Comparative Safety and Effectiveness of Bevacizumab Biosimilars to Originator for the Treatment of Metastatic Colorectal Cancer

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Abstract

Background: Ontario has publicly funded biosimilar bevacizumab for first-line metastatic colorectal cancer (mCRC) since 2019. Clinical trials demonstrate comparable efficacy and safety of bevacizumab biosimilars to originator bevacizumab. The objective of this study was to assess real-world safety and effectiveness of the implementation of bevacizumab biosimilars compared with originator bevacizumab in patients with mCRC. **Methods:** This was a population-based, retrospective study comparing Ontario patients starting treatment with bevacizumab biosimilars between August 12, 2019, and March 31, 2021, and starting treatment with originator bevacizumab between July 2, 2008, and August 11, 2019. Safety outcomes included death within 30 days of the last dose received, any hospitalization, direct hospitalization, and hospitalization resulting from bevacizumab-related toxicity, chemotherapy-related toxicity, and febrile neutropenia. Event rates were assessed using negative binomial and logistic regression. The effectiveness outcome was overall survival, calculated using Kaplan-Meier and Cox proportional hazards regression. A subgroup analysis compared safety and effectiveness outcomes between patients on bevacizumab biosimilar products and matched comparators. **Results:** We identified 8,996 patients who initiated first-line treatment of bevacizumab for mCRC. Accounting for duration of follow-up, no significant differences were observed in the rate of hospitalization between treatment groups. No differences in overall survival (log-rank $P>.05$) or hazard ratios (propensity score–matched hazard ratio, 1.03; 95% CI, 0.92–1.16) were observed in the crude and propensity score–matched cohorts. Subgroup analysis demonstrated similar safety and effectiveness patterns. **Conclusions:** The demonstrated similarity in safety and effectiveness between bevacizumab biosimilars and originator bevacizumab provides further support for the use of and confidence in biosimilar products.

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Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in Canada, with late-stage CRC (stage III/IV) accounting for almost half of new diagnoses.[1] Bevacizumab is the standard of care for first-line treatment of patients with metastatic CRC (mCRC).[2–6] First-line bevacizumab with chemotherapy was universally funded in Ontario in 2008. Since 2008, Ontario has updated its universal funding policy for bevacizumab regimens to include administration of bevacizumab plus capecitabine for first-line treatment of mCRC.[7] A 2021 real-world cost-effectiveness analysis suggested that bevacizumab could not be considered cost-effective at its list price in Canada. Furthermore, the large number of patients with mCRC requiring treatment results in considerable budget impact.[8] The introduction of bevacizumab biosimilars provides an opportunity for cost savings for the treatment of mCRC. Although biosimilars share similarities with generics, there is a significant distinction in that biosimilars are not exact copies of their reference originator biologic product due to complex molecular structure.[9] The earliest bevacizumab biosimilars approved by Health Canada for treatment of patients with mCRC were MVASI (Amgen) and Zirabev (Pfizer).[10,11] In Ontario, MVASI has been publicly funded since August 12, 2019,[12] and Zirabev has been publicly funded since October 7, 2019 (organizational communication; Cancer Care Ontario Provincial Drug Reimbursement Programs, "Funding announcement for biosimilars," August 8, 2019). Ontario's bevacizumab biosimilar policy requires all new patients receiving bevacizumab for mCRC to start on a biosimilar.

Bevacizumab biosimilar was first compared with originator bevacizumab in the MAPLE randomized controlled trial (RCT) of patients with non–small cell lung cancer (NSCLC). Similarly, bevacizumab biosimilar was compared with originator bevacizumab in the B7391003 RCT of patients with NSCLC.[13–15] Both trials compared efficacy, safety, and immunogenicity between bevacizumab biosimilar and originator bevacizumab, demonstrating no statistically or clinically meaningful difference in the primary endpoint of objective response rate, in incidence and severity of adverse events, or immunogenicity.[13–15] Trials have also been conducted demonstrating comparable efficacy, safety, and immunogenicity of bevacizumab biosimilars to originator bevacizumab for treatment of patients with mCRC, though these trials have used alternate bevacizumab biosimilar products than the MAPLE and B7391003 trials.[16,17]

Although no clinically meaningful differences have been demonstrated between bevacizumab biosimilars and originator bevacizumab in terms of safety and efficacy in RCTs,[13–17] challenges remain with clinical uptake. One recent study demonstrated that biosimilar bevacizumab uptake in the United States was only 36%.[18] Additionally, a report from March 2023 demonstrated that biosimilar uptake in the United States has remained

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low (only ~15%) among people with employer-sponsored insurance despite potential cost savings.[19] Real-world evidence (RWE) is a key enabler for successful implementation of biosimilars, providing payers, patients, and clinicians with direct insights from general practice to assess clinical impact and guide future policy approaches. RWE may improve patient and health care provider confidence in biosimilars and provide additional evidence with which to assess the implementation of bevacizumab biosimilars and shape policies around their use and funding. Thus, the purpose of this study was to assess real-world safety and effectiveness of bevacizumab biosimilars compared with originator bevacizumab in patients with mCRC.

