

Treatment Patterns and Outcomes in Patients with KRAS Wild-Type Metastatic Colorectal Cancer Treated in First Line with Bevacizumab- or Cetuximab-Containing Regimens

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Abstract

Purpose Patients with Kirsten rat sarcoma viral oncogene wild-type (KRAS WT) metastatic colorectal cancer (mCRC) treated in first line with bevacizumab (B) or cetuximab (C) plus standard chemo backbones had comparable outcomes in phase III Cancer and Leukemia Group B (CALGB) 80405. We examined comparative effectiveness of B and C regimens in real-world community settings.

Methods This retrospective study examined progression-free survival (PFS) and OS in a US community sample of KRAS WT mCRC patients treated with first-line B ($n = 254$) or C ($n = 146$) regimens. Medical records from the Vector Oncology Data Warehouse were used. Disease progression

was determined from patient charts. OS was measured from the start of first-line treatment until death.

Results There were no significant difference in either PFS or OS respectively between B-treated compared to C-treated patients (HR = 1.324, 95% CI 0.901, 1.947; HR = 1.080, 95% CI 0.721, 1.617). More B patients received oxaliplatin backbones (74.8 vs. 36.3%), and more C patients received irinotecan backbones (51.4 vs. 20.1%), $ps < 0.001$. Multivariate survival analyses showed a significant difference indicating a greater risk for death among C-treated patients with right-sided tumors vs. left-sided tumors (HR = 2.263, 95% CI 1.394, 3.673, $p = 0.0009$), but not for B-treated patients (HR = 1.209, 95% CI 0.825, 1.771, $p = 0.3297$).

Conclusions Consistent with CALGB 80405, median PFS and OS for these community oncology KRAS WT mCRC patients treated with first-line B or C regimens did not differ significantly.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the USA. In 2016, it is projected that 134,490 people will be diagnosed with CRC, and 50,270 people will die from the disease [1]. About 20% of newly diagnosed patients present with metastatic disease and among those about 80–90% of patients' tumors are unresectable [2].

The current approach to treating metastatic CRC (mCRC) includes doublet combinations of fluorouracil, leucovorin, and irinotecan (FOLFIRI); infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX); and capecitabine plus oxaliplatin

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(XELOX), as well as the triplet combinations of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) [3–5]. The introduction of targeted biologic agents (cetuximab, panitumumab [EGFR inhibitors], bevacizumab, ziv-aflibercept, ramucirumab [VEGF inhibitors], regorafenib [multiple kinase inhibitor]) into clinical practice has improved response rates and overall survival (OS) [6–11].

Post hoc analyses and population-based studies of cetuximab and panitumumab have demonstrated that patients with CRC tumors who have wild-type KRAS benefit from these treatments, whereas patients with certain KRAS mutations in metastatic tumors do not derive benefit [12, 13]. Approximately 60% of patients with CRC have the wild-type KRAS gene [12–14]. Bevacizumab has also been combined with either FOLFOX or FOLFIRI in the large CALGB/Southwest Oncology Group (SWOG) 80405 trial. Patients with KRAS wild-type mCRC treated in the first-line setting with cetuximab (C) or bevacizumab (B) plus FOLFOX or FOLFIRI have demonstrated comparable outcomes in the CALGB 80405 trial [median progression-free survival (PFS), C = 10.45 (95% CI 9.66, 11.33) and B = 10.84 months (95% CI 9.86, 11.40) and median OS, C = 29.93 (95% CI 27.56, 31.21) and B = 29.04 months (95% CI 25.66, 31.21)] [15]. The comparative effectiveness of these two biological agents in real-world community settings remains unknown.

Considerable attention has recently been called to the prognostic value of tumor sidedness to predict outcomes in mCRC patients. Using Surveillance Epidemiology and End Results (SEER) data, Schrag et al. reported that among large samples of stage III ($n = 20,142$) and IV ($n = 12,363$) patients (2007–2013), adjusted OS favored patients with right- vs. left-sided tumors (respectively, HR = 1.20 [95% CI 1.15, 1.25] and HR = 1.17 [95% CI = 1.11, 1.23]) [16]. Earlier evidence from the FIRE 3 trial suggested that KRAS wild-type mCRC patients with left-sided tumors as opposed to right-sided tumors had longer adjusted survival, and this effect was significant in cetuximab/FOLFIRI-treated patients but not in bevacizumab/FOLFIRI-treated patients (respectively, HR = 0.34, $p < 0.0001$, and HR = 1.04, $p = 0.89$) [17]. Further, a recent secondary analysis of the AIO KKK-0104 trial reported that among KRAS wild-type mCRC patients treated with combined cetuximab and capecitabine plus either oxaliplatin- or irinotecan-based regimens, there was a significant impact of primary tumor location with left-sided tumors as opposed to right-sided tumors having longer OS (HR = 0.63, $p = 0.016$) and PFS (HR = 0.67, $p = 0.02$). The same effect was not observed in KRAS mutant patients. The investigators interpreted this finding as suggesting that among KRAS wild-type mCRC patients, left-sided tumor location could be a predictor of cetuximab efficacy [18]. Additional analyses of tumor location have recently been reported for the CALGB 80405 trial [19]. Using adjusted analyses of OS, Venook et al. reported that in CALGB 80405 cetuximab-treated patients with left as opposed

