Real-World Outcomes of Patients With *BRAF*-Mutated Metastatic Colorectal Cancer Treated in the United States

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ABSTRACT

Background: *BRAF* mutations portend a poor prognosis in metastatic colorectal cancer (mCRC). Whether these patients may benefit from more aggressive frontline chemotherapy with a triplet regimen such as FOLFOXIRI remains unclear. We used real-world data from a cohort of patients in the United States to assess the *BRAF* testing rate, determine the prevalence of FOLFOXIRI use, and compare survival outcomes in mCRC, stratified by *BRAF* mutation status and first-line therapy. **Methods:** A nationwide electronic health record-derived deidentified database was reviewed for patients diagnosed with mCRC between 2013 and 2018. Those with documented *BRAF* mutation testing who received standard first-line therapy were included. Kaplan-Meier estimates with corresponding log-rank tests and Cox proportional hazards modeling compared survival outcomes stratified by *BRAF* status and first-line therapy. **Results:** Of 4,457 included patients, 3,991 (89.5%) had *BRAF* wild-type (*BRAF*wt) and 466 (10.5%) had *BRAF*-mutated (*BRAF*mt) mCRC. Median overall survival (OS) was 15.4 months in the *BRAF*mt group versus 28.1 months in the *BRAF*wt group (hazard ratio [HR], 0.48; 95% CI, 0.41–0.56; $P < .001$). Only 3% of patients with *BRAF* mutations received first-line FOLFOXIRI ± bevacizumab, with a median OS of 13.8 months compared with 15.5 months in those treated with doublet chemotherapy ± bevacizumab ($P = .38$). In patients with *BRAF* mutations, propensity-weighted analysis did not detect a significant improvement in OS with FOLFIRI + bevacizumab (HR, 0.90; 95% CI, 0.58–1.39; $P = .63$) or FOLFOX/CAPEOX + bevacizumab (HR, 0.81; 95% CI, 0.52–1.26; $P = .35$) versus doublet chemotherapy alone. In 2018, only 56% of patients diagnosed with mCRC had documented *BRAF* testing at any time. **Conclusions:** This real-world data analysis confirms the negative prognostic impact of *BRAF* mutations in mCRC and suggests that FOLFOXIRI has not been widely adopted in the United States. The proportion of patients with documented *BRAF* testing in this real-world population was low at 56%. We were unable to show any significant difference in OS of patients with *BRAF*mt mCRC based on the first-line therapy received.

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Background

Colorectal cancer (CRC) remains one of the most common causes of morbidity and mortality in the world and is the second most common cause of cancer death in the United States, with approximately 53,200 deaths annually.¹ Advances in molecular biology and genomic profiling have led to the identification of several genetic aberrations and tumor characteristics that allow for distinct subgroups of metastatic CRC (mCRC) with both prognostic and predictive implications. One of these subgroups is *BRAF*-mutated (*BRAF*mt) CRC. *BRAF* mutations are present in roughly 10% of patients with mCRC² and portend a particularly unfavorable prognosis, with a median survival for patients with metastatic disease of <12 months.^{3,4} *BRAF*mt mCRC tumors are typically right-sided, poorly differentiated, and T4 staged, and they characteristically affect older women.⁵

BRAF mutations can be predictive of response to targeted therapy, as shown in the recently published BEACON trial.⁶ In this study, 655 patients with *BRAF*mt mCRC whose disease progressed on at least one prior line of therapy were randomized to cetuximab + the investigator's choice of either FOLFIRI or irinotecan versus encorafenib (*BRAF* inhibitor) + cetuximab (anti-endothelial growth factor receptor [EGFR]) or encorafenib + cetuximab + binimetinib (MEK inhibitor). Objective responses were significantly higher and overall survival (OS) was significantly improved in the doublet and triplet arms compared with chemotherapy.⁶ Based on these results, encorafenib gained regulatory approval by the FDA, and the doublet of encorafenib + anti-EGFR therapy has become the second-line standard of care in this patient population.