Methods

Study Design and Population

A population-based retrospective cohort study was conducted assessing comparative safety and effectiveness of bevacizumab biosimilars in Ontario, Canada, using administrative databases at Ontario Health (Cancer Care Ontario) and ICES with propensity score matching (PSM) methods. Ontario provides universal public coverage for intravenous oncology drugs administered in outpatient hospital clinics subject to clinical eligibility criteria.

This study included patients aged ≥18 years receiving bevacizumab for first-line treatment of mCRC between July 2, 2008, and March 31, 2021, after diagnosis of CRC (ICD-O-3 C18–20).[20,21] During the time period involved in our cohort, the broader treatment landscape for mCRC did not change; notably, TAS-102 and regorafenib were not recommended for funding by Canada's health technology assessment agency yet and therefore were not publicly available, and funding for pembrolizumab for MSI-H and encorafenib for *BRAF* mutation did not start until after the end of our cohort. A demonstrated balance in baseline treatment between the treatment groups after PSM suggests that a change in treatment availability and recommendation is not a confounder in our study, allowing the use of historical versus contemporaneous comparators.

The treatment group included patients starting treatment with bevacizumab biosimilars between the start of funding of bevacizumab biosimilar through the New Drug Funding Program (NDFP) in Ontario on August 12, 2019, and March 31, 2021.[12] The historical comparator group included patients starting treatment with originator bevacizumab between July 2, 2008, and August 11, 2019.[7] The index date was the first record of a bevacizumab biosimilar or originator bevacizumab for first-line treatment of mCRC in treatment and comparator groups, respectively. Patients were followed up until March 31, 2022 (Figure 1).

Patients were excluded if they had no record of CRC diagnosis in the Ontario Cancer Registry (OCR) prior to/within 60 days of index treatment, a bevacizumab claim without concurrent first-line chemotherapy within 3-months of claim, a bevacizumab claim prior to funding approval of biosimilar or originator bevacizumab, no unique patient identifier for data linkage or missing regional health authority, or a record of bevacizumab for first-line treatment of mCRC after a recorded death date.

Data Sources

Patients receiving bevacizumab were identified through NDFP, which reimburses Ontario hospitals and cancer centers for the cost of many injectable cancer drugs administered.[22] CRC diagnosis was identified from the OCR. Vital status and death dates were identified from the Registered Persons Database. Baseline demographic and clinical characteristics and health care utilization records were identified using the OCR, Ontario Drug Benefit outpatient pharmacy claims database, cancer Activity Level Reporting systemic therapy and radiation databases, and the Canadian Institute of Health Information Discharge Abstract database (CIHI-DAD) for hospital admissions. Datasets were linked using unique patient identifiers and analyzed at ICES. ICES is a prescribed entity under Ontario's privacy legislation and is thus allowed to conduct analyses using private health data aimed at managing and evaluating the health system. Strict policies and procedures on access to and use of these data are approved by the Information and Privacy Commissioner of Ontario.[23] This analysis was approved by Sunnybrook Research Institute Research Ethics Board.

Outcomes

The primary safety outcome was death within 30 days of last dose received for mCRC. Secondary safety outcomes included any hospitalization, direct hospitalization, bevacizumab-related toxicity hospitalization, chemotherapy-related toxicity hospitalization, and febrile neutropenia–related hospitalization captured from CIHI-DAD during or within 30 days of the last dose received for mCRC. Direct hospitalization is defined as hospital admission without having first received care in an emergency department. The outcome of chemotherapy-related hospitalization was included given patients' receipt of combination, or backbone, chemotherapy (ie, oxaliplatin or irinotecan) with bevacizumab and the desire to explore safety events related to receipt of chemotherapy. The accrual period of the bevacizumab biosimilar group was during the COVID-19 pandemic, which may have affected health service use specifically in this group. However, data limitations prevented us from exploring any hospitalization not due to COVID-19. Chemotherapy-related visits were identified using a previously established algorithm[21,24] that includes common conditions such as neutropenia, fever, infection, and gastrointestinal toxicity defined using Most Responsible Diagnosis (MRD) ICD-9 and ICD-10 codes. Bevacizumab-related safety events were defined

