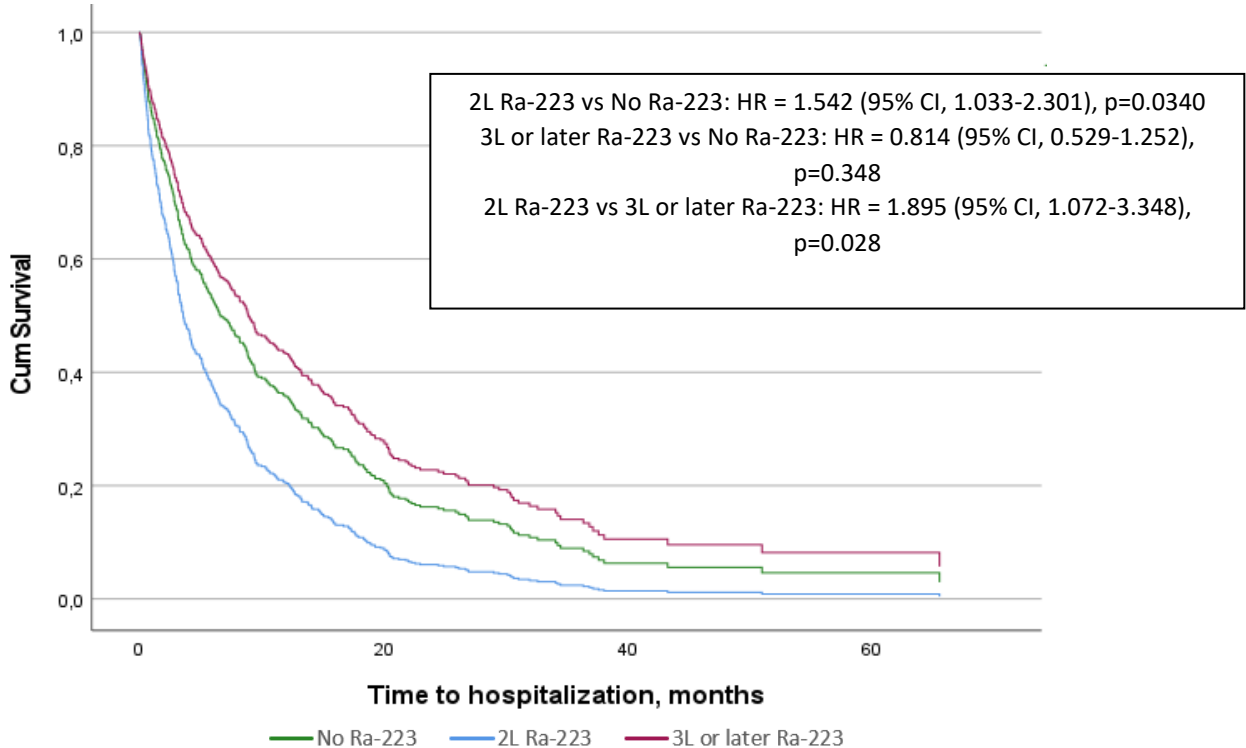
IQR: interquartile range; LPT: life-prolonging therapy

**Supplementary Figure 6. Adjusted survival curves of hospitalizations, adjusted for all variables in Cox model analysis**

**a. Adjusted time to hospitalizations, Ontario**



**b. Adjusted time to first hospitalization**



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<b>Supplementary Table 8. Emergency room visits in Ontario and Quebec only</b>					
<b>Ontario</b>					
		<b>No Use of Ra-223 N=1820</b>	<b>2L Use of Ra-223 N=253</b>	<b>3L+ Use of Ra-223 N=345</b>	<b>Total N=2418</b>
ED visits after the initiation of second-line LPT: n (%)		1,585 (87.1%)	220 (87.0%)	315 (91.3%)	2,120 (87.7%)
Number of hospitalizations after second-line LPT: n (%)	0	235 (12.9%)	33 (13.0%)	30 (8.7%)	298 (12.3%)
	1	394 (21.6%)	59 (23.3%)	61 (17.7%)	514 (21.3%)
	2	299 (16.4%)	42 (16.6%)	47 (13.6%)	388 (16.0%)
	3	263 (14.5%)	41 (16.2%)	48 (13.9%)	352 (14.6%)
	4	169 (9.3%)	24 (9.5%)	34 (9.9%)	227 (9.4%)
	5	143 (7.9%)	15 (5.9%)	27 (7.8%)	185 (7.7%)
	6+	317 (17.4%)	39 (15.4%)	98 (28.4%)	454 (18.8%)
	Median (IQR)	107 (31-259)	140 (59-276)	234 (66-520)	122 (36-291)
<b>Quebec</b>					
		<b>No Use of Ra-223 N=445</b>	<b>2L Use of Ra-223 N=32</b>	<b>3L+ Use of Ra-223 N=69</b>	<b>Total N=546</b>
ED visits after the initiation of second-line LPT, n (%)		409 (91.9)	30 (93.8)	64 (92.8)	503 (92.1)