to right-sided tumors had significantly longer survival (HR = 1.87, $p < 0.0001$). The same pattern favoring left-sided tumors was seen in the bevacizumab-treated cohort, but the effect was not as large (HR = 1.32, $p = 0.01$) [19].

This study was a retrospective, descriptive study of treatment patterns and efficacy outcomes among KRAS wild-type mCRC patients who received cetuximab or bevacizumab as part of first-line treatment for metastatic disease in the community oncology setting. We also examined tumor location (right side vs. left side) as a predictor of outcomes.

Patients and Methods

Study Design

This was a retrospective, observational study using data from the Vector Oncology Data Warehouse and an affiliate Data Warehouse, each a repository of electronic medical record (EMR) data, billing data, and healthcare provider notes for cancer patients. The provider notes supported the collection of key information not otherwise available in structured data fields (e.g., performance status, confirmation and dates of disease progression, tumor location) through review by experienced clinical research nurses. The protocol for this study received IRB approval from IntegReview (Austin, TX).

Patients

Patients were included if the following criteria were met: metastatic/stage IV CRC first diagnosed prior to March 1, 2014, documentation of KRAS testing with affirmation of wild-type status at any point, received cetuximab or bevacizumab in the first-line metastatic setting, and at least 18 years old at metastatic diagnosis. Figure 1 shows the screening process and final samples of cetuximab- and bevacizumab-treated patients. The final sample included 146 patients receiving a first-line cetuximab-containing regimen and 254 patients receiving a first-line bevacizumab-containing regimen.

Study Endpoints and Assessments

The primary endpoints were PFS and OS. PFS was defined as the interval from the start of a line of therapy until occurrence of disease progression, death, or end of the medical record, whichever occurred first. Dates of all disease progressions after diagnosis of mCRC were directly determined from radiological scan notes and progress notes. OS was defined as the interval from the start of first-line therapy until death. Dates of death were determined from the medical record and Social Security Death Index.