Optimal first-line (1L) treatment of patients with *BRAF*-positive mCRC remains to be defined. Given the poor prognosis of *BRAF*mt mCRC, it has been hypothesized that giving FOLFOXIRI up front may give patients the best chance to be exposed to the most active agents

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in this disease. Indeed, a phase II trial with FOLFOXIRI in *BRAF*mt mCRC resulted in a median OS of 24.1 months, which compared favorably with historical control patients.⁷ A randomized phase III study recently evaluated 1L FOLFOXIRI + bevacizumab versus FOLFIRI + bevacizumab in patients with mCRC.⁸ The triplet arm resulted in improved OS (29.9 vs 25.8 months; hazard ratio [HR], 0.80; 95% CI, 0.65–0.98) at the expense of increased toxicity. The survival benefit seemed to be independent of *BRAF* mutations. However, the study only enrolled a small number of patients with *BRAF* mutations (n=28). Median OS in the *BRAF* and *RAS* wild-type (wt) group was 37.1 months compared with 13.4 months for the *BRAF*mt group (HR, 2.79; 95% CI, 1.75–4.46; *P*<.0001). These results again highlight the poor outcomes associated with *BRAF*mt mCRC.

Although potential improvement in survival with FOLFOXIRI has been suggested, current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer (Version 4.2020) still do not give preference to one specific 1L cytotoxic regimen for patients with *BRAF*mt mCRC.⁹ As such, in this study we sought to use real-world data from a large cohort of patients in the United States to assess changes in *BRAF* testing rate over time, to determine the prevalence of FOLFOXIRI use, and to compare survival outcomes in mCRC stratified by *BRAF* mutation status and 1L therapy.

Methods

Data Source

This study used the nationwide Flatiron Health electronic health record (EHR)-derived deidentified database. During the study period, the deidentified data originated from a geographically diverse group of approximately 280 US cancer clinics (~800 centers of care), representing a mixture of academic and community care centers. Deidentified patient-level data in the longitudinal Flatiron Health database include structured data, such as laboratory values, and unstructured data extracted from patient charts using a technology-enabled abstraction process.^{10,11} University of Utah Institutional Review Board approval of the study protocol was obtained before study conduct and included a waiver of informed consent.

Study Population

We reviewed the EHR-derived deidentified database for patients diagnosed with mCRC between January 1, 2013, and December 31, 2018. Patients who had documented *BRAF* mutation testing at any time within 6 months of metastatic diagnosis and received standard 1L chemotherapy were included for analysis. Standard 1L chemotherapy

was defined as FOLFOX, CAPEOX, FOLFIRI, or FOLFOXIRI. Patients who did not have a visit or medication order within 90 days of metastatic diagnosis were excluded to ensure that patients were engaged with care at the data-providing institution.

Statistical Analysis

Statistical differences between groups were determined using chi-square tests for categorical variables and Wilcoxon rank sum tests for quantitative variables. Kaplan-Meier estimates with corresponding log-rank tests and Cox proportional hazards modeling were used to compare survival outcomes stratified by *BRAF* mutation status and 1L therapy received. Treatment comparative effectiveness was assessed for *BRAF*mt tumors via a matching weighted Cox proportional hazards model.^{12,13} Matching weights were constructed via treatment propensity scores estimated via a random forest¹⁴ based on age at metastatic diagnosis, sex, metastatic diagnosis year, mismatch repair (MMR) status, ECOG performance status at 1L initiation, and de novo versus non-de novo metastatic disease. Proportional hazards assumptions for multivariate Cox proportional hazards models were assessed using Schoenfeld tests and graphical inspection for no pattern in the scaled Schoenfeld residuals across time. An additional multivariate analysis controlled for the same potential confounders. The primary outcome of interest was OS, defined as the time from the date of metastatic diagnosis to the date of death. Statistical analysis was performed using R version 3.5.2 (R Foundation for Statistical Computing).¹⁵

Results

Study Cohort and Patient Characteristics

We selected 20,333 patients diagnosed with mCRC between 2013 and 2018. Within this group, we included 9,948 patients who received standard 1L chemotherapy and had a recorded visit or medication order within 90 days of diagnosis. Of these patients, 4,457 had documented *BRAF* testing results, with 466 (10.5%) listed as having tumors harboring a *BRAF*mt (Figure 1). Of the 423 *BRAF*mt tumors included in our multivariate analysis, 311 (73.5%) were V600E, 3 (0.7%) were V600K, 52 (12%) were “other,” and 57 (13%) were unknown.