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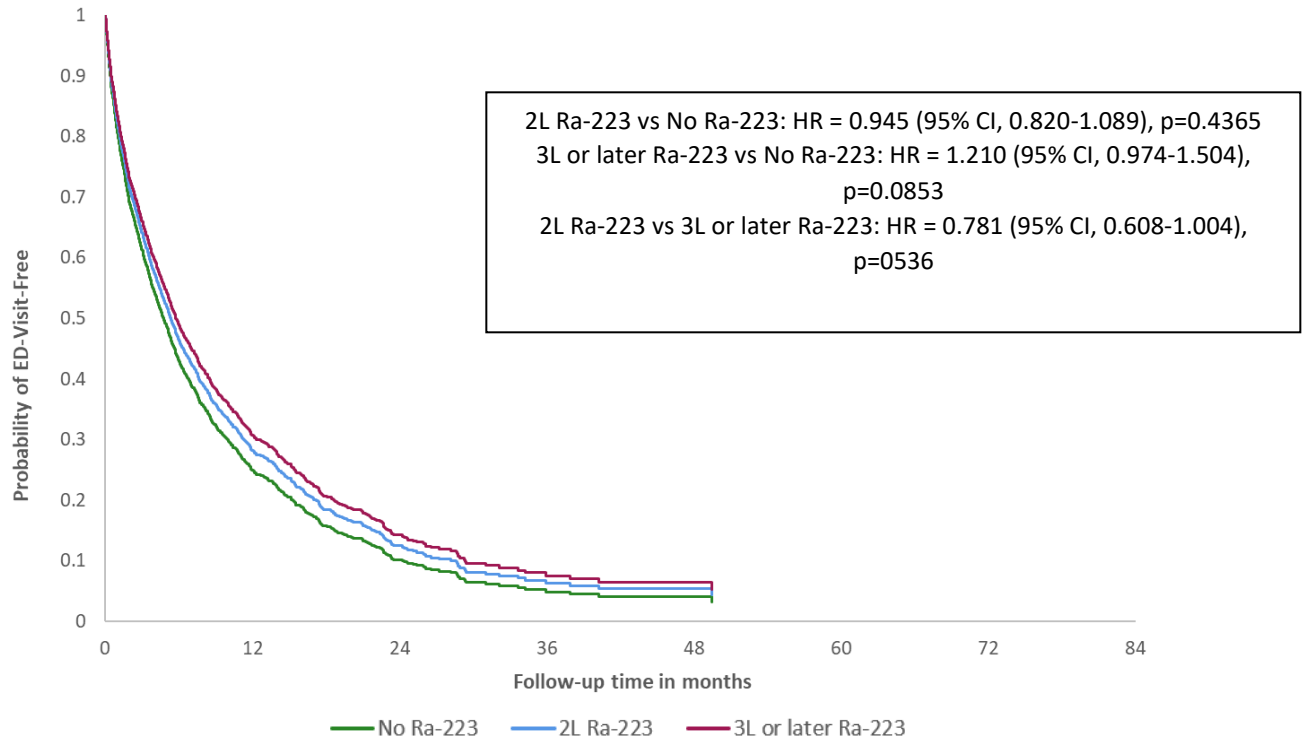
Number of hospitalizations after second-line LPT: n (%)	0	35 (7.9)	2 (6.2)	5 (7.2)	42 (7.7)
	1-3	55 (12.4)	3 (9.4)	3 (4.3)	61 (11.2)
	4-6	161 (36.2)	12 (37.5)	19 (27.5)	192 (35.2)
	7-9	99 (22.2)	4 (12.5)	12 (17.4)	115 (21.1)
	10-12	43 (9.7)	5 (15.6)	17 (24.6)	65 (11.9)
	13-15	17 (3.8)	2 (6.2)	2 (2.9)	21 (3.8)
	16+	35 (7.9)	4 (12.5)	11 (15.9)	50 (9.2)
	Median (IQR)	4.0 (2.0 - 7.0)	4.0 (2.0 - 8.0)	6.0 (3.0 - 10.0)	4.0 (2.0 - 7.2)

ED: emergency department; IQR: interquartile range; LPT: life-prolonging therapy.

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**Supplementary Figure 7.** Survival curves for ED visits, adjusted for all variables in Cox model analysis

**a. Ontario**



**b. Quebec**