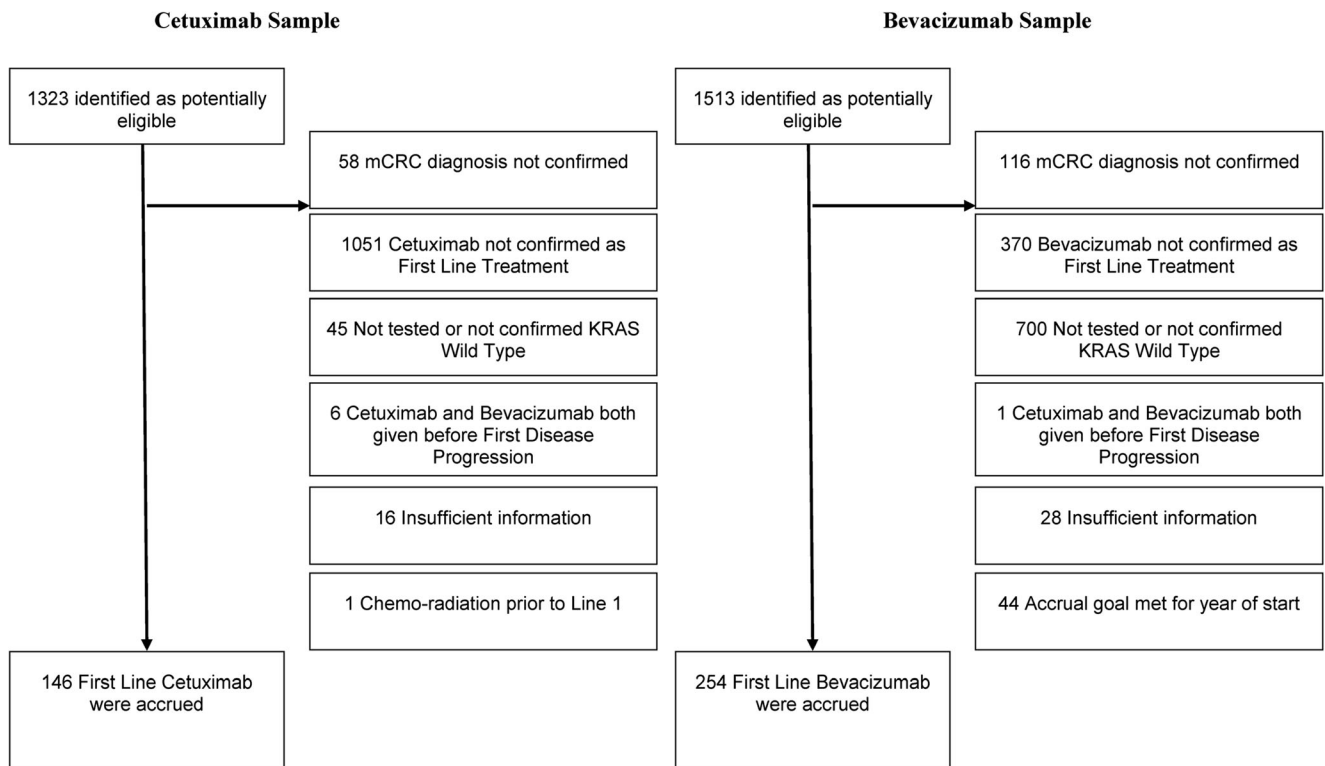


Fig. 1 Sample development and screening process for cetuximab and bevacizumab samples

Treatment patterns included classification of patients to a biologic therapy group (cetuximab or bevacizumab) and included description of oxaliplatin- and irinotecan-based chemotherapy backbones, as those were typically given in combination with cetuximab or bevacizumab. For analysis of treatment patterns across lines of therapy (i.e., sequencing), lines were defined by documented disease progressions rather than mere changes in regimen. That is, treatment regimen changes that followed first-line therapy were defined as new lines of therapy only if they were given following a disease progression. Because regimen changes could occur for reasons other than disease progression, it was possible for patients to have more than one regimen within a single line of therapy. Sequencing of treatments was defined by the initial treatment delivered within a given line, with a focus on the pattern of treatments across the first two lines of therapy. This produced the following sequencing groups: cetuximab followed by cetuximab, cetuximab followed by bevacizumab, cetuximab followed by other treatment, bevacizumab followed by bevacizumab, bevacizumab followed by cetuximab or panitumumab, and bevacizumab followed by other treatment.

Other study variables collected as part of this investigation included patient demographic (age, race, sex) and clinical characteristics (performance status, number of metastatic sites, side of primary tumor location, prior adjuvant therapy status, and tumor resection status).

Statistical Analysis

Fisher’s exact test or chi-square and *t* test or Wilcoxon rank sum test were used to compare patient characteristics by treatment groups on categorical and continuous variables. Unadjusted PFS and OS were calculated using Kaplan–Meier with a log rank test. PFS and OS were assessed from the start of line 1 and compared bevacizumab- and cetuximab-containing regimen groups. Multivariate Cox regression models with covariates (age, gender, race [minority vs. white], body mass index (BMI), number of metastatic sites, performance status [impaired vs. unimpaired]) were also used to examine PFS and OS.

Data Availability Vector Oncology does not make datasets publicly available because study data are used under license from source practices. Vector Oncology will consider requests to access study datasets on a case-by-case basis.

Results

Patient Characteristics

Table 1 shows the demographic and clinical characteristics of patients, by biologic therapy group and overall. Demographic characteristics were comparable between the cetuximab and bevacizumab samples. In general,

Table 1 Demographic and clinical characteristics of mCRC patients treated in first line with cetuximab or bevacizumab regimens