Our analysis of the 466 *BRAF*mt mCRC tumors suggested that patients with these tumors are more likely to be female (55% vs 42% for patients with *BRAF*wt; *P*<.0001). *BRAF*mt mCRC tends to present at a later age, with a mean age at metastatic diagnosis of 64 years for *BRAF*mt versus 60 years for *BRAF*wt (*P*<.0001). We found that 7% of *BRAF*mt tumors had concurrent mutations in

Figure 1. Patient cohort selection flowchart.

Abbreviations: 1L, first-line; mCRC, metastatic colorectal cancer.

KRAS; 29% of these (10/34) were V600E, and the remaining were either unknown or “other.” In patients who were tested for microsatellite instability (MSI)/MMR, we found that 16% of *BRAF*mt tumors were MMR-deficient, compared with 3% of *BRAF*wt tumors ($P<.0001$). Demographic and clinical characteristics of the patients included in the study are summarized in Table 1.

Uptake of *BRAF* Testing

Testing at any time in the patient disease course for the presence of the *BRAF* mutation was documented in only 14.1% of our study patients diagnosed with mCRC in 2013 (Figure 2). Although the proportion of patients with documented *BRAF* testing increased with each subsequent year, even in the most recent year (2018), only 56% of patients in this population had documented testing for a *BRAF* mutation (supplemental eTable 1, available with this article at JNCCN.org). In sum, of all the patients who met our inclusion criteria, only 34.9% had a documented test for the *BRAF* mutation.

Prognosis of *BRAF* Mutations and Uptake of FOLFOXIRI

The median OS was 15.4 months in the *BRAF*mt group compared with 28.1 months in the *BRAF*wt group (Figure 3). A multivariate analysis adjusting for potential confounders, including 1L treatment, also showed the negative prognostic implications of a mutation in *BRAF* (HR, 0.48; 95% CI, 0.41–0.56; $P<.001$; supplemental eTable 2).

Only 3% ($n=16$) of patients with *BRAF*mt tumors received 1L FOLFOXIRI, with a median OS of 13.8 months compared with 15.5 months in those receiving a chemotherapy doublet (FOLFOX, CAPEOX, or FOLFIRI; 95% CI, 4.9–not reached vs 14.3–19.0, respectively; $P=.38$; Figure 4).

In addition, in *BRAF*mt tumors, matching weighted analysis did not detect a significant improvement in OS with the use of FOLFIRI + bevacizumab (HR, 0.90; 95% CI, 0.58–1.39; $P=.63$) or FOLFOX/CAPEOX + bevacizumab (HR, 0.81; 95% CI, 0.52–1.26; $P=.35$) when compared with a chemotherapy doublet alone. Notably, matching weights achieved well-balanced comparison groups on age at metastatic diagnosis, gender, metastatic diagnosis year, MMR status, ECOG performance status at 1L initiation, and de novo versus non-de novo metastatic disease (all standardized mean differences <0.20). Results based on multivariate analysis were similar (Table 2).

Discussion

There has been a recent surge of interest in the field of oncology to evaluate the efficacy of various treatment strategies in real-world populations. These analyses can help confirm whether the standard of care as determined in tightly controlled clinical trials is truly applicable to a more general population. This is the largest study evaluating real-world outcomes of *BRAF*mt mCRC with front-line therapies. There are several key findings from our study. First, we were able to confirm the negative prognostic implication of a *BRAF* mutation in mCRC in this large, real-world population. Second, we showed that although the documented *BRAF* testing rate in this US cohort has increased over time, in 2018 the testing rate still remained quite low at 56%. Third, we showed that the use of up-front triplet chemotherapy has not been widely adopted by oncologists in the United States for treatment of *BRAF*mt mCRC. Finally, our study did not detect a significant difference in OS between the most commonly used 1L treatment strategies for *BRAF*mt mCRC.