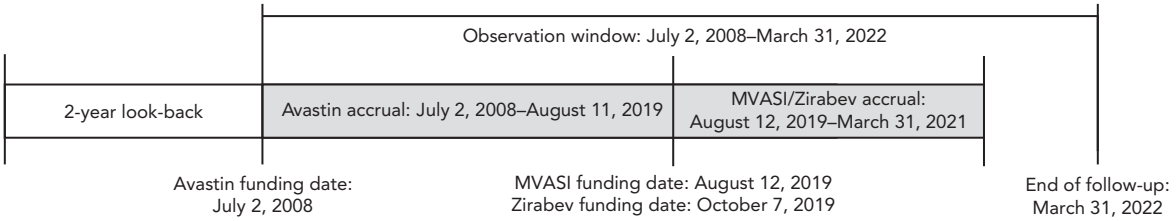

Figure 1. Study timeline.

as conditions established in the literature as being associated with bevacizumab toxicity, including cardiac disorders, thromboembolic disease, intestinal problems, hemorrhage, fistular formation, circulatory diseases, and genitourinary diseases, and were captured using MRD codes identified by clinical experts.[21] Febrile neutropenia–related safety events were identified with a predefined algorithm.[24]

The primary effectiveness outcome was overall survival (OS), defined as time from index date to date of death from any cause or censoring, measured in months. Patients were censored if they remained alive at the end of the maximum follow-up date on March 31, 2022, or if they were alive but the date of last contact was before the maximum follow-up date.

Covariates

Demographic characteristics included age and sex. Data on health region, neighborhood income quintile, and rurality were obtained using postal codes and 2016 Canadian census data. Clinical characteristics included CRC type (malignant neoplasm of the colon [C18], malignant neoplasm of the rectosigmoid junction [C19], malignant neoplasm of the rectum [C20]), year of first bevacizumab treatment, first-line chemotherapy drug received (irinotecan, oxaliplatin), any prior cancer diagnosis, days from initial CRC diagnosis to treatment initiation, Charlson comorbidity index (CCI) score, Aggregated Diagnostic Groups to inform Adjusted Clinical Group (ACG) comorbidity score, and prior therapies between diagnosis and index date (adjuvant chemotherapy, radiation, colorectal surgery). The CCI score and ACG comorbidity score were calculated with a 2-year look back from index year of treatment using CIHI-DAD hospitalization codes, excluding cancer codes. ACG comorbidity scores were calculated by combining physician billings and CIHI-DAD data.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were reported as mean [SD] or median (IQR), with differences between treatment groups assessed using nonparametric tests without assumption of normality. Categorical variables were reported as frequencies and percentages, with differences between treatment groups assessed using Fisher exact tests.

PSM was used to balance baseline demographic and clinical characteristics between treatment groups and minimize any potential confounding due to imbalanced cohorts.[25] Propensity scores estimated the probability of a patient receiving bevacizumab biosimilars and were calculated using a multivariable logistic regression model including age at treatment (years), sex (male, female), type of cancer (colon, rectosigmoid, rectum), any prior cancer diagnosis, prior colorectal surgery, days from initial CRC diagnosis to start of first-line mCRC therapy, type of chemotherapy (irinotecan, oxaliplatin), rurality, neighborhood income quintile, health region, CCI score, total ACG score, prior adjuvant oxaliplatin, prior capecitabine, prior fluorouracil, prior radiation treatment, and prior radiation of the rectum. PSM estimated the average treatment effect in the population treated with bevacizumab, with a caliper distance of 0.2, sampled without replacement, and matched 1:4 between patients in the biosimilar and originator groups. Standardized differences of baseline characteristics $<10\%$ indicated acceptable balance between matched groups.[26]

For safety outcomes, odds ratios from crude and PSM cohorts were estimated using binomial logistic regression for mortality within 30 days of last dose received. Rate ratios from crude and PSM cohorts were estimated using negative binomial regression for all other safety outcomes, accounting for differences in duration of treatment or follow-up time using an offset function. For effectiveness outcomes in crude and PSM cohorts, univariate analysis used the Kaplan-Meier method to assess OS for each treatment group and the log-rank test to assess the difference in OS between treatment groups. A Cox proportional hazards function was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of death from crude and PSM cohorts. A subgroup analysis of PSM cohorts comparing safety and effectiveness outcomes between patients on different bevacizumab biosimilar products and their matched comparator groups was conducted to explore potential differences in safety events and survival by biosimilar product. A sensitivity analysis was conducted, including a time-dependent covariate for liver resection as an independent variable in the primary outcome model of the PSM analysis to explore potential confounding effects. Statistical significance was $<.05$ for all 2-sided P values. Analyses were conducted using SAS 9.4 (SAS Institute Inc). This study followed International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Reporting Guidelines.[27]

