Response to Biologics in Patients With Early-Onset Treatment-Naïve Metastatic Colorectal Cancer—An Aide et Recherche en Cancérologie Digestive Database Analysis

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ABSTRACT

PURPOSE Colorectal cancer (CRC) incidence and mortality have decreased since the 1970s, but the incidence in young adults (<50 years, named early-onset CRC [eoCRC]) has been increasing.

PATIENTS AND METHODS Individual patient data on 13,365 patients with metastatic CRC enrolled between 2000 and 2012 in 17 first-line randomized trials in the Aide et Recherche en Cancérologie Digestive database were pooled. The distribution of demographics, clinicopathologic features, biomarkers, and outcome data were summarized and compared by age groups. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier curves and Cox models stratified by treatment arms within studies, adjusting for potential confounders. Predictive value of age group on clinical outcomes was evaluated by testing interaction effect between treatment and age variables.

RESULTS Overall, 2,045 patients with eoCRC (median age, 42.5) and 11,320 patients with average-onset CRC (aoCRC; median age, 63.8) were included in this analysis. Within the eoCRC population, treatment with bevacizumab in addition to chemotherapy improved PFS (9.9 *v* 6.8 months; hazard ratio [HR], 0.66 [95% CI, 0.54 to 0.80]; $P < .0001$), which was similar to the findings in aoCRC population (9.4 *v* 7.3 months; HR, 0.73 [95% CI, 0.67 to 0.80]; $P < .001$; interaction $P = .5415$). However, epithelial growth factor receptor inhibitor (EGFRi) did not improve PFS in *RAS* wild-type (WT) patients with eoCRC who had left-sided primary tumors (8.3 *v* 8.9 months; HR, 1.20 [95% CI, 0.81 to 1.77]; $P = .36$), whereas EGFRi significantly improved PFS in the aoCRC population (9.9 *v* 8.5 months; HR, 0.74 [95% CI, 0.64 to 0.86]; $P < .0001$; interaction $P = .083$).

CONCLUSION Treatment-naïve patients with metastatic eoCRC appear to derive similar benefit from bevacizumab as patients with aoCRC. However, patients with eoCRC with left-sided RAS/RAF WT tumors did not appear to derive benefit from first-line EGFRi.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Colorectal cancer (CRC) is a major public health concern, being the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide, with more than 1.8 million new cases and 915,880 deaths reported in 2020.[1] In the United States, although the incidence of CRC has declined in recent years and mortality has decreased by 53% in male patients since 1980 and 59% in female patients since 1969, it remains a significant issue, ranking as the third most commonly diagnosed cancer and the third and fourth leading cause of cancer-related deaths for male and female patients, respectively.[2,3] Of particular concern is the increasing incidence of early-onset CRC (eoCRC), defined as a diagnosis of CRC in individuals age younger than 50 years. Data from the SEER registry show that the incidence of eoCRC has been rising since 1995 and is predicted to increase by 90% and 27.7% (for colon cancer)

CONTEXT

Key Objective
Are biologics beneficial for treatment-naïve patients with metastatic colorectal cancer (CRC) in early-onset CRC (eoCRC) compared with average-onset CRC (aoCRC)?

Knowledge Generated
Bevacizumab benefits patients with metastatic eoCRC and aoCRC. However, first-line epithelial growth factor receptor inhibitor only demonstrated survival benefit in patients with metastatic aoCRC.

Relevance *(A. Parikh)*
There is tremendous interest in eoCRC given the rising incidence and understanding the differences between treatment outcomes is important as we continue to understand the difference between early-onset and average-onset patients. This study evaluates the differences in outcomes between two biologics and can be used for further hypothesis generating research as to why there may be differences in responses.*

Plain Language Summary *(A. Parikh)*
When dividing patients with metastatic colon cancer by age (either older or younger than age 50 at time of diagnosis), the younger (early-onset) patients with tumors arising in the left colon did not derive as much benefit from antibodies targeting the epidermal growth factor receptor (which is also found on the skin, leading to rash as a frequent side effect).†

*Relevance section written by *JCO Oncology Advances* Associate Editor Aparna Parikh, MD.
†Plain Language Summary written by *JCO Oncology Advances* Associate Editor Aparna Parikh, MD.

and by 124% and 46.0% (for rectal cancer) by 2030 in the 20-34 and 35-49 year-old age groups, respectively.[4,5] This increase in eoCRC incidence has also been observed worldwide,[6,7] and currently, eoCRC is the second most common cancer, and the first and second leading cause of cancer-related mortality in the United States among men and women age <50 years.[3,6]

There is limited evidence to suggest that patients with locally advanced eoCRC may have similar clinical outcomes to patients with average-onset CRC (aoCRC; CRC diagnosed at age 50 years or older).[7,8] The data on metastatic eoCRC are limited and inconsistent. One early study showed comparable outcomes to aoCRC,[9] but a later study with a larger patient population reported that younger age, as a continuous variable, was associated with worse overall survival (OS) and progression-free survival (PFS).[10] Despite these findings, current treatment guidelines for metastatic CRC (mCRC) do not differentiate on the basis of age at disease onset. It is worth noting, however, that most clinical studies have only included a limited number of patients with eoCRC.[9,11]

In this study, we analyzed the response to treatment with bevacizumab or an epithelial growth factor receptor inhibitor (EGFRi) in treatment-naïve metastatic patients with eoCRC. Our data were drawn from the Aide et Recherche en Cancérologie Digestive (ARCAD) advanced CRC database, which included individual patient records from 11 first-line randomized bevacizumab-containing studies and eight first-line randomized EGFRi-containing studies.

PATIENTS AND METHODS

Study Population and Patient Characteristics

The ARCAD advanced CRC database, established in 2008, is a collection of individual patient-level data from phase III clinical trials in advanced CRC conducted worldwide.[10,12] The study proposal for this research was reviewed and approved by the Mayo Clinic Institutional Review Board and the ARCAD steering committee. The data used in this study were collected up until May 20, 2021.

In the ARCAD advanced CRC database, there are 16,886 patients enrolled in 17 first-line randomized trials that included bevacizumab and/or EGFRi agents. Among 17 studies, nine trials included bevacizumab only, six trials included EGFRi only, and two trials included both bevacizumab and EGFRi. Among the 17 trials, 3,521 patients were excluded because of receiving other biologic agents, receiving both bevacizumab and EGFRi, missing *KRAS* status while receiving EGFRi, or missing age data (Fig 1; Appendix Table A1). In both bevacizumab and EGFRi analyses, four trials each (2,928 and 3,773 patients, respectively), which included concurrently randomized treatment arms of the respective biologic agents plus chemotherapy versus chemotherapy only or chemotherapy plus placebo, were used for predictive analysis. The chemotherapy backbone in these trials included fluoropyrimidine alone or with oxaliplatin or irinotecan. The patients provided consent and were monitored regularly according to individual study protocols, with all