Previous studies have reported the clinicoepidemiologic characteristics of patients with *BRAF*mt CRC. Our analysis of real-world data is consistent with prior results and shows that patients with *BRAF* mutations are older, more likely to be female, and more likely to have MMR deficiency compared with patients with *BRAF*wt. Although we did not subanalyze OS based on *BRAF* and MSI/MMR status combined, it is known that *BRAF*mt/microsatellite stable subgroups tend to fare the worst, and therefore consideration of MSI/MMR status may be a useful additional tool for prognostication in *BRAF*mt mCRC.¹⁶ In addition, we were surprised at how many patients had concurrent *KRAS* and *BRAF* mutations (7%).

Table 1. Patient Characteristics

	BRAF Mutation n (%)	BRAF Wild-Type n (%)	P Value
Total, n	466	3,991	
Mean [SD] age at metastatic diagnosis, y	64 [12]	60 [12]	<.0001
Gender			<.0001
Female	257 (55)	1,681 (42)	
Male	209 (45)	2,310 (58)	
Race/Ethnicity			.018
Asian	9 (2)	90 (2)	
Black or African American	24 (5)	368 (10)	
Hispanic or Latino	1 (0)	12 (0)	
Other	45 (10)	395 (11)	
White	325 (74)	2,505 (68)	
Missing	35 (8)	312 (8)	
Year of metastatic diagnosis			.34
2013	37 (8)	315 (8)	
2014	55 (12)	446 (11)	
2015	96 (21)	660 (17)	
2016	97 (21)	872 (22)	
2017	104 (22)	953 (24)	
2018	77 (17)	745 (19)	
KRAS status			<.0001
Mutated	34 (7)	1,562 (39)	
Wild-type	338 (73)	1,800 (45)	
Unknown	94 (21)	629 (16)	
MMR/MSI status			<.0001
MSI-H/MMR-D	76 (16)	111 (3)	
MSS or MMR proficient	235 (50)	2,472 (62)	
Unknown	155 (33)	1408 (31)	
ECOG performance status			.12
0	154 (33)	1,511 (38)	
1	140 (30)	1,162 (29)	
2	41 (9)	246 (6)	
3–4	4 (1)	45 (1)	
Missing	127 (27)	1,027 (26)	
Disease presentation			.5
De novo metastatic disease	156 (33)	1,277 (32)	
Recurrent disease	309 (66)	2,712 (68)	
Type of standard 1L therapy received			.13
FOLFOX/CAPEOX/FOLFIRI	121 (26)	1,082 (27)	
FOLFOX/CAPEOX/FOLFIRI + Bev	302 (65)	2,491 (62)	
FOLFOX/CAPEOX/FOLFIRI + anti-EGFR	27 (6)	305 (8)	
FOLFOXIRI	1 (0)	35 (1)	
FOLFOXIRI + Bev	15 (3)	74 (2)	
FOLFOXIRI + anti-EGFR	0 (0)	4 (0)	

Abbreviations: 1L, first-line; Bev, bevacizumab; EGFR, epidermal growth factor receptor; MMR, mismatch repair; MMR-D, mismatch repair deficient; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Figure 2. Documented testing for *BRAF* mutation within 6 months of metastatic colorectal cancer diagnosis in patients receiving standard first-line treatment between 2013 and 2018.

*May not have 6 months of follow-up in the testing data for those diagnosed in 2018.

Prior literature has also highlighted the poor OS associated with mCRC harboring *BRAF* mutations.¹⁷ Our real-world data analysis supports this observation. We found that the median OS of patients with *BRAF*wt disease was almost double that of patients with *BRAF*mt tumors (28.1 vs 15.4 months). Multivariate analysis showed a similar pattern.

The TRIBE study showed numerically improved OS/ progression-free survival in patients with *BRAF*mt mCRC treated with FOLFOXIRI + bevacizumab versus FOLFIRI + bevacizumab in the first-line setting. Although this finding was not statistically significant, the lower HR in this group compared with the *RAS*wt group suggested a greater mag-

nitude of benefit with the triplet in patients with *BRAF* mutations.⁸ However, the TRIBE2 trial did not confirm the benefit with triplet therapy in patients with *BRAF*mt mCRC (HR for second progression-free survival [PFS2], 1.23; 95% CI, 0.72–2.09, with PFS2 representing the time from randomization to objective tumor progression on next-line treatment, or death from any cause).¹⁸ A recent meta-analysis in patients with unresectable mCRC demonstrated improvement in OS with triplet chemotherapy + bevacizumab when compared with doublet chemotherapy + bevacizumab for mCRC in general.¹⁹ However, when looking specifically at *BRAF*mt tumors, that same benefit from triplet therapy was not demonstrated. Although only 3% of the patients in our analysis received 1L triplet chemotherapy with FOLFOXIRI + bevacizumab, our real-world data study showed no evidence of a survival benefit for triplet over doublet therapy (13.8 vs 15.5 months; $P=.38$).