Results

Study Cohort

In total, 10,463 patients received bevacizumab through the NDFP. After exclusions were applied, the final cohort included 8,996 patients; 747 received bevacizumab biosimilars and 8,249 received originator bevacizumab (Figure 2). The PSM cohort stratified by

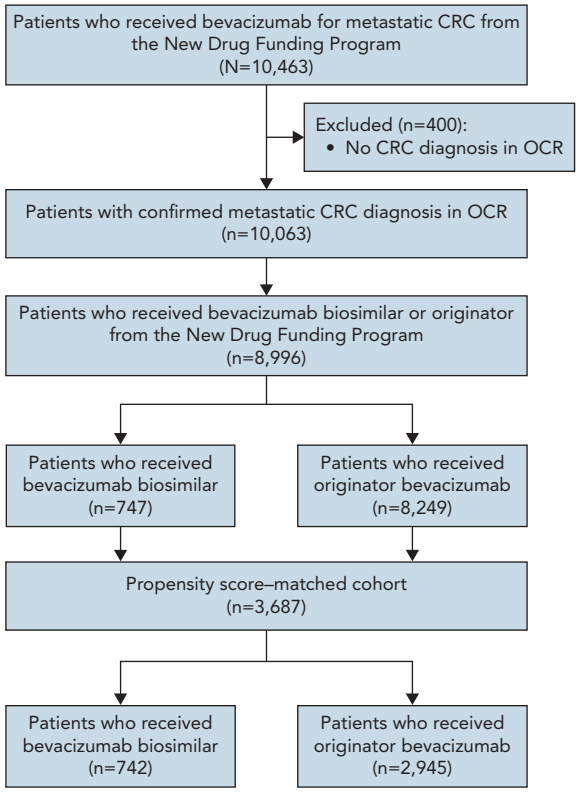

Figure 2. Study cohort.
Abbreviations: CRC, colorectal cancer; OCR, Ontario Cancer Registry.

Table 1. Baseline Demographic and Clinical Characteristics for All Balancing Variables After PSM

	Crude Cohort			PSM-Adjusted Cohort		
	Bevacizumab Biosimilars n (%)	Originator Bevacizumab n (%)	Standardized Difference	Bevacizumab Biosimilars n (%)	Originator Bevacizumab n (%)	Standardized Difference
Total, N	747	8,249		742	2,945	
Age						
Mean [SD], y	63.31 [11.43]	62.47 [11.35]	0.07	63.28 [11.4]	63.22 [11.6]	0.01
Median (IQR), y	64 (56–72)	63 (55–71)	0.07	64 (56–72)	64 (55–72)	0.00
Age group						
18–44 y	46 (6.2)	558 (6.8)	0.02	46 (6.2)	181 (6.1)	0.00
45–54 y	106 (14.2)	1,362 (16.5)	0.06	105 (14.2)	497 (16.9)	0.08
55–64 y	227 (30.4)	2,514 (30.5)	0.00	226 (30.5)	813 (27.6)	0.06
65–74 y	259 (34.7)	2,628 (31.9)	0.06	257 (34.6)	948 (32.2)	0.05
≥75 y	109 (14.6)	1,187 (14.4)	0.01	108 (14.9)	506 (17.2)	0.07
Sex						
Female	296 (39.6)	3,313 (40.2)	0.01	295 (39.8)	1,175 (39.9)	0.00
Male						
CRC type						
Malignant neoplasm of colon	504 (67.5)	5,451 (66.1)	0.03	500 (67.4)	1,978 (67.2)	0.00
Malignant neoplasm of rectosigmoid junction	68 (9.1)	883 (10.7)	0.05	68 (9.2)	280 (9.5)	0.01
Malignant neoplasm of rectum	175 (23.4)	1,915 (23.2)	0.01	174 (23.5)	687 (23.3)	0.00
Bevacizumab product						
Avastin	0 (0)	8,249 (100)	—	0 (0)	2,945 (100)	—
MVASI	635 (85)	0 (0)	3.37	631 (85.0)	0 (0)	—
Zirabev	112 (15)	0 (0)	0.59	111 (15.0)	0 (0)	—
Chemotherapy backbone drug						
Irinotecan	611 (81.8)	7,333 (88.9)	0.20	609 (82.1)	2,438 (82.8)	0.02
Oxaliplatin	136 (18.2)	916 (11.1)	0.20	133 (17.9)	507 (17.2)	0.02
Days from initial CRC diagnosis to first dose of first-line treatment						
Mean [SD]	615.90 [1,080.45]	531.25 [871.22]	0.09	599.5 [1,016.3]	593.2 [1,041.4]	0.01
Median (IQR)	190 (78–772)	150 (68–697)	0.11	188 (78–765)	166 (71–722)	0.07
Prior cancer diagnosis	77 (10.3)	740 (9.0)	0.05	77 (10.4)	304 (10.3)	0.00
CCI score						
0	411 (55.0)	4,839 (58.7)	0.07	409 (55.1)	1,625 (55.2)	0.00
1	82 (11.0)	918 (11.1)	0.00	82 (11.1)	313 (10.6)	0.01
≥2	41 (5.5)	437 (5.3)	0.01	41 (5.5)	185 (6.3)	0.03
No hospitalization in look-back period	213 (28.5)	2,055 (24.9)	0.08	210 (28.3)	822 (27.9)	0.01