Variable/statistic	First-line treatment			<i>p</i> value ^a
	Cetuximab (<i>N</i> = 146)	Bevacizumab (<i>N</i> = 254)	Overall (<i>N</i> = 400)	
Age (years) at mCRC diagnosis				0.8979
Mean ± SD	61.8 ± 12.65	61.7 ± 11.77	61.7 ± 12.08	
Median	62.0	62.0	62.0	
Gender, <i>n</i> (%)				0.0939
Male	93 (63.7%)	140 (55.1%)	233 (58.3%)	
Female	53 (36.3%)	114 (44.9%)	167 (41.8%)	
Race, <i>n</i> (%)				0.8301
Asian	1 (0.7%)	4 (1.6%)	5 (1.3%)	
Black or African-American	22 (15.1%)	34 (13.4%)	56 (14.0%)	
Hispanic or Latino	1 (0.7%)	3 (1.2%)	4 (1.0%)	
White	103 (70.5%)	189 (74.4%)	292 (73.0%)	
Other	15 (10.3%)	19 (7.5%)	34 (8.5%)	
Not documented	4 (2.7%)	5 (2.0%)	9 (2.3%)	
Composite performance status, <i>n</i> (%)				0.2291
Impaired	14 (9.6%)	16 (6.3%)	30 (7.5%)	
Not impaired	132 (90.4%)	238 (93.7%)	370 (92.5%)	
Metastatic site(s), <i>n</i> (%)				
Bone	5 (3.4%)	7 (2.8%)	12 (3.0%)	0.7645
Brain	1 (0.7%)	2 (0.8%)	3 (0.8%)	1.0000
Liver	93 (63.7%)	168 (66.1%)	261 (65.3%)	0.6213
Liver only	52 (35.6%)	102 (40.2%)	154 (38.5%)	0.3681
Lung	43 (29.5%)	64 (25.2%)	107 (26.8%)	0.3547
Other site	50 (34.2%)	76 (29.9%)	126 (31.5%)	0.3700
Peritoneum	32 (21.9%)	41 (16.1%)	73 (18.3%)	0.1499
Small intestine	4 (2.7%)	5 (2.0%)	9 (2.3%)	0.7294
Total number of metastatic sites				0.0691
Mean ± SD	1.6 ± 0.73	1.4 ± 0.64	1.5 ± 0.68	
Side of primary tumor location, <i>n</i> (%)				0.6085 ^a
Left	92 (68.1%)	162 (67.2%)	254 (67.6%)	
Right	43 (31.9%)	79 (32.8%)	122 (32.4%)	
Undocumented	11 (7.5%)	13 (5.1%)	24 (6.0%)	
Prior adjuvant chemotherapy received, <i>n</i> (%)				0.4783
No	103 (70.5%)	193 (76.0%)	296 (74.0%)	
Yes	41 (28.1%)	59 (23.2%)	100 (25.0%)	
Undocumented	2 (1.4%)	2 (0.8%)	4 (1.0%)	
Primary tumor still in place at time of metastatic diagnosis, <i>n</i> (%)				0.0023
No	70 (47.9%)	86 (33.9%)	156 (39.0%)	
Yes	73 (50.0%)	167 (65.7%)	240 (60.0%)	
Undocumented	3 (2.1%)	1 (0.4%)	4 (1.0%)	

^a *p* values are from a chi-square or Fisher's exact test for categorical variables and a *t* test or Wilcoxon rank sum test for continuous variables

clinical characteristics of the two samples were comparable with two exceptions. A higher proportion of patients had their primary tumor still in place at time of metastatic diagnosis among the bevacizumab group (65.7%)

compared to the cetuximab group (50.0%), *p* = 0.02. Not shown in the table, a higher proportion of the cetuximab group (31.5%) had rectal cancer compared to the bevacizumab group (19.7%), *p* = 0.008.

Treatment Patterns

The proportion of bevacizumab regimens with oxaliplatin backbones (74.8%) was larger than with cetuximab regimens (36.3%), $p < 0.001$. Also, the proportion of cetuximab regimens with irinotecan backbones (51.4%) was larger than the corresponding proportion of bevacizumab regimens (20.1%), $p < 0.0001$. Use of capecitabine or 5FU monotherapy was not significantly different among bevacizumab (5.12%) or cetuximab (2.74%)-containing regimens.

PFS and OS in Line 1

Figure 2 shows the Kaplan–Meier plot of PFS from the start of line 1, by biological therapy group. PFS did not differ across the groups ($p = 0.7758$), with median unadjusted PFS of 10.19 months (95% CI 8.35, 12.23) for cetuximab-treated patients and 10.82 months (95% CI 10.09, 11.77) for bevacizumab-treated patients. In multivariate survival analysis adjusting for age, gender, race, BMI, number of metastatic sites, and performance status, there was no significant difference in PFS among patients receiving bevacizumab compared to cetuximab (HR = 1.324, 95% CI 0.901, 1.947). In this Cox model, the number of metastatic sites was found to be a significant predictor of risk for disease progression (HR = 1.533, 95% CI 1.171, 2.006).