Although adding antiangiogenics to cytotoxics in patients with *BRAF* mutations is often done in clinical practice, the role of antiangiogenics in the treatment of *BRAF*mt tumors remains to be definitively established.^{20–22} Post hoc analysis from studies in both the first- and second-line settings suggests that adding bevacizumab improves survival in patients with *BRAF*mt tumors. A limitation of this analysis is the small sample size. In the IFL trial, which evaluated the addition of bevacizumab to bolus fluorouracil + irinotecan in the 1L setting in mCRC, a trend toward improved survival was seen in the *BRAF*mt group (15.9 vs 7.9; HR, 0.11; 95% CI, 0.01–1.06). However, only 10 *BRAF*mt tumors were included in this analysis. The RAISE trial tested ramucirumab (a monoclonal antibody against VEGFR-2) in the second line in combination with FOLFIRI. In the *BRAF*mt subset ($n=41$), there was a nonstatistically significant trend toward improved OS in the ramucirumab arm (9 vs 4.2 months;

Figure 3. Kaplan-Meier curve showing overall survival of patients with metastatic colorectal cancer stratified by *BRAF* mutational status.

Figure 4. Kaplan-Meier curve showing overall survival of patients with *BRAF* mutation receiving doublet chemotherapy (FOLFOX, CAPEOX, or FOLFIRI) versus triplet chemotherapy (FOLFOXIRI).

Table 2. Multivariate Survival Analysis of 1L Therapy Groups in Patients With BRAF Mutation

	n (%)	HR (95% CI)	P Value
Total	423		
Type of 1L therapy received			
FOLFOX/CAPEOX/FOLFIRI	121 (29)	Ref	
FOLFIRI + Bev	68 (16)	0.88 (0.50–1.56)	.666
FOLFOX/CAPEOX + Bev	234 (55)	0.89 (0.59–1.34)	.577
Mean [SD] age at metastatic diagnosis			
64.4 [12] y	—	1.00 (0.99–1.02)	.803
Gender			
Female	236 (56)	Ref	
Male	187 (44)	0.93 (0.67–1.31)	.695
Year of metastatic diagnosis, mean [SD]			
2015.9 [1.5]	—	1.16 (1.02–1.33)	.029
MMR status			
Non-MMR	207 (49)	Ref	
MMR	70 (16)	1.31 (0.76–2.23)	.328
Not tested/unknown	146 (34)	0.99 (0.68–1.43)	.948
ECOG performance status			
0	106 (25)	Ref	
1	105 (25)	1.87 (1.29–2.70)	.001
2	30 (7)	2.47 (1.45–4.20)	.001
3–4	3 (1)	1.95 (0.60–6.34)	.268
Metastatic diagnosis			
Non-de novo	142 (34)	Ref	
De novo	280 (66)	1.55 (1.01–2.37)	.045

Abbreviations: 1L, first-line; Bev, bevacizumab; HR, hazard ratio; MMR, mismatch repair.

HR, 0.54; 95% CI, 0.25–1.13). The VELOUR trial evaluated the benefit of adding aflibercept (a fusion protein that binds VEGF) to second-line FOLFIRI in patients with mCRC. The study showed a trend toward improved OS in the *BRAF*mt group (n=36) that received aflibercept (10.3 vs 5.5 months; 95% CI, 0.16–1.09).²³ In our analysis (*BRAF*mt n=466), we were not able to show a survival benefit for patients with *BRAF* mutations who received any doublet therapy (FOLFOX/CAPEOX/FOLFIRI) + bevacizumab compared with those who did not receive

bevacizumab. It is possible that the benefit seen in controlled study patients does not translate when this regimen is applied to all-comers with *BRAF*mt mCRC. However, additional efforts are needed to better understand the role of antiangiogenics in combination with cytotoxics or targeted therapy in *BRAF*mt tumors.