(*continued on next page*)

bevacizumab biosimilars and originator included 3,687 patients, with a 1:4 ratio of patients receiving bevacizumab biosimilars (n=742) to patients receiving originator (n=2,945). Baseline characteristics of the PSM cohort are summarized in Table 1; all matching variables were well balanced. Baseline characteristics of bevacizumab biosimilar products and propensity score–matched originator comparator groups are reported in Supplementary Tables S1 and S2 (available in the supplementary materials online at JNCCN.org).

Safety Analysis

In the PSM cohort, mean follow-up time for capturing toxicity outcomes in the originator group was 392.57 days (median, 240 [IQR, 30–3,621] days) and in the biosimilar group was 246.55 days (median, 197 [IQR, 30–737] days). No significant difference in death within 30 days of last dose received was observed between treatment groups (Table 2). After accounting for duration of follow-up, no significant differences in rates of hospitalization, direct hospitalization, bevacizumab-related toxicity hospitalization, chemotherapy-related toxicity hospitalization, and febrile neutropenia–related hospitalization between treatment groups were observed.

Effectiveness Analysis

In the PSM cohort, median survival OS was 20.8 months (95% CI, 20.2–21.7 months) in the originator group and 21.0 months (95% CI, 18.9–23.0 months) in the biosimilars group (Figure 3). No significant differences in OS between treatment groups were identified for the PSM cohort (log-rank test $P=.90$), nor was there a significant difference in reduced mortality identified between treatment groups (HR, 1.03; 95% CI, 0.92–1.16). Of the 742 patients in the PSM cohort who received a biosimilar, 85% received the bevacizumab biosimilar MVASI and 15% received the bevacizumab biosimilar Zirabev. No significant differences in survival were observed in subgroup analyses between patients receiving bevacizumab biosimilar MVASI versus their matched originator comparators (HR, 0.98; 95% CI, 0.87–1.12) and bevacizumab biosimilar Zirabev versus their matched originator comparators (HR, 0.76; 95% CI, 0.54–1.07) (Figure 3). The findings of the sensitivity analysis were consistent with those of the primary analysis. Liver resection was reported for 7.8% of patients in the bevacizumab biosimilar group and 8.8% of patients in the originator comparator group ($P=.38$). No significant difference in risk of morality was identified between treatment groups (HR, 0.95; 95% CI, 0.86–1.04).

Table 1 (cont.). Baseline Demographic and Clinical Characteristics for All Balancing Variables After PSM