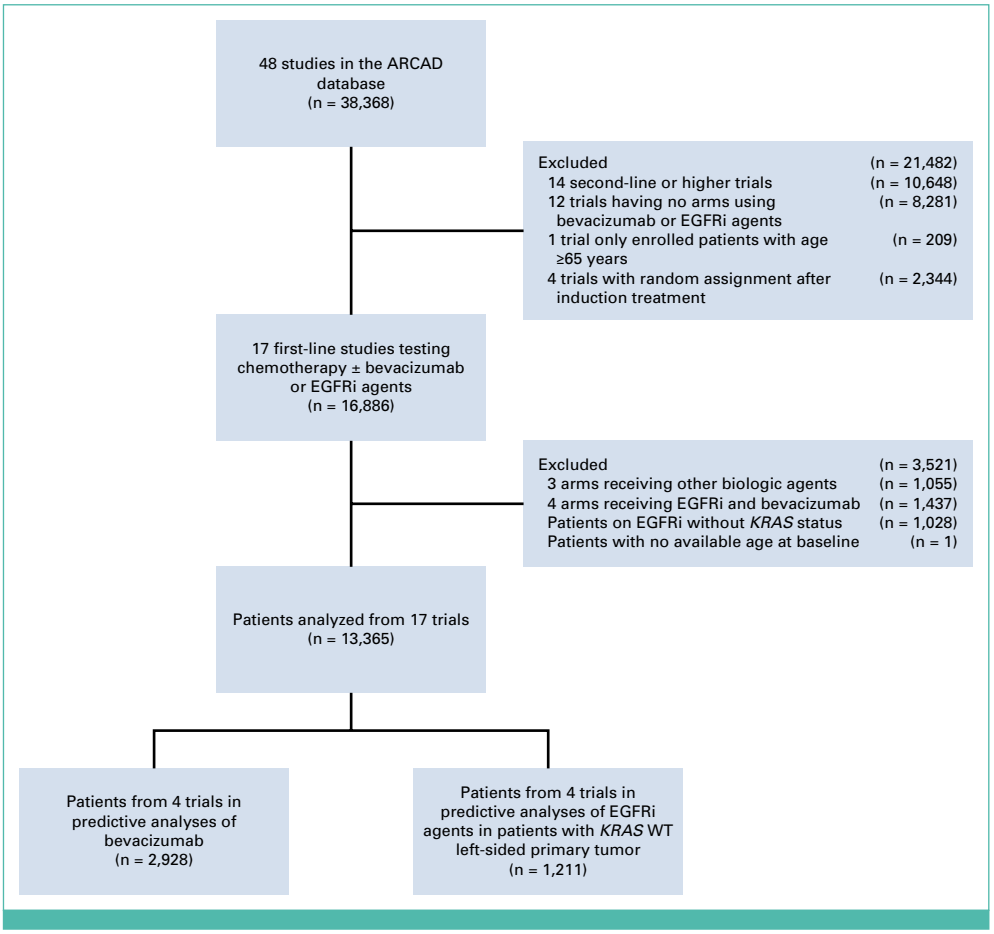

FIG 1. Study cohort diagram. ARCAD, Aide et Recherche en Cancérologie Digestive; EGFRi, epithelial growth factor receptor inhibitor; WT, wild type.

clinicopathologic variables including molecular markers collected at the time of enrollment.

Statistical Analysis

This study focused on PFS and OS, respectively, as the primary and secondary outcome measures for patients with mCRC who are undergoing first-line treatment. Because patients with mCRC usually have multiple lines of treatment affecting OS and this study focuses on effects of biologics in the treatment-naïve population, we chose PFS instead of OS to serve as the primary end point for this analysis. PFS was defined as the time from random assignment to the first occurrence of progression or death due to any cause, and OS was defined as the time from random assignment until death due to any cause. Demographic and clinical data, molecular biomarker status, and treatment-related information were compared between age groups (<50 *v* ≥50 years) using the Chi-squared test. The distributions of PFS and OS were estimated using Kaplan-Meier curves. To evaluate the prognostic value, all patients from the studies were pooled, and PFS/OS was compared between eoCRC and aoCRC groups using a Cox model stratified by treatment arm within trial, with and without adjusting patient demographics and disease characteristics. To assess the impact of eoCRC on the effect of bevacizumab or EGFRi treatment (ie, predictive values), only patients from four studies with concurrent randomized treatment arms with chemotherapy ± bevacizumab or chemotherapy ± an EGFRi were included. The predictive value was evaluated by testing the interaction term between treatment and age group in the stratified multivariable Cox model. The independent prognostic factors within the eoCRC subpopulation were explored using a backward elimination procedure in a multivariable Cox model. A two-sided $P < .05$ was considered statistically significant.

RESULTS

Comparisons of Clinical, Pathologic, and Molecular Characteristics Between Age Groups

Baseline characteristics of patients with eoCRC (n = 2,045) and aoCRC (n = 11,320) were compared (Table 1; Appendix Fig A1). The median age for the study population was 60.6 years. Patients with eoCRC had a median age of

42.5 years while the median age for patients with aoCRC was 63.8 years. Compared with aoCRC, eoCRC had a higher proportion of female patients (47.2% *v* 37.1%; *P* < .0001), better performance status (PS; Eastern Cooperative Oncology Group [ECOG] score 0: 60.1% *v* 55.1%; *P* < .0001), higher proportion of left-sided or rectal primary tumor (74.5% *v* 71.0%; *P* = .026), more likely had prior metastasectomy (14.1% *v* 9.7%; *P* = .0003), and had distant lymph node involvement (43.0% *v* 39.0%; *P* = .021). However, eoCRC was less likely to have lung metastatic disease (32.6% *v* 38.9%; *P* < .0001) and had fewer metastatic sites (number of sites 0-1: 43.1% *v* 40.0%; *P* = .026).

There were no significant differences in prior primary tumor resection, liver involvement, and peritoneal involvement, between patients with eoCRC and aoCRC. The limited molecular biomarker results showed that patients with eoCRC were less likely to have *KRAS* mutations (30.9% *v* 35.4%; *P* = .0026) but had similar *BRAF* mutation status compared with patients with aoCRC.

The Comparison of Clinical Outcomes (PFS and OS) Between Age Groups

The median follow-up time for these analyses was 32.9 months for PFS and 35.4 months for OS. In the univariable analyses, the median PFS was the same (8.7 months) in both eoCRC and aoCRC with a hazard ratio (HR) of 1.03 (95% CI, 0.97 to 1.08; *P* = .36; Fig 2A). The median OS was also comparable between eoCRC (21.5 months) and aoCRC (20.2 months) with a HR of 0.95 (95% CI, 0.89 to 1.01; *P* = .082; Fig 2B). These results remain after adjusting for sex, PS, number of metastasis, and chemotherapy backbone among all patients, patients treated with chemotherapy only, or chemotherapy plus bevacizumab (Table 2; Appendix Table A2). The results of adjusting additional disease characteristics and biomarkers are included in Appendix Table A3.

Predictive Value of Age at Onset for Bevacizumab and EGFRi Treatment

To evaluate the predictive value of age at onset for clinical benefits from adding biologics to chemotherapy, we divided these patients into two groups (bevacizumab study and EGFRi study). For bevacizumab study, only trials with concurrently randomized arms of bevacizumab versus no bevacizumab were included. A total of 2,928 patients from four trials were included in this predictive analysis. Adding bevacizumab treatment provided statistically significant PFS benefits for both eoCRC (mPFS increased from 6.8 months to 9.9 months; HR, 0.66 [95% CI, 0.54 to 0.80]; *P* < .0001) and aoCRC (mPFS increased from 7.3 months to 9.4 months; HR, 0.73 [95% CI, 0.67 to 0.80]; *P* < .0001). There was no significant evidence that the treatment effects of bevacizumab differed between age at onset groups (interaction *P* = .54; Figs 3A and 4). Adjusting for sex, PS, number of metastases, and chemotherapy backbone, the findings remain consistent with significant PFS benefits for both eoCRC (HR, 0.64 [95% CI, 0.53 to 0.78]; *P* < .0001) and aoCRC (HR, 0.73 [95% CI, 0.67 to 0.80]; *P* < .0001; interaction *P* = .41; Fig 4).