Figure 3 shows Kaplan–Meier plot of OS from the start of line 1, by biological therapy group. As shown in the figure, OS did not differ across groups ($p = 0.5539$), with median unadjusted OS of 30.64 months (95% CI 23.77, 38.01) for cetuximab-treated patients and 31.04 months (95% CI 26.33, 36.13) for bevacizumab-treated patients. In multivariate survival analysis adjusting for the same aforementioned variables, there was no significant difference in OS among patients receiving bevacizumab compared to patients receiving

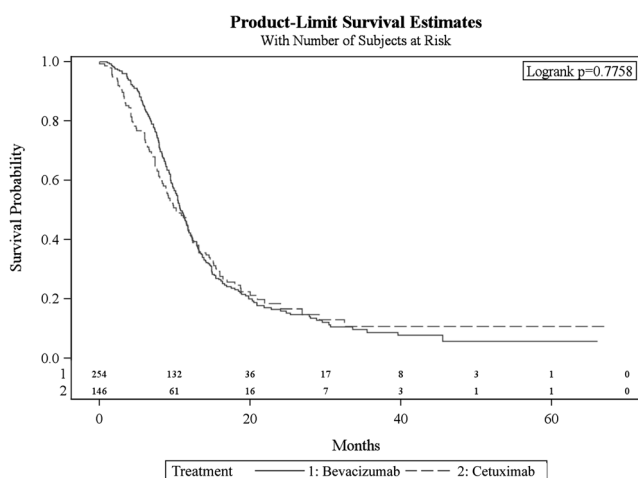


Fig. 2 Progression-free survival from the start of first-line treatment by cetuximab and bevacizumab regimen groups

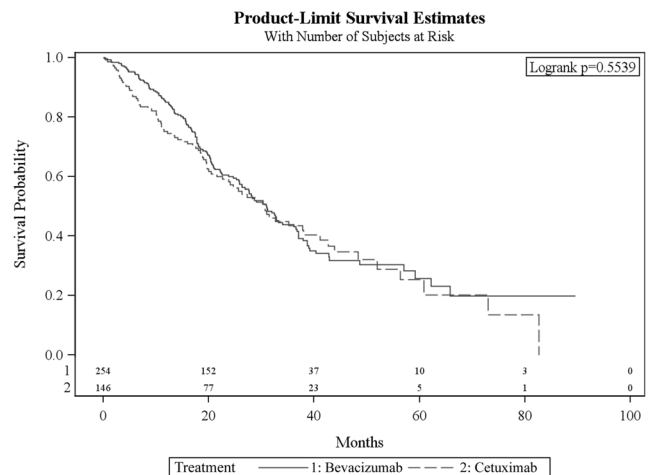


Fig. 3 Overall survival from the start of first-line treatment by cetuximab and bevacizumab regimen groups

cetuximab (HR = 1.080, 95% CI 0.721, 1.617). In this Cox model of OS, the number of metastatic sites was again found to be a significant predictor of mortality (HR = 1.618, 95% CI 1.230, 2.127).

Additional Cox regression analyses from the start of line 1 were conducted to examine the interaction of biological therapy group (cetuximab vs. bevacizumab) with history of prior adjuvant therapy and status of the primary tumor still in place at the time of metastatic diagnosis. The interactions were found to be nonsignificant (data not shown).

PFS and OS by Chemotherapy Backbone

We also examined PFS and OS from the start of line 1 to compare oxaliplatin- and irinotecan-based backbones in cetuximab- and bevacizumab-treated subsets. Among patients who received cetuximab in the first-line, unadjusted median PFS from the start of line 1 did not differ significantly for oxaliplatin-based backbones (11.97 months, 95% CI 8.98, 15.42) compared to irinotecan-based backbones (10.19 months, 95% CI 8.02, 12.23). Likewise, among patients who received bevacizumab in the first line, unadjusted median PFS did not differ significantly for oxaliplatin-based backbones (10.72 months, 95% CI 9.67, 11.74) compared to irinotecan-based backbones (12.16 months, 95% CI 10.36, 13.68). Using multivariate survival analyses adjusting for age, gender, race, BMI, number of metastatic sites, and performance status, there was no significant interaction between biological therapy group and chemotherapy backbone group in predicting PFS.

Among first-line cetuximab patients, unadjusted median OS from the start of line 1 did not differ significantly for oxaliplatin-based backbones (35.15 months, 95% CI 19.63, 60.79) compared to irinotecan-based backbones (30.67 months, 95% CI 21.53, 43.89). Likewise, among

first-line bevacizumab patients, unadjusted median OS did not differ significantly for oxaliplatin-based backbones (31.04 months, 95% CI 26.30, 36.53) compared to irinotecan-based backbones (33.99 months, 95% CI 22.13, 48.62). As with the analysis of PFS, multivariate OS analyses adjusting for age, gender, race, BMI, number of metastatic sites, and performance status showed no significant interaction between biological therapy group and chemotherapy backbone group in predicting OS.