	Crude Cohort			PSM-Adjusted Cohort		
	Bevacizumab Biosimilars n (%)	Originator Bevacizumab n (%)	Standardized Difference	Bevacizumab Biosimilars n (%)	Originator Bevacizumab n (%)	Standardized Difference
Total ACG score						
Mean [SD]	8.66 [3.26]	8.70 [3.25]	0.01	8.7 [3.3]	8.6 [3.3]	0.02
Median (IQR)	9 (6–11)	9 (6–11)	0.02	9 (6–11)	9 (6–11)	0.01
Local integrated health network						
1	57 (7.6)	500 (6.1)	0.06	56 (7.5)	228 (7.7)	0.01
2	55 (7.4)	532 (6.4)	0.04	54 (7.3)	199 (6.8)	0.02
3	31 (4.1)	464 (5.6)	0.07	31 (4.2)	120 (4.1)	0.01
4	83 (11.1)	960 (11.6)	0.02	83 (11.2)	322 (10.9)	0.01
5	50 (6.7)	422 (5.1)	0.07	50 (6.7)	198 (6.7)	0.00
6	56 (7.5)	637 (7.7)	0.01	56 (7.5)	236 (8.0)	0.02
7	73 (9.8)	615 (7.5)	0.08	71 (9.6)	291 (9.9)	0.01
8	97 (13.0)	972 (11.8)	0.04	97 (13.1)	382 (13.0)	0.00
9	60 (8.0)	927 (11.2)	0.11	60 (8.1)	243 (8.3)	0.01
10	10 (1.3)	254 (3.1)	0.12	10 (1.3)	40 (1.4)	0.00
11	64 (8.6)	837 (10.1)	0.05	63 (8.5)	248 (8.4)	0.00
12	35 (4.7)	403 (4.9)	0.01	35 (4.7)	137 (4.7)	0.00
13	64 (8.6)	545 (6.6)	0.07	64 (8.6)	253 (8.6)	0.00
14	12 (1.6)	181 (2.2)	0.04	12 (1.6)	48 (1.6)	0.00
Neighborhood income quintile						
1 (lowest)	147 (19.7)	1,544 (18.7)	0.02	145 (19.5)	578 (19.6)	0.00
2	150 (20.1)	1,645 (19.9)	0.00	150 (20.2)	581 (19.7)	0.01
3	151 (20.2)	1,675 (20.3)	0.00	151 (20.4)	624 (21.2)	0.02
4	159 (21.3)	1,698 (20.6)	0.02	159 (21.4)	627 (21.3)	0.00
5 (highest)	135–139[a]	1,667–1,671[a]	0.04	137 (18.5)	535 (18.2)	0.01
Rural residence	78–82[a]	1,133–1,137[a]	0.09	80 (10.8)	298 (10.1)	0.02
Prior colorectal surgery	569 (76.2)	5,923 (71.8)	0.10	565 (76.1)	2,237 (76.0)	0.00
Prior adjuvant oxaliplatin	214 (28.6)	2,711 (32.9)	0.09	214 (28.8)	863 (29.3)	0.01
Prior capecitabine	138 (18.5)	820 (9.9)	0.25	135 (18.2)	525 (17.8)	0.01
Prior fluorouracil	377 (50.5)	5,061 (61.4)	0.22	376 (50.7)	1,501 (51.0)	0.01
Prior radiation treatment	187 (25.0)	1,811 (22.0)	0.07	185 (24.9)	728 (24.7)	0.00
Prior radiation of the rectum	112 (15.0)	1,149 (13.9)	0.03	110 (14.8)	427 (14.5)	0.01

Abbreviations: ACG, Adjusted Clinical Group; CCI, Charlson comorbidity index; CRC, colorectal cancer; PSM, propensity score matching.
[a]Cell value suppressed to prevent back calculation.

Discussion

We assessed real-world safety and effectiveness of the first 2 approved and publicly-funded bevacizumab biosimilars compared with originator bevacizumab for first-line treatment of patients with mCRC in Ontario, Canada. We did not observe any differences in safety and effectiveness outcomes of bevacizumab biosimilars compared with originator, consistent with existing evidence demonstrating no clinically meaningful differences in safety and efficacy between bevacizumab biosimilars and originator bevacizumab.[13,14,16,28]

We did not observe safety signals for the safety events of interest, evidenced by the lack of significant difference in the risk of safety events between the treatment groups. Given limited follow-up and small frequencies of events, point estimates may be sensitive to small differences but do not suggest any additional or reduced risks across the treatment duration. A postmarket study of

Table 2. Toxicity Outcomes During Treatment Plus 30 Days Following Last Dose of First-Line Treatment in the PSM Cohort

	Incidence Rate per 100 Person-Years (95% CI)				
	Bevacizumab Biosimilars	Originator Bevacizumab	*P* Value	Odds ratio (95% CI)	*P* Value
Death within 30 days of last dose of first-line treatment	6.68 (4.6–9.71)	4.5 (3.81–5.32)	.05	0.84 (0.60–1.20)	.34
				Rate Ratio (95% CI)	
Any hospitalization	70.0 (61.0–80.3)	70.6 (66.4–75.0)	.54	0.90 (0.45–1.78)	.75
Direct hospitalization	15.84 (12.2–20.6)	20.49 (18.4–22.78)	.04	0.77 (0.34–1.71)	.52
Chemotherapy-related hospitalization	29.31 (24.1–35.7)	25.76 (23.5–28.3)	.09	0.94 (0.36–2.44)	.90
Bevacizumab-related hospitalization	29.05 (23.5–35.9)	27.28 (24.7–30.1)	.10	1.07 (0.31–3.69)	.91
Febrile neutropenia-related hospitalization	4.02 (2.45–6.58)	4.99 (4.17–5.99)	.49	0.62 (0.04–10.16)	.74

Abbreviation: PSM, propensity score–matched.