Four studies with total of 3,733 patients with randomized arms including chemotherapy with or without an EGFRi met the inclusion criteria to evaluate the predictive value of age at disease onset for clinical benefits from an EGFRi treatment in the first-line setting. According to previously published literature, survival benefits of EGFRi are limited to patients with left-sided *KRAS*^{WT} CRC;[13,14] we focused our predictive value analysis in this subgroup. In patients with *KRAS*^{WT} left-sided primary tumor, the addition of an EGFRi in patients with aoCRC (n = 1,049) significantly increased mPFS from 8.5 months to 9.9 months (HR, 0.74 [95% CI, 0.64 to 0.86]; *P* < .0001), whereas such benefit was not observed in the eoCRC population (n = 162), mPFS was 8.3 months with an EGFRi versus 8.9 months without an EGFRi (HR, 1.20 [95% CI, 0.81 to 1.77]; *P* = .3592). The interaction effect is moderately significant (interaction = 0.083; Figs 3B and 4). Adjusting for sex, PS, number of metastases, and chemotherapy backbone, the findings remain consistent with significant PFS benefits for aoCRC (HR, 0.81 [95% CI, 0.68 to 0.96]; *P* = .018) and no observed benefit for eoCRC (HR, 1.39 [95% CI, 0.77 to 2.51]; *P* = .27; interaction *P* = .17; Fig 4).

In the predictive analysis for OS, adding bevacizumab treatment did not provide statistically significant OS benefits for patients with eoCRC (mOS from 19.0 months to 18.7 months; HR, 1.00 [95% CI, 0.77 to 1.29]; *P* = .98), but did in patients with aoCRC (mOS from 17.8 months to 19.9 months; HR, 0.78 [95% CI, 0.69 to 0.88]; *P* < .0001) with an interaction *P* value of .12 (Fig 3C). Similarly, adding an EGFRi did not improve OS in patients with *KRAS*^{WT} left-sided primary tumor in eoCRC (mOS from 23.9 months to 21.8 months; HR, 1.06 [95% CI, 0.74 to 1.51]; *P* = .76), whereas OS benefit was detected in aoCRC (mOS from 20.2 months to 22.8 months; HR, 0.86 [95% CI, 0.75 to 0.98]; *P* = .028; Fig 3D). These results were mostly consistent in multivariable models where first-line treatment with bevacizumab in addition to chemotherapy showed a significant OS benefit for patients with aoCRC (HR, 0.79 [95% CI, 0.70 to 0.88]; *P* < .0001), but no significant OS benefit for patients with eoCRC (HR, 0.98 [95% CI, 0.76 to 1.27]; *P* = .88; interaction *P* = .22) and first-line treatment with EGFRi in addition to chemotherapy showed no OS benefit for either aoCRC (HR, 0.97 [95% CI, 0.81 to 1.15]; *P* = .70) or eoCRC (HR, 0.94 [95% CI, 0.52 to 1.68]; *P* = .83; interaction *P* = .76; Fig 4).

Prognostic Factors Within eoCRC Population

Multivariable analysis showed that poor PS (ECOG 1+; HR, 1.31 [95% CI, 1.17 to 1.48]; *P* < .0001) and ≥two metastatic sites (HR, 1.34 [95% CI, 1.19 to 1.51]; *P* < .0001) were associated with decreased PFS, whereas poor PS (ECOG 1+; HR, 1.37 [95% CI, 1.09 to 1.72]; *P* = .0061)and metastatic disease involving liver (HR, 1.40 [95% CI, 1.05 to 1.85]; *P* = .0209) were associated with decreased OS, and prior primary tumor

TABLE 1. Clinical, Pathological, and Molecular Characteristics

Baseline Characteristic	aoCRC (n = 11,320)	eoCRC (n = 2,045)	*P*
EGFRi, No. (%)			.0249[a]
No EGFRi	8,540 (75.4)	1,590 (77.8)	
EGFRi	2,780 (24.6)	455 (22.2)	
Bevacizumab, No. (%)			.0003[a]
No Bev	6,929 (61.2)	1,164 (56.9)	
Bev	4,391 (38.8)	881 (43.1)	
Age at enrollment			<.0001[b]
Mean (SD)	63.8 (7.78)	42.5 (6.25)	
Median (range)	64.0 (50.0-89.0)	44.0 (18.0-49.0)	
Sex, No. (%)			<.0001[a]
Female	4,199 (37.1)	965 (47.2)	
Male	7,121 (62.9)	1,080 (52.8)	
Performance score, No. (%)			<.0001[a]
0	6,225 (55.1)	1,228 (60.1)	
1+	5,081 (44.9)	814 (39.9)	
Missing	14	3	
Primary tumor sidedness, No. (%)			.026[a]
Rectum/left colon	4,190 (71.0)	717 (74.5)	
Right colon	1,708 (29.0)	245 (25.5)	
Missing	5,422	1,083	
Prior primary tumor surgery/resection, No. (%)			.5605[a]
No	1,159 (22.2)	165 (23.2)	
Yes	4,053 (77.8)	546 (76.8)	
Missing	6,108	1,334	
Prior metastatic surgery/resection, No. (%)			.0003[a]
No	4,391 (90.3)	593 (85.9)	
Yes	469 (9.7)	97 (14.1)	
Missing	6,460	1,355	
Metastatic site: liver, No. (%)			.1618[a]
No involvement	1,957 (22.8)	352 (22.3)	
Involvement	2,436 (28.4)	485 (30.8)	
Involvement and 1+ other site	4,183 (48.8)	740 (46.9)	
Missing	2,744	468	
Metastatic site: lung, No. (%)			<.0001[a]
No involvement	4,873 (60.1)	997 (67.4)	
Involvement	439 (5.4)	65 (4.4)	
Involvement and 1+ other site	2,790 (34.4)	418 (28.2)	
Missing	3,218	565	
Metastatic site: lymph nodes, No. (%)			.0213[a]
No involvement	4,457 (61.0)	692 (57.0)	
Involvement	236 (3.2)	49 (4.0)	
Involvement and 1+ other site	2,614 (35.8)	473 (39.0)	
Missing	4,013	831	
Metastatic site: peritoneal, No. (%)			.4776[a]
No involvement	5,007 (88.0)	747 (86.8)	
Involvement	76 (1.3)	15 (1.7)	
Involvement and 1+ other site	608 (10.7)	99 (11.5)	
Missing	5,629	1,184	

(continued on following page)

TABLE 1. Clinical, Pathological, and Molecular Characteristics (continued)