Of the 9,948 patients included in our study, we were intrigued to note that even in the year of highest testing (2018), only slightly more than half of the patients had a documented test for *BRAF* mutation (Figure 2). Importantly, of the 5,251 patients (44%) without documented *BRAF* testing, only 1,620 (30.7%) had a *KRAS* or *NRAS* mutation detected at any time. Thus, using the detection of a *RAS* mutation as an explanation for the absence of *BRAF* testing seems to be the case in only a fraction of patients. It is also important to note that this low *BRAF* testing rate was observed prior to publication of the BEACON trial results in 2019, which showed improved survival with targeted therapy compared with cytotoxics in the second line in V600E *BRAF* mCRC tumors.⁶ Ideally, these results should drive implementation of universal *BRAF* testing in this patient population, because encorafenib plus anti-EGFR has been established as a new standard of care in the second line in these patients, especially in the absence of MMR deficiency.

Our study has some limitations. We were able to include only patients who underwent palliative chemotherapy and had standard follow-up and documented *BRAF* testing. However, the characteristics of our *BRAF* patient population recapitulate what has been reported in other series and validate our data. The specific *BRAF* mutation was “unknown” for approximately 25% of our patient population, which may lead to some dilution of our analysis in patients with non-V600E mutations. In our study, only 16 patients received triplet chemotherapy in the front line, which precludes any definitive conclusion regarding the benefit of triplet therapy in this patient population. In addition, because this is a nonrandomized trial, there is a possibility for selection bias regarding which patients were offered FOLFIRI. Concerning *BRAF* testing, it is possible that there are missing data from patient charts, because the patients may have been tested out of the network our data were drawn from. Consequently, we cannot extrapolate the testing rate to the entire US mCRC population. In addition, because our inclusion was *BRAF* testing known within 6 months of diagnosis, it is possible that we missed patient testing data from 2018 due to a patient being diagnosed late in the year without mutational testing yet resulted. Final limitations include the retrospective study design and the potential for inclusion bias and unmeasured confounders.

Conclusions

In this real-world data analysis, we did not find significant differences in the OS of patients with *BRAF*mt mCRC based on which type of 1L therapy they received. This analysis supports that the presence of *BRAF*mt portends poor survival outcomes in mCRC. Finally, despite the known negative prognostic impact from *BRAF* mutations, documented testing rates remain low, with only 56% of our study patients undergoing testing in 2018. The results of the BEACON trial, published in 2019,⁶ are likely to drive an increase in *BRAF* testing in the future.

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eTable 1: Demographic and Patient Factors at Time of CRC Diagnosis

eTable 2: Multivariate Survival Analysis for Patients With mCRC and Documented Results From *BRAF*
Mutation Testing

eTable 1. Demographic and Patient Factors at Time of CRC Diagnosis by BRAF Testing Status

	BRAF Not Ever Tested n (%)	BRAF Tested at Any Time n (%)	P Value
Total, n	5,251	4,697	
Type of 1L therapy received			<.0001
FOLFOX/CAPEOX/FOLFIRI	1,594 (30)	1,271 (27)	
FOLFOX/CAPEOX/FOLFIRI + Bev	3,309 (63)	2,945 (63)	
FOLFOX/CAPEOX/FOLFIRI + anti-EGFR	295 (6)	345 (7)	
FOLFOXIRI	20 (0)	40 (1)	
FOLFOXIRI + Bev	31 (1)	92 (2)	
FOLFOXIRI + anti-EGFR	2 (0)	4 (0)	
Mean age at metastatic diagnosis [SD]	64 [12]	61 [12]	<.0001
Race/Ethnicity			.0002
Asian	151 (3)	118 (3)	
Black or African American	619 (12)	445 (9)	
Hispanic or Latino	26 (0)	18 (0)	
Other	644 (12)	515 (11)	
White	3,386 (64)	3,190 (68)	
Missing	425 (8)	411 (9)	
Census region			<.001
Midwest	849 (16)	669 (14)	
Northeast	924 (18)	945 (20)	
South	2,095 (40)	1,876 (40)	
West	937 (18)	774 (16)	
Puerto Rico	192 (4)	99 (2)	
No state listed	254 (5)	334 (7)	
Gender			.21
Female	2,242 (43)	2,065 (44)	
Male	3,009 (57)	2,632 (56)	
Year of metastatic diagnosis			<.0001
2013	849 (16)	669 (14)	
2014	254 (5)	334 (7)	
2015	924 (18)	945 (20)	
2016	192 (4)	99 (2)	
2017	2,095 (40)	1,876 (40)	
2018	937 (18)	774 (16)	
KRAS status			<.0001
Mutated	1,583 (30)	1,966 (42)	
Wild-type	3,668 (70)	2,731 (58)	
MMR status			<.0001
Non-MMR	1,634 (31)	2,812 (60)	
MMR	96 (2)	196 (4)	
Not tested/unknown	3,521 (67)	1,689 (36)	