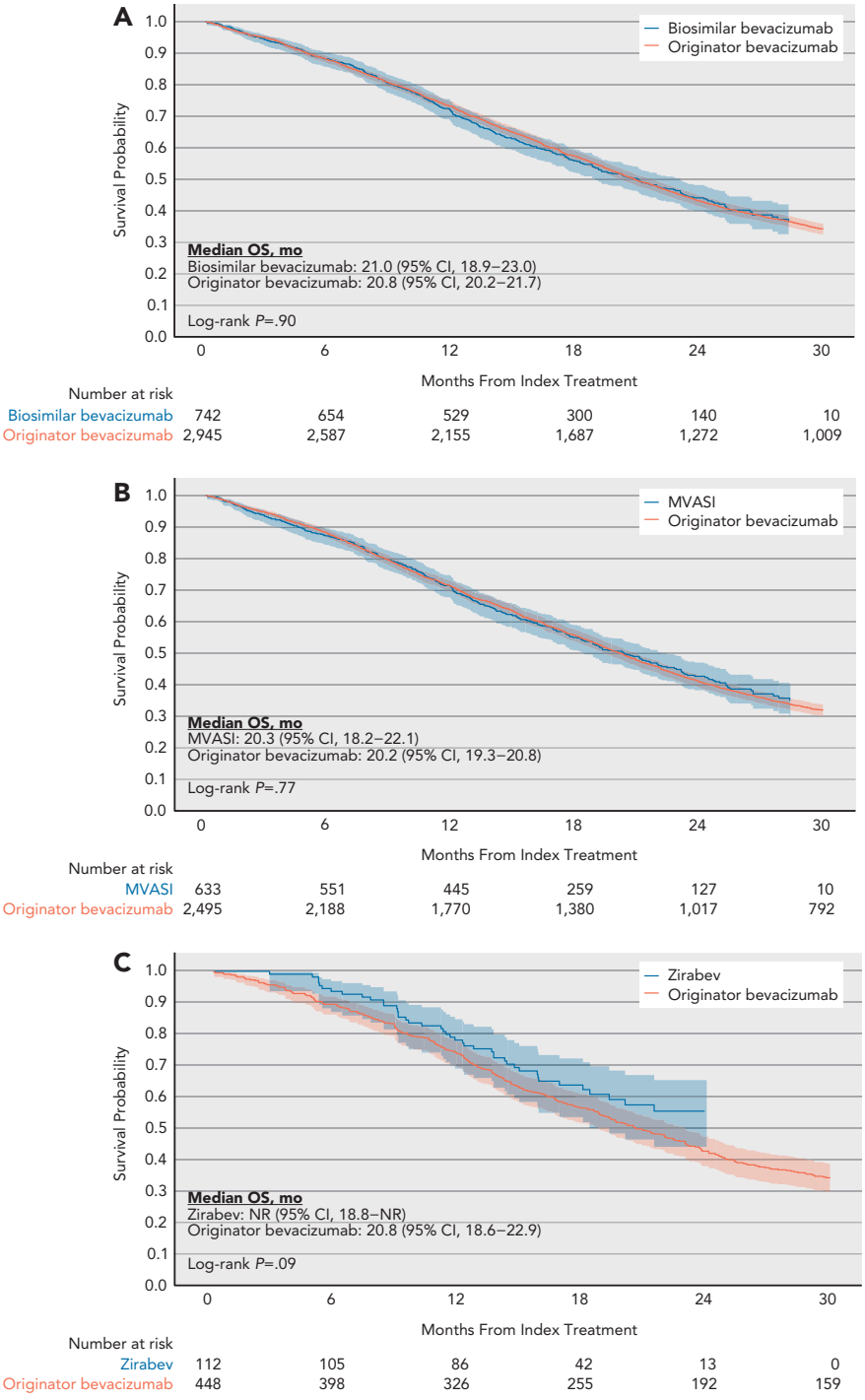

Figure 3. Survival curves for **(A)** the complete study cohort stratified by treatment group after propensity score matching, **(B)** bevacizumab biosimilar MVASI compared with matched comparators, and **(C)** bevacizumab biosimilar Zirabev compared with matched comparators.
Abbreviations: NR, not reached; OS, overall survival.

patients with CRC, gynecologic cancer, glioblastoma, hepatocellular carcinoma, or NSCLC receiving biosimilar or originator bevacizumab reported similar safety outcomes between treatment groups regarding hypertension, proteinuria, gastrointestinal perforation, hemorrhage, and venous and arterial thromboembolism.[28]

The MAPLE and B7391003 RCTs also reported similar safety outcomes between patients receiving biosimilar and originator bevacizumab.[13–15] The findings of our safety analysis are not directly comparable to those in the prospective clinical trials due to differences in how safety events have been defined. However,

we demonstrated similarity in the frequency of health care utilization events that were likely to be related to toxicity management between patients on bevacizumab biosimilars and originator bevacizumab, aligning with findings reported in the postmarket study comparing bevaccizumab biosimilar versus originator bevacizumab in the MAPLE and B7391003 RCTs.