Baseline Characteristic	aoCRC (n = 11,320)	eoCRC (n = 2,045)	*P*
No. of metastatic sites, No. (%)			.0255[a]
0-1	3,216 (40.0)	658 (43.1)	
2+	4,818 (60.0)	869 (56.9)	
Missing	3,286	518	
Chemotherapy backbone, No. (%)			.3709[a]
Neither	366 (3.2)	57 (2.8)	
Irinotecan-based	3,242 (28.6)	610 (29.8)	
Oxaliplatin-based	7,504 (66.3)	1,334 (65.2)	
Both	208 (1.8)	44 (2.2)	
KRAS mutation status, No. (%)			.0026[a]
MT	2,505 (35.4)	354 (30.9)	
WT	4,564 (64.6)	793 (69.1)	
Missing	4,251	898	
BRAF mutation status, No. (%)			.6113[a]
MT	462 (9.0)	65 (8.4)	
WT	4,697 (91.0)	709 (91.6)	
Missing	6,161	1,271	
Combined *KRAS* and *BRAF* status, No. (%)			.3428[a]
Double-WT	3,042 (59.0)	478 (61.8)	
KRAS-MT	1,653 (32.1)	231 (29.8)	
BRAF-MT	462 (9.0)	65 (8.4)	
Missing	6,163	1,271	

Abbreviations: aoCRC, average-onset CRC; Bev, bevacizumab; CRC, colorectal cancer; EGFRi, epithelial growth factor receptor inhibitor; eoCRC, early-onset CRC; SD, standard deviation; WT, wild type.
[a]Chi-square *P* value.
[b]Kruskal-Wallis *P* value.

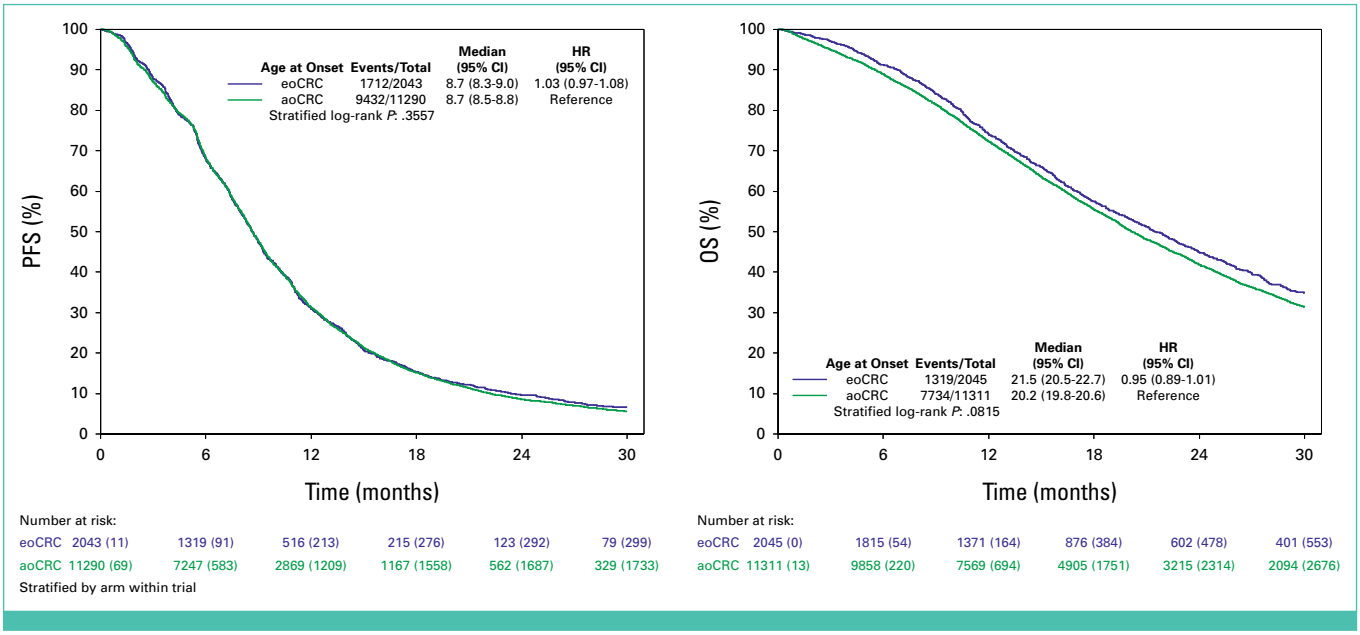

FIG 2. PFS and OS eoCRC compared with aoCRC. aoCRC, average-onset CRC; CRC, colorectal cancer; eoCRC, early-onset CRC; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

TABLE 2. Multivariable Analysis to Assess the Effects of eoCRC on PFS and OS

	PFS				OS			
Variable	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]
All patients								
Partially adjusted model[b]								
50 years or older	6,954/8,002	8.4 (8.3 to 8.5)	Reference		5,384/8,023	19.8 (19.4 to 20.2)	Reference	
Younger than 50 years	1,319/1,524	8.3 (8.0 to 8.7)	1.02 (0.96 to 1.08)	.5287	962/1,526	21.1 (19.3 to 22.5)	0.94 (0.88 to 1.01)	.0940
Chemotherapy alone								
Partially adjusted model[b]								
50 years or older	2,878/3,215	6.9 (6.6 to 7.1)	Reference		2,257/3,227	17.3 (16.7 to 17.9)	Reference	
Younger than 50 years	494/545	6.3 (5.9 to 6.9)	1.10 (1.00 to 1.21)	.0628	345/546	17.0 (15.6 to 19.4)	0.96 (0.86 to 1.08)	.4916
Bev + chemotherapy								
Partially adjusted model[b]								
50 years or older	2,639/3,215	10.2 (9.9 to 10.5)	Reference		1,794/3,221	22.8 (21.9 to 23.8)	Reference	
Younger than 50 years	578/698	10.2 (9.4 to 10.9)	1.02 (0.93 to 1.12)	.6567	398/698	23.6 (21.7 to 25.1)	1.02 (0.91 to 1.13)	.7695
EGFRi + chemotherapy								
Partially adjusted model[b]								
50 years or older	1,437/1,572	8.2 (7.9 to 8.6)	Reference		1,333/1,575	19.8 (19.0 to 20.9)	Reference	
Younger than 50 years	247/281	9.2 (8.6 to 10.1)	0.89 (0.77 to 1.02)	.0879	219/282	23.2 (19.7 to 27.7)	0.80 (0.69 to 0.93)	.0033

Abbreviations: Bev, bevacizumab; CRC, colorectal cancer; EGFRi, epithelial growth factor receptor inhibitor; eoCRC, early-onset CRC; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

[a]Covariate Wald *P* value; adjusted Kaplan-Meier Methods (direct adjustment method) stratified by arm within trial.

[b]Adjusted for sex, performance score, No. of metastatic sites, and chemotherapy backbone.