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eTable 1. Demographic and Patient Factors at Time of CRC Diagnosis by <i>BRAF</i> Testing Status (cont.)			
	<i>BRAF</i> Not Ever Tested n (%)	<i>BRAF</i> Tested at Any Time n (%)	P Value
ECOG performance status			<.0001
0	1,637 (31)	1,751 (37)	
1	1,392 (27)	1,369 (29)	
2	375 (3)	299 (6)	
3–4	94 (2)	53 (1)	
Missing	1,753 (33)	1,225 (26)	
Metastatic diagnosis			.002
Non–de novo	1,840 (35)	1,507 (32)	
De novo	3,406 (65)	3,187 (68)	

Abbreviations: 1L, first-line; Bev, bevacizumab; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HR, hazard ratio; MMR, mismatch repair.

eTable 2. Multivariate Survival Analysis for Patients With mCRC and Documented Results From BRAF Mutation Testing

	n	HR (95% CI)	P Value
Total, n	4,457		
BRAF status			
Mutated (any time)	466	—	
Wild-type	3,991	0.48 (0.41–0.56)	<.001
Type of 1L therapy received			
FOLFOX/CAPEOX/FOLFIRI	1,203	—	
FOLFOX/CAPEOX/FOLFIRI + Bev	2,793	0.96 (0.8–1.08)	.477
FOLFOX/CAPEOX/FOLFIRI + anti-EGFR	332	0.78 (0.60–1.00)	.054
FOLFOXIRI	36	0.95 (0.47–1.92)	.886
FOLFOXIRI + Bev	89	0.67 (0.40–1.14)	.140
FOLFOXIRI + anti-EGFR	4	4.55 (1.13–18.35)	.033
Mean age at metastatic diagnosis [SD], y			
60.6 [12.1]		1.00 (1.00–1.01)	.058
Race/Ethnicity			
Asian	109	—	
Black or African American	423	1.40 (0.95–2.06)	.091
Hispanic or Latino	16	2.10 (1.00–4.42)	.051
Other	483	1.16 (0.78–1.71)	.467
White	3,041	1.24 (0.87–1.76)	.242
Gender			
Female	1,938	—	
Male	2,519	1.09 (0.98–1.22)	.117
Year of metastatic diagnosis [SD]			
2016 [1.5]		1.20 (1.14–1.26)	<.001
KRAS status			
Mutated	1,596	—	
Wild-type	2,138	0.75 (0.66–0.85)	<.001
Not tested	692	0.65 (0.56–0.77)	<.001
Unknown	31	1.44 (0.83–2.50)	.200
MMR status			
Non-MMR	2,707	—	
MMR	187	1.09 (0.83–1.42)	.535
Not tested/unknown	1,563	1.03 (0.91–1.16)	.660
ECOG performance status			
0	1,665	—	
1	1,302	1.48 (1.32–1.66)	<.001
2	287	2.11 (1.75–2.53)	<.001
3–4	49	2.59 (1.74–3.85)	<.001
Metastatic diagnosis			
Non-de novo	1,433	—	
De novo	3,021	1.17 (1.05–1.32)	.007

Abbreviations: 1L, first-line; Bev, bevacizumab; EGFR, epidermal growth factor receptor; HR, hazard ratio; mCRC, metastatic colorectal cancer; MMR, mismatch repair.