OS by Left- vs. Right-Sided Tumors

Additional Cox regression analysis examined the interaction of tumor location and biological therapy group (cetuximab vs. bevacizumab) on OS from the start of first-line therapy. The interaction of tumor location (right vs. left vs. unknown) with biological therapy was near significant ($p = 0.081$) and was followed up with subset analyses that compared patients with right- vs. left-sided tumors in separate cetuximab and bevacizumab subsets.

Among first-line cetuximab patients, OS from the start of line 1 differed significantly ($p = 0.0002$) for right ($n = 43$) (14.10, 95% CI 10.06, 28.77) compared to left ($n = 92$) (41.10, 95% CI 30.31, 60.79)-sided tumors as seen in Fig. 4a. In multivariate survival analyses adjusting for age, gender, race, BMI, number of metastatic sites, and performance status, there was a significant effect of tumor location indicating a lower survival among cetuximab-treated patients with right-sided tumors (HR = 2.263, 95% CI 1.394, 3.673, $p = 0.0009$) vs. left-sided tumors. As shown in Fig. 4b, median OS from the start of line 1 among first-line bevacizumab patients did not differ significantly for right ($n = 79$) (28.31, 95% CI 18.03, 33.27) compared to left ($n = 162$) (32.88, 95% CI 26.89, 42.84) sided tumors. The omnibus log rank test was significant, but this appeared attributable to the contrast between left side and unknown side in the analysis. This conclusion is supported by multivariate analysis which controlled for demographic and clinical characteristics and in which the direct pairwise contrast of right- vs. left-sided tumors was not significant in predicting OS among bevacizumab-treated patients (HR = 1.209, 95% CI 0.825, 1.771, $p = 0.3297$).

Treatment Sequences Across First Two Lines of Therapy

Table 2 summarizes the Kaplan–Meier analysis of PFS from the start of first-line treatment for six sequence groups (first line–second line) and overall. There were 263 patients who received a biologic agent in line 1 and line 2. Among the three sequence types starting with bevacizumab ($n = 176$), the largest single group was bevacizumab followed by bevacizumab (74/176, 42.1%), and the next largest group was bevacizumab followed by either cetuximab or panitumumab (65/176, 36.9%). Among the three sequence types starting with

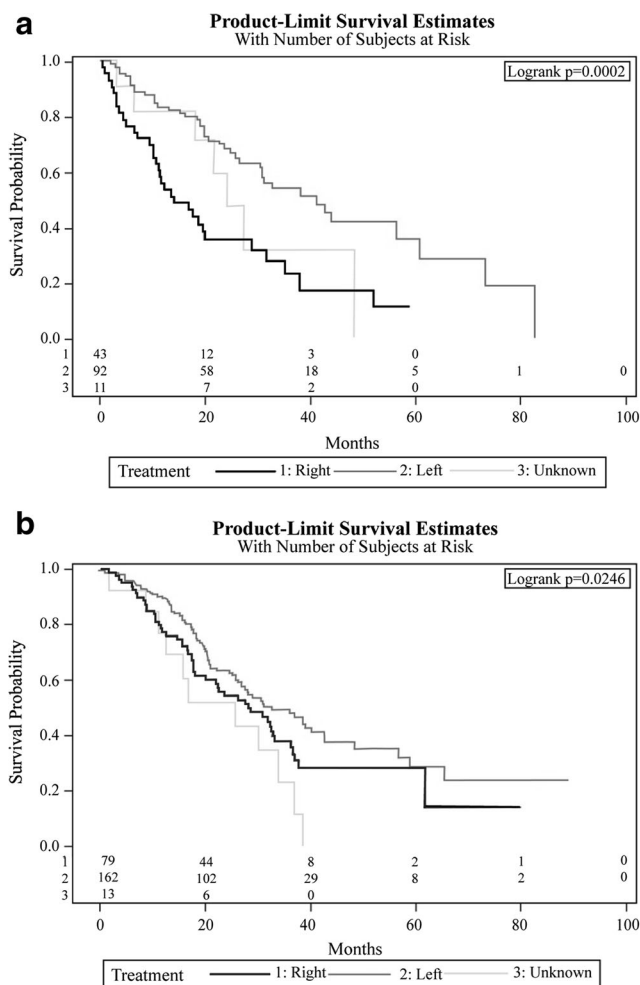


Fig. 4 **a** Overall survival from the start of first-line treatment by tumor side in cetuximab-treated patients ($n = 146$). **b** Overall survival from the start of first-line treatment by tumor side in bevacizumab-treated patients ($n = 254$)