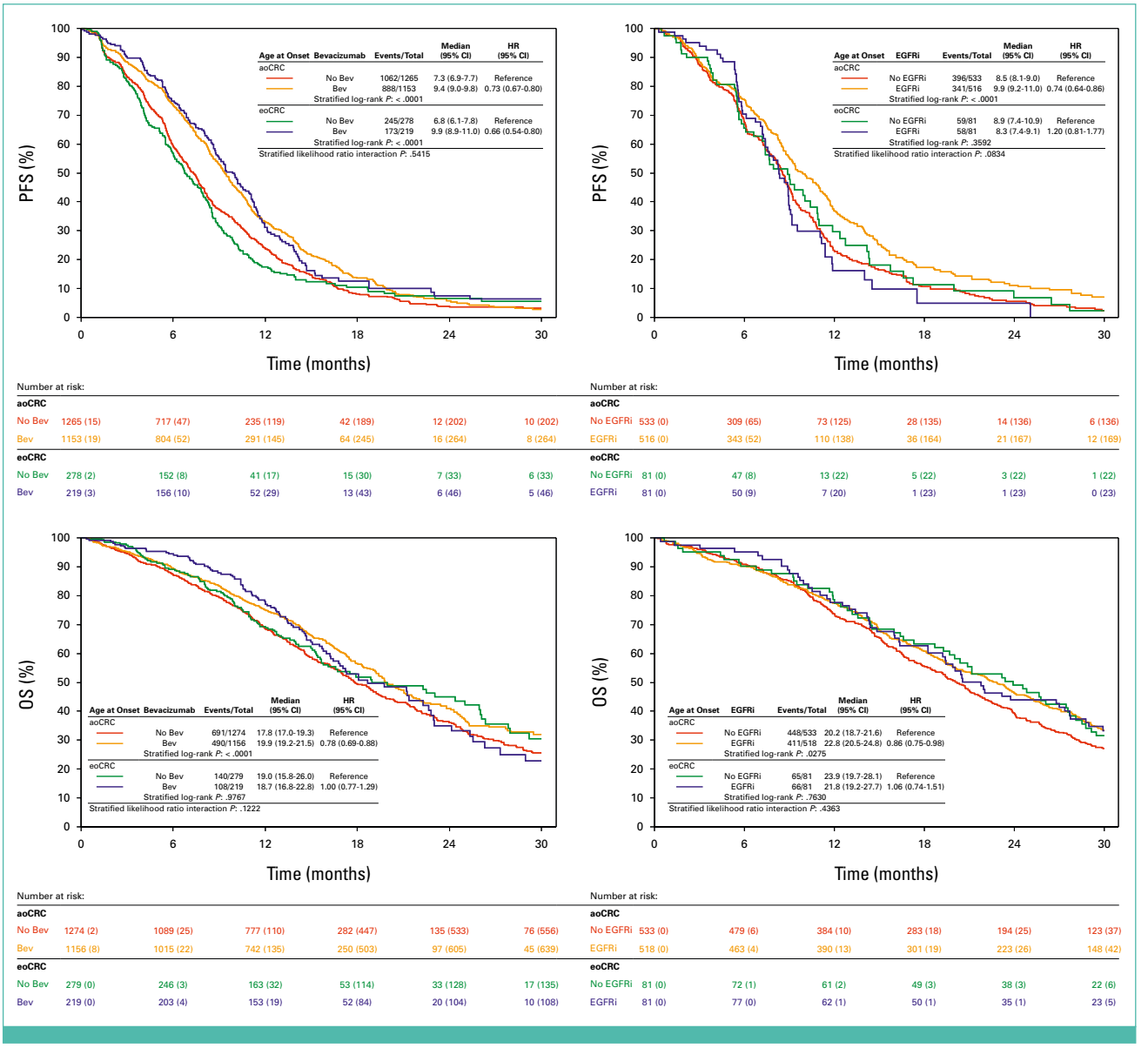

FIG 3. PFS and OS within eoCRC and aoCRC—with versus without Bev/EGFRi. Stratified by comparison unit; EGFRi models include only patients with *KRAS* WT left-sided primary tumor. aoCRC, average-onset CRC; Bev, bevacizumab; CRC, colorectal cancer; EGFRi, epithelial growth factor receptor inhibitor; eoCRC, early-onset CRC; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

resection was associated with increased OS (HR, 0.72 [95% CI, 0.56 to 0.94]; $P = .014$) in the eoCRC population (Table 3).

DISCUSSION

Our analysis of the ARCAD database with more than 13,000 patients with mCRC demonstrates that treatment-naïve patients with eoCRC derive benefit from bevacizumab treatment but no additional benefits from an EGFRi compared with aoCRC. To our knowledge, this is the first study evaluating the benefit of bevacizumab and an EGFRi in addition to systemic chemotherapy in a large sample size of eoCRC versus aoCRC.

The incidence of eoCRC has increased by 22% with a 13% increase in CRC-related mortality from 2000 to 2013 in the United States.[15] eoCRC has a strong birth cohort effect, which is defined as age-specific incidence and mortality changes that travel along with a particular generation. It has been shown that people born in the 1990s have double the risk of colon cancer (incidence rate ratio [IRR], 2.40 [95% CI, 1.11 to 5.19]) and quadruple the risk of rectal cancer (IRR, 4.32 [95% CI, 2.19 to 8.51]) when compared with people born in the 1950s.[16] The strong birth cohort effect suggests that exposomal elements play key roles in the eoCRC tumorigenesis although the exact etiology remains largely unknown.