OS curves appeared to overlap and no differences in probability of survival between treatment groups were observed. Similarly, no differences in survival between treatment groups by biosimilar product were found; however, only 15% of patients receiving a biosimilar product received Zirabev, making these results preliminary. Our findings align with OS curves and estimated HR (0.99; 95% CI, 0.55–1.80) reported in an RCT comparing bevacizumab biosimilar BE1040V and originator bevacizumab among patients with mCRC.[16] Although the original MAPLE and B7391003 RCTs were conducted in patients with NSCLC, OS curves and estimated HRs comparing bevacizumab biosimilar to originator bevacizumab (HR, 1.03; 90% CI, 0.83–1.29) and bevacizumab biosimilar to originator bevacizumab (HR, 0.92; 90% CI, 0.73–1.16) also indicated similarity in efficacy of biosimilar compared with originator bevacizumab.[13,14]

One strength of this study is the use of population-based real-world data from a publicly funded system, which includes all patients receiving bevacizumab for mCRC, providing a sample of patients with diverse demographic and clinical characteristics. Another strength is the large sample size due to using population-based administrative databases, increasing generalizability and validity of our study findings. Clinical trials and recent RWEs have compared the effectiveness and safety of bevacizumab biosimilar and originator in the past.[13,15,17,29,30] These studies have included smaller sample sizes, and, to our knowledge, our study has been able to include the largest number of patients with mCRC through use of population-based administrative databases. However, future studies with larger samples may be better equipped to detect statistical significance more precisely in their outcomes compared with our study. It should be noted that due to Ontario's policy to require all new patients receiving bevacizumab for mCRC to start on a biosimilar, clinical factors would not affect choice between biosimilar or originator bevacizumab, and each treatment group represents the full population of patients eligible for and receiving bevacizumab for their accrual period (except for the month of overlap when patients could start therapy with either option). Thus, the risk of confounding by indication is minimal.

This study was not without limitations. Due to the retrospective observational design, patients were not randomized to the biosimilar or originator treatment group, possibly resulting in a lack of comparability between treatment groups. Although all patients receiving bevacizumab were included, baseline characteristics appeared similar, and PSM methods were used to address potential differences in the baseline demographic and clinical characteristics between patients, it is conceivable that residual confounding may have existed among unobserved characteristics. Another limitation was the timing of the introduction of biosimilars in late 2019, which occurred shortly before the start of the COVID-19 pandemic and impacted cancer- and noncancer-related health services use.[20,21] COVID-19 may have specifically impacted patients receiving bevacizumab biosimilars toward the start of the pandemic and possibly contributed to lower health services utilization, such as lower visits to emergency departments, thus, we did not examine emergency department visits as part of the safety assessment.

Real-world utilization studies have demonstrated clinical adoption of bevacizumab biosimilars in the United States, suggesting acceptance of the use of bevacizumab biosimilars by oncologists for treating mCRC.[28,31] However, to our knowledge, this is the first real-world study comparing the effectiveness, and the largest real-world study comparing the safety, of multiple bevacizumab biosimilars versus originator bevacizumab. Real-world studies provide evidence of the comparability of the safety and effectiveness of biosimilar products to their originator biologics across diverse patient populations, and the availability of evidence from large study cohorts provides confidence regarding the reliability and generalizability of study findings. Evidence showing the similarity of safety and survival outcomes among real-world patients receiving biosimilar and originator drugs can increase the confidence clinicians and patients have in biosimilars, contributing to their continued use for treating mCRC. Furthermore, similarity between multiple biosimilar products and their originators may increase clinical and patient comfort in switching between biosimilar products. RWE studies should also assess the cost-effectiveness and budget impact of biosimilars compared with originator drugs, given the cost-saving potential. Ongoing work aims to quantify savings achieved through the implementation of bevacizumab biosimilars for treating patients with mCRC.

Conclusions

Our study showed that bevacizumab biosimilars are associated with similar safety and effectiveness as originator bevacizumab in the real-world setting among patients with mCRC in Ontario, Canada. The findings can help to increase patient and provider confidence in the use of bevacizumab biosimilars, and be used to guide assessments of other publicly funded biosimilar products and shape policies outlining their use and funding.

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