cetuximab ($n = 87$), the largest group was cetuximab followed by cetuximab (38/87, 43.7%), and the next largest group was cetuximab followed by bevacizumab (33/87, 37.9%). An omnibus log rank test indicated the presence of significant differences in PFS across the groups ($p = 0.0200$). Median PFS in the groups ranged from 7.40 months (95% CI = 4.44, 9.11) for the cetuximab–other sequence group, to 10.65 months (95% CI = 9.44, 11.77) for the bevacizumab–bevacizumab group.

Discussion

Consistent with CALGB 80405 results [15], median PFS and OS for these community oncology patients with KRAS wild-type mCRC who were treated with either first-line cetuximab or bevacizumab-containing regimens did not differ significantly. The median values for PFS in first-line treatment observed in this community sample (C = 10.19 months and B = 10.82 months) are similar to those reported in CALGB 80405

Table 2 Summary of Kaplan–Meier PFS from the start of first-line treatment

Progression-free survival	Bev–bev	Bev–cetux/panitumumab	Bev–other ^b	Cetux–cetux	Cetux–bev	Cetux–other ^c	Overall
No. of events/no. of subjects	74/74	65/65	37/37	38/38	33/33	16/16	263/263
Mean (months) ^a	12.50	9.40	11.80	10.07	10.13	7.50	10.68
STD	0.83	0.69	1.32	1.00	1.31	0.96	0.42
Median (months)	10.65	8.35	9.76	8.91	8.94	7.40	9.44
95% CI of median	[9.44, 11.77]	[7.17, 9.90]	[8.78, 11.70]	[6.58, 11.74]	[6.02, 11.47]	[4.44, 9.11]	[8.75, 10.19]
Log rank χ^2 (5) = 13.4, $p = 0.0200$							

The time origin was the start of first-line therapy. All patients who got first and second line

Bev bevacizumab, *Cetux* cetuximab

^a Mean is biased downward because there are censoring times greater than the largest event time

^b Other included the following: aflibercept irinotecan ($n = 6$), capecitabine ($n = 10$), 5FU ($n = 2$), 5FU irinotecan ($n = 9$), 5FU oxaliplatin ($n = 4$), irinotecan ($n = 4$), and ramucirumab ($n = 2$)

^c Other included the following: aflibercept containing ($n = 2$), capecitabine ($n = 6$), 5FU ($n = 1$), 5FU irinotecan ($n = 1$), 5FU oxaliplatin ($n = 1$), panitumumab containing ($n = 4$), and regorafenib ($n = 1$)

($C = 10.45$ months and $B = 10.84$ months). Likewise, OS results from the start of first-line in this study ($C = 30.64$ months and $B = 31.04$ months) are very similar to those reported from CALGB 80405 ($C = 29.93$ months and $B = 29.04$ months). Overall, findings from this real-world study appear to replicate those of the large randomized CALGB phase III study.

We also conducted analyses of PFS and OS to evaluate the possible interaction of biologic therapy group with irinotecan-based vs. oxaliplatin-based chemotherapy backbone regimen groups. Tests of the interaction and follow-up subset analyses that compared chemotherapy backbone groups among cetuximab and bevacizumab subsets were all nonsignificant. The failure to detect any significant interaction of biological therapy group and chemotherapy backbone group is consistent with a recent meta-analysis which examined interactions between chemotherapy backbones and angiogenesis inhibitors in mCRC patients [20]. However, that meta-analysis did report a significant interaction with modestly improved OS ($HR = 0.90$, 95% CI 0.81, 1.00, $p = 0.04$) when an EGFR inhibitor was combined with irinotecan-based vs. oxaliplatin-based chemotherapy backbones in KRAS wild-type patients. Our samples of irinotecan-based patients treated with bevacizumab ($n = 51$) and cetuximab ($n = 75$) were relatively small, so the failure to detect a significant interaction could have been due to reduced power. Also, our nonsignificant HRs were very close to 1.0 suggesting no effect for backbone type.