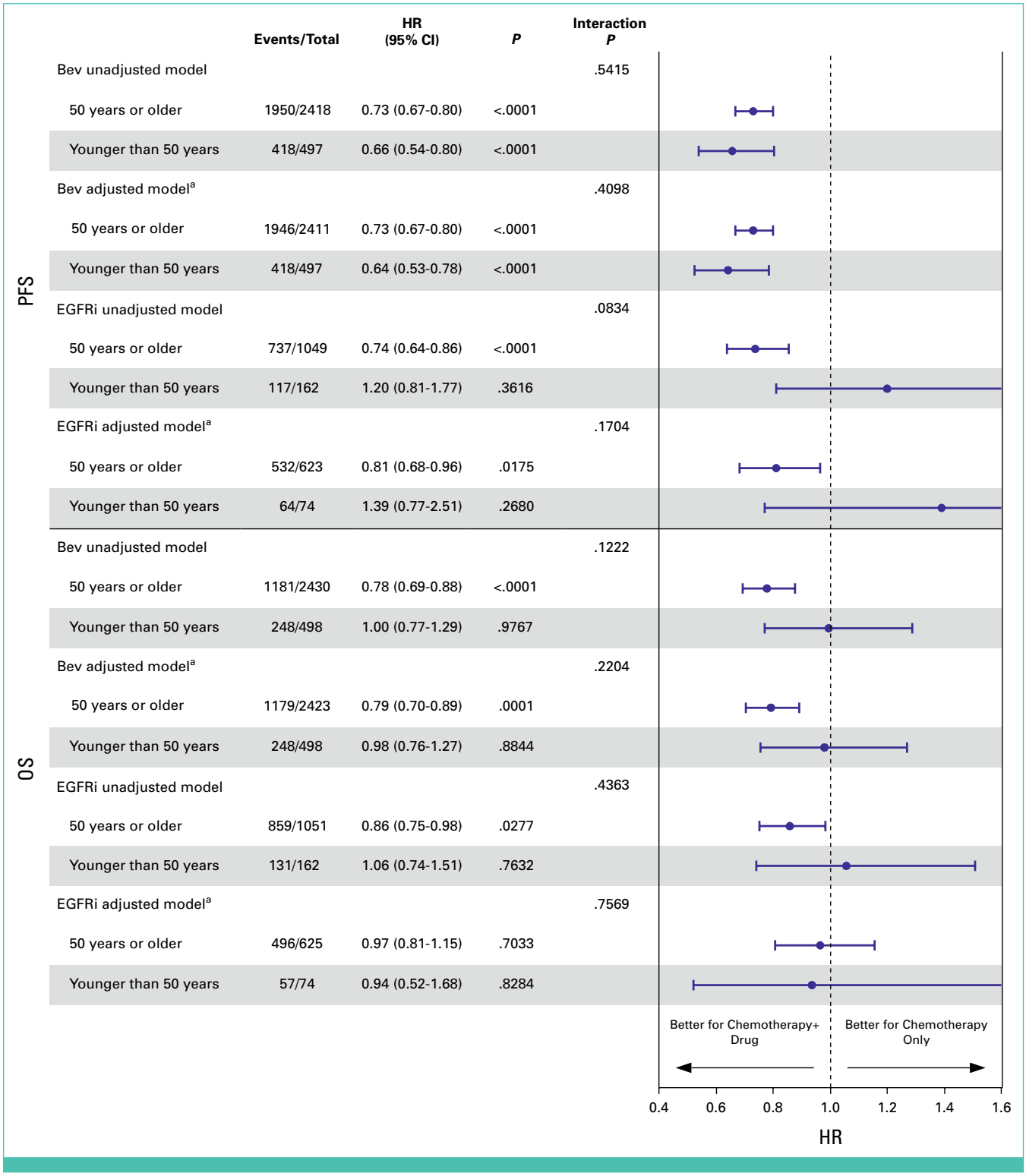

FIG 4. Multivariable analysis to assess age at disease onset as a predictive factor for PFS and OS. Stratified by comparison unit. EGFRi models include only patients with KRAS WT left-sided primary tumor. [a]Adjusted for sex, performance score, number of metastatic sites, and chemotherapy backbone. Bev, bevacizumab; EGFRi, epithelial growth factor receptor inhibitor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; WT, wild type.

eoCRC could be a different entity compared with aoCRC with its own epidemiologic, clinicopathologic, and molecular biologic features.[17,18] eoCRCs are more commonly seen in the rectum and left-sided colon with a high percentage of poorly differentiated histology with mucinous and signet ring cell features relative to aoCRC.[19,20] In this study, patients with

TABLE 3. Multivariable Analysis to Assess Prognostic Factors for PFS and OS Within eoCRC Population

Variable	Events/Total	Hazard Ratio (95% CI)	*P*
PFS model	1,319/1,524		
Performance score			<.0001[a]
0	774/906	Reference	
1+	545/618	1.31 (1.17 to 1.48)	<.0001[b]
No. of metastatic sites			<.0001[a]
0-1	535/657	Reference	
2+	784/867	1.34 (1.19 to 1.51)	<.0001[b]
OS model	376/552		
Performance score			.0061[a]
0	209/331	Reference	
1+	167/221	1.37 (1.09 to 1.72)	.0059[b]
Prior primary tumor surgery/resection			.0150[a]
No	123/146	Reference	
Yes	253/406	0.72 (0.56 to 0.94)	.0142[b]
Metastatic site: liver			.0176[a]
No involvement	73/118	Reference	
Involvement	303/434	1.40 (1.05 to 1.85)	.0209[b]

Abbreviations: CRC, colorectal cancer; eoCRC, early-onset CRC; OS, overall survival; PFS, progression-free survival.
[a]Stratified type 3 likelihood-ratio *P* value.
[b]Stratified covariate Wald *P* value; stratified by arm within trial.

eoCRC were associated with more left-sided colon and rectal primary (74.5% *v* 71.0%; *P* = .0261) compared with aoCRC. Female patients with eoCRC are more commonly seen relative to aoCRC (47.2% *v* 37.1%; *P* < .0001). This is consistent with the observation from a recent National Cancer Database analysis which showed female patients with eoCRC were 47.3%, whereas female patients with aoCRCs (defined as cancer diagnosis at age 51-55 years in that specific study) were 43.8% (*P* < .001).[21] More patients with eoCRC had metastasectomy before they start first-line systemic treatment (14.1% *v* 9.7%; *P* = .0003), which is also consistent with observations that patients with eoCRC usually get more aggressive treatment.[22]

Our study showed that patients with eoCRC had similar PFS and OS compared with patients with aoCRC. Although multiple statistically significant prognostic factors for PFS and OS were identified in the univariable and multivariable analyses, age at disease onset itself was not a statistically significant prognostic factor. This observation is consistent with several studies that showed eoCRC had similar or better clinical outcomes compared with aoCRC with same stage disease.[11,21,23]

Vascular endothelial growth factor (VEGF) family is an essential regulator of blood vessel growth, and VEGF-A constitutes the rate-limiting step in controlling blood vessel growth which includes tumor angiogenesis.[27] Bevacizumab is a humanized anti-VEGF monoclonal antibody that has strong antiangiogenic activity by neutralizing all VEGF-A isoforms and its proteolytic fragments.[28] Bevacizumab has demonstrated antitumor activity with clinical benefits including improved response rate, PFS, and OS in mCRC and has been widely used in mCRCs, including eoCRC since early 2000.[28,29] However, we do not have data regarding its activity in eoCRC. In this study, we found that treatment-naïve patients with eoCRC with metastatic disease derive significant benefits from bevacizumab with prolonged PFS compared with patients with aoCRC. It is noticed that bevacizumab did not demonstrate OS benefit in eoCRC; however, given this study only evaluates the role of bevacizumab in first-line treatment setting while OS can be strongly influenced by later-lines of treatment, PFS should be our main focus in this analysis. Further study showed there was no interaction between age at disease onset and benefits from bevacizumab treatment (both univariable and multivariable analyses).

EGFR is a member of the receptor tyrosine kinase family playing a critical role in CRC oncogenesis.[30] EGFRi such as panitumumab (a fully human monoclonal antibody) and cetuximab (a chimeric monoclonal antibody) demonstrated a clear clinical benefit in *RAS*^{WT} mCRC.[31] Growing evidence further suggests that clinical benefit derived from EGFRi is associated with primary tumor location. The phase III Cancer and Leukemia Group B/Southwest Oncology Group 80405 and FIRE 3 studies demonstrated that OS was prolonged with cetuximab in patients with left-sided primary disease and was further confirmed in other studies especially in the prospective phase III Paradigm study.[13,14,32-34] In this study, we focused our EGFRi analysis on patients with mCRC with *KRAS*^{WT} left-sided primary tumors.

EGFRi demonstrated significant PFS and OS benefits in aoCRC, but such benefit was not observed in eoCRC (the absolute mPFS and mOS decreased 0.6 and 2.1 months, respectively, when EGFRi was used in eoCRC). This unexpected finding suggests that we should carefully evaluate the role of EGFRi in eoCRC. However, this is an exploratory subgroup analysis with limited patients with eoCRC (n = 162); these data need to be validated in future analyses although a recent separate analysis using the real-world FLATIRON database reported similar result.[35] Further prospective studies are needed to confirm our observation and explore the potential causes that led to this observation that patients with eoCRC do not derive benefit from EGFRi when compared with patients with aoCRC. Because patients with eoCRC are more likely to have aggressive treatment including metastasectomy while study (such as the New Epoc trial) demonstrated perioperative EGFRi may lead to a significant survival disadvantage. This could be one explanation for our observation.[36] Another possibility is that human epidermal growth factor receptor 2 (HER2) amplification is rare in mCRC, and the prevalence is higher in *RAS/BRAF*^{WT} tumors.[37] HER2 amplification is a predictive marker for unresponsiveness to EGFRi in *RAS/BRAF*^{WT} tumors.[38-40] HER2 amplification status was not available in this study to explore the possibility that there is imbalanced HER2 amplification in eoCRC compared with aoCRC. Recent data suggested that molecular alterations in genes other than *RAS* and *BRAF* could also lead to primary resistance to EGFRi (a phenomenon called negative hyperselection).[41,42] Unfortunately, this study only has limited molecular biomarker data so we cannot explore the possibility that patients with eoCRC with *RAS/BRAF*^{WT} tumors may have higher prevalence of other gene mutations resulting in primary resistance to EGFRi. However, our separate analysis using the results from a next-generation sequencing panel test did not reveal any significant somatic mutations difference between eoCRC and aoCRC to support such a hypothesis.[43]

A key strength of this study is the large number of patients with prospectively collected individual outcome data from large clinical trials. However, this study has its limitations. First, all data were collected through each clinical trial, so the patient population is limited with selection bias secondary to each study-specific eligibility criteria. Second, some clinical characteristic information was unavailable (eg, primary tumor location, prior metastasectomy history) which limited our analysis power. Third, molecular profiles were only available in a small portion of the study population, and no germline test results were available which weaken the power of this analysis.

In conclusion, our study demonstrated that treatment-naïve patients with metastatic eoCRC derive similar benefit from bevacizumab treatment but not from an EGFRi compared with aoCRC. To our knowledge, this is the first study evaluating the clinical benefits of bevacizumab and EGFRi in eoCRC population.

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APPENDIX

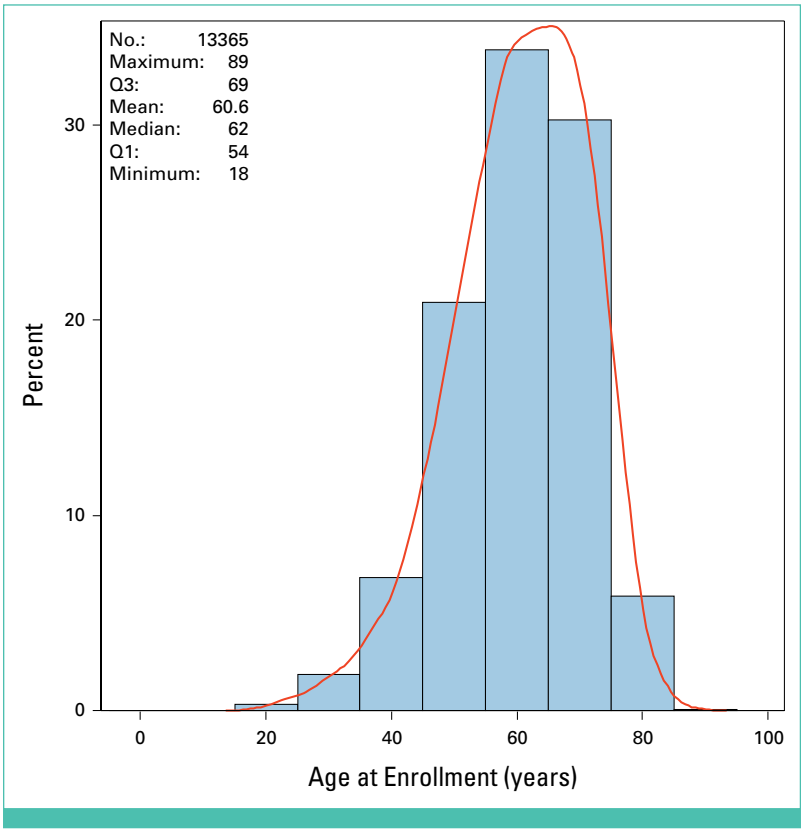

FIG A1. Age distribution of patients. Q, quaque.

TABLE A1. Clinical Trial Details

Study	Arm Index	Treatment	No.	*KRAS*	*KRAS*, %	eoCRC	eoCRC, %
BICC-C	2.01	FOLFIRI	144	0	0.00	22	15.28
BICC-C	2.02	mIFL	141	0	0.00	24	17.02
BICC-C	2.03	FOLFIRI + bevacizumab	57	0	0.00	12	21.05
BICC-C	2.04	mIFL + bevacizumab	60	0	0.00	13	21.67
BICC-C	2.05	CAPIRI	145	0	0.00	22	15.17
AVF2107g	3.01	IFL + placebo	411	0	0.00	87	21.17
AVF2107g	3.02	IFL + bevacizumab	402	0	0.00	68	16.92
AVF2107g	3.03	5FULV + bevacizumab	110	0	0.00	25	22.73
N016966	4.01	FOLFOX4	317	0	0.00	52	16.40
N016966	4.02	CAPOX	317	0	0.00	55	17.35
N016966	4.03	FOLFOX4 + placebo	351	0	0.00	62	17.66
N016966	4.04	CAPOX + placebo	350	0	0.00	70	20.00
N016966	4.05	FOLFOX4 + bevacizumab)	349	0	0.00	49	14.04
N016966	4.06	CAPOX + bevacizumab	350	0	0.00	59	16.86
PACCE (C249)	12.01	FOLFOX + bevacizumab	410	127	30.98	70	17.07
PACCE (C249)	12.03	FOLFIRI + bevacizumab	115	40	34.78	27	23.48
PRIME (C203)	13.01	FOLFOX4	550	219	39.82	83	15.09
PRIME (C203)	13.02	FOLFOX4 + panitumumab	546	221	40.48	67	12.27
CAIRO2	16.01	CAPOX + bevacizumab	378	122	32.28	40	10.58
CRYSTAL	18.01	FOLFIRI + cetuximab	529	212	40.08	80	15.12
CRYSTAL	18.02	FOLFIRI	533	183	34.33	80	15.01
COIN	19.01	Continuous FOLFOX	205	78	38.05	23	11.22
COIN	19.02	Continuous CAPOX	430	190	44.19	40	9.30
COIN	19.03	Continuous FOLFOX + cetuximab	218	101	46.33	23	10.55
COIN	19.04	Continuous CAPOX + cetuximab	441	196	44.44	43	9.75
COIN	19.05	Intermittent FOLFOX	225	83	36.89	15	6.67
COIN	19.06	Intermittent CAPOX	424	172	40.57	42	9.91
Macro	23.01	CAPOX + bevacizumab → CAPOX + bevacizumab	239	81	33.89	27	11.30
Macro	23.02	CAPOX + bevacizumab → bevacizumab	241	95	39.42	28	11.62
AGITG (MAX)	24.01	Capecitabine	156	0	0.00	14	8.97
AGITG (MAX)	24.02	Capecitabine + bevacizumab	157	0	0.00	18	11.46
FIRE II (CIOX)	29.01	CAPIRI + cetuximab	74	30	40.54	9	12.16
FIRE II (CIOX)	29.02	CAPOX + cetuximab	71	20	28.17	6	8.45
HORIZON III	33.01	mFOLFOX6 + bevacizumab	704	0	0.00	131	18.61
OPUS	34.01	FOLFOX + cetuximab	162	77	47.53	27	16.67
OPUS	34.02	FOLFOX	159	61	38.36	18	11.32
FIRE III	38.01	FOLFIRI + cetuximab	297	0	0.00	24	8.08
FIRE III	38.02	FOLFIRI + bevacizumab	295	0	0.00	26	8.81
TRIBE	39.01	FOLFIRI + bevacizumab	256	96	37.50	35	13.67
TRIBE	39.02	FOLFOXIRI + bevacizumab	252	102	40.48	44	17.46
COIN-B	43.01	Intermittent FOLFOX + intermittent cetuximab	102	24	23.53	13	12.75
COIN-B	43.02	Intermittent FOLFOX + cetuximab maintenance	106	15	14.15	14	13.21
CALGB-80405	48.01	Chemotherapy + bevacizumab	897	162	18.06	209	23.30
CALGB-80405	48.02	Chemotherapy + cetuximab	689	152	22.06	149	21.63