To evaluate clinical characteristics that might have functioned as moderators of efficacy, we examined whether or not outcomes varied based on history of prior adjuvant treatment and based on whether the primary tumor was still in place at metastatic diagnosis. Neither of these patient level variables was significantly associated with clinical outcome differences for the primary treatments. The interaction between tumor location (right vs. left sided) and biologic therapy

group (cetuximab vs. bevacizumab) was not statistically significant but showed a trend, which was further assessed in subset analyses. In unadjusted OS analyses from the start of first-line therapy among cetuximab-treated patients, there was a significant difference in the median OS in favor of patients with a left-sided as opposed to a right-sided primary tumor. Multivariate analyses were also consistent, showing lower survival for cetuximab-treated patients with right-sided tumor.

Similar findings were reported in the secondary analysis of the AIO KRK-0104 trial by von Einem et al. which showed that among mCRC patients with wild-type tumors treated in first line with cetuximab, those with left as opposed to right-sided tumors had significantly longer OS ($HR = 0.62$, $p = 0.016$) and PFS ($HR = 0.67$, $p = 0.02$) [18]. Those investigators concluded that left-sided tumor location may be a predictor of cetuximab efficacy. Similar results were reported by Venook et al. using evidence from CALGB 80405 where cetuximab-treated patients had significantly worse survival if their tumor was right (16.7 months) vs. left sided (36 months), $p < 0.0001$. Venook et al. also observed a significant but smaller effect in bevacizumab-treated patients favoring left (31.4 months)- vs. right (24.2 months)-sided tumor, $p = 0.01$. Possibly due to small sample size, our present investigation did not show a significant tumor side difference in bevacizumab-treated patients, though the effect observed in this study was also smaller than that reported by Venook et al. There appears to be a consistent pattern showing worse outcomes in right- vs. left-sided tumors among KRAS wild-type mCRC patients treated with cetuximab. This contrast can be interpreted as possibly favoring the use of cetuximab in left-sided tumors. However, the contrast might also be interpreted as not favoring use of cetuximab in right-sided tumors. Treatment effect of bevacizumab seems independent of tumor location, and bevacizumab-treated patients appear to have a smaller outcome difference in left- vs. right-sided tumors. Our Kaplan–

Meier analysis of cetuximab vs. bevacizumab in right-sided tumors only showed that median OS for patients with right-sided tumors was longer with bevacizumab (28.31 months, 95% CI 18.03, 33.27) than with cetuximab (14.10 months, 95% CI 10.06, 28.77), $p = 0.0167$. However, when other variables were taken into account in the comparable multivariate survival analysis of OS in right side only tumor patients, the regimen differences were not significant ($p = 0.1416$). Further studies with larger sample sizes are warranted to confirm findings in left- vs. right-sided tumors.

Our analysis of treatment sequences was intended to be descriptive in order to observe patterns of use for the two main biological agents over the first two lines of therapy where a new line of therapy was defined by disease progression in the first line. The results for PFS most likely reflected selection bias in that patients who appeared to do well on one agent tended to get that same agent in the second line following a disease progression.

This study has some limitations. For example, as a retrospective study the RAS testing was limited to KRAS rather than all or extended RAS determination for wild-type status [21–23]. Also, there could have been differences in prescribing patterns and reporting practices among different community oncology settings such that the treatment patterns observed are limited by region and participation in different reimbursement networks. For example, groups belonging to different reimbursement networks or practice organizations may have different standing clinical treatment pathways. Our multivariate analyses were also limited by the number of events and did not include such variables as socioeconomic status of patients [24] and comorbidity burden [25]. Finally, our analyses of treatment sequences were limited by the number of patients who had a disease progression ($n = 263$) and went on to a second line of treatment. Due to sample size limitations, it was not possible to assess the effects of different sequences of biologic agents on OS.

Conclusion

Two major findings from this research are important. First, this retrospective study conducted in community oncology patients suggested that the CALGB 80405 finding of comparable outcomes between bevacizumab-based regimens and cetuximab-based regimens in KRAS wild-type patients with mCRC in a randomized clinical trial is consistent with what was observed in a real-world setting. Second, the observation that community oncology patients treated with cetuximab-based regimens have worse outcomes if their tumor is right vs. left sided also provides real-world evidence consistent with that available from a clinical trial and points to an important consideration in clinical management of patients with mCRC.

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Compliance with Ethical Standards

Conflict of Interest AH reported no conflict of interest. SO and NS are employed by and own stock in Genentech, Inc. SSH and MW are consultants for Genentech. Genentech sponsored this study and provided financial support for the conduct of the research and for preparation of the article. Genentech collaborated on the design of the study, interpretation of the analyses, and in the decision to submit the article for publication, but did not have a direct role in data collection, data analysis, or writing of the report.

Research Involving Human Participants This research was reviewed and approved by IntegReview Institutional Review Board, in Austin, TX. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study, formal consent is not required.

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