Abbreviations: 5FULV, fluorouracil and leucovorin; CAPIRI, capecitabine irinotecan; CAPOX, capecitabine and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOX4, fluorouracil and leucovorin bolus infusion followed by 22 hours continuous fluorouracil infusion on day 1 and 2 with oxaliplatin infusion on day 1 every 2 weeks; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; IFL, fluorouracil, leucovorin, and irinotecan infusion once a week with 4 weeks on and 2 week off schedule; mFOLFOX6, modified FOLFOX with fluorouracil and leucovorin bolus on day 1 followed by continuous fluorouracil infusion over 46 hours and oxaliplatin infusion on day 1; mIFL, modified irinotecan, fluorouracil, and leucovorin—weekly treatment with 4 weeks on and 2 weeks off schedule but fluorouracil was given weekly with continuous infusion over 6-8 hours.

TABLE A2. Univariable Analysis to Assess the Effects of a Variable on Time-to-Event Outcomes (with molecular biomarker included)

	PFS			OS		
Variable	Events/Total	HR (95% CI)	*P*	Events/Total	HR (95% CI)	*P*
Age at onset	11,144/13,333		.3581[a]	9,053/13,356		.0799[a]
50 years or older	9,432/11,290	Reference		7,734/11,311	Reference	
Younger than 50 years	1,712/2,043	1.03 (0.97 to 1.08)	.3529[b]	1,319/2,045	0.95 (0.89 to 1.01)	.0817[b]
Sex	11,144/13,333		.0040[a]	9,053/13,356		.0648[a]
Female	4,276/5,154	Reference		3,464/5,162	Reference	
Male	6,868/8,179	0.94 (0.91 to 0.98)	.0036[b]	5,589/8,194	0.96 (0.92 to 1.00)	.0631[b]
Performance score	11,134/13,319		<.0001[a]	9,045/13,342		<.0001[a]
0	6,038/7,435	Reference		4,611/7,448	Reference	
1+	5,096/5,884	1.35 (1.30 to 1.40)	<.0001[b]	4,434/5,894	1.61 (1.54 to 1.68)	<.0001[b]
Primary tumor sidedness	5,909/6,848		<.0001[a]	5,625/6,856		<.0001[a]
Rectum/left colon	4,193/4,898	Reference		3,962/4,904	Reference	
Right colon	1,716/1,950	1.26 (1.19 to 1.34)	<.0001[b]	1,663/1,952	1.38 (1.30 to 1.46)	<.0001[b]
Prior primary tumor surgery/ resection	5,333/5,909		<.0001[a]	4,332/5,917		<.0001[a]
No	1,247/1,319	Reference		1,106/1,322	Reference	
Yes	4,086/4,590	0.83 (0.77 to 0.89)	<.0001[b]	3,226/4,595	0.68 (0.64 to 0.74)	<.0001[b]
Prior metastatic surgery/ resection	4,986/5,533		<.0001[a]	4,019/5,541		<.0001[a]
No	4,524/4,969	Reference		3,711/4,976	Reference	
Yes	462/564	0.73 (0.66 to 0.81)	<.0001[b]	308/565	0.58 (0.51 to 0.65)	<.0001[b]
Metastatic site: liver	8,830/10,129		.0303[a]	6,860/10,152		<.0001[a]
No involvement	1,974/2,305	Reference		1,450/2,309	Reference	
Involvement	6,856/7,824	1.06 (1.01 to 1.11)	.0312[b]	5,410/7,843	1.21 (1.14 to 1.28)	<.0001[b]
Metastatic site: lung	8,333/9,573		<.0001[a]	6,413/9,581		.0027[a]
No involvement	4,986/5,863	Reference		3,871/5,870	Reference	
Involvement	3,347/3,710	1.15 (1.10 to 1.20)	<.0001[b]	2,542/3,711	1.08 (1.03 to 1.14)	.0026[b]
Metastatic site: lymph nodes	7,305/8,497		<.0001[a]	5,520/8,520		<.0001[a]
No involvement	4,300/5,129	Reference		3,115/5,148	Reference	
Involvement	3,005/3,368	1.16 (1.10 to 1.21)	<.0001[b]	2,405/3,372	1.31 (1.24 to 1.39)	<.0001[b]
Metastatic site: peritoneal	5,684/6,545		<.0001[a]	4,346/6,551		<.0001[a]
No involvement	4,967/5,748	Reference		3,742/5,753	Reference	
Involvement	717/797	1.27 (1.18 to 1.38)	<.0001[b]	604/798	1.44 (1.32 to 1.57)	<.0001[b]
No. of metastatic sites	8,280/9,537		<.0001[a]	6,351/9,560		<.0001[a]
0-1	3,198/3,866	Reference		2,315/3,874	Reference	
2+	5,082/5,671	1.31 (1.25 to 1.37)	<.0001[b]	4,036/5,686	1.51 (1.44 to 1.60)	<.0001[b]
Chemotherapy backbone	11,144/13,333		.9528[a]	9,053/13,356		.4378[a]
Neither	398/423	—		305/423	—	
Irinotecan-based	2,944/3,836	1.00 (0.89 to 1.13)	.9528[b]	2,826/3,852	0.95 (0.84 to 1.08)	.4451[b]
Oxaliplatin-based	7,589/8,823	Reference		5,791/8,829	Reference	
Both	213/251	—		131/252	—	
KRAS mutation status	6,955/8,205		<.0001[a]	6,365/8,212		<.0001[a]
MT	2,458/2,854	1.23 (1.17 to 1.30)	<.0001[b]	2,302/2,857	1.31 (1.24 to 1.38)	<.0001[b]
WT	4,497/5,351	Reference		4,063/5,355	Reference	
BRAF mutation status	5,024/5,922		<.0001[a]	4,799/5,929		<.0001[a]
MT	480/527	1.76 (1.60 to 1.94)	<.0001[b]	472/527	1.92 (1.75 to 2.12)	<.0001[b]
WT	4,544/5,395	Reference		4,327/5,402	Reference	

(continued on following page)

TABLE A2. Univariable Analysis to Assess the Effects of a Variable on Time-to-Event Outcomes (with molecular biomarker included) (continued)

	PFS			OS		
Variable	Events/Total	HR (95% CI)	*P*	Events/Total	HR (95% CI)	*P*
Combined *KRAS* and *BRAF* status	5,022/5,920		<.0001[a]	4,798/5,927		<.0001[a]
Double-WT	2,938/3,514	Reference		2,738/3,518	Reference	
KRAS-MT	1,604/1,879	1.32 (1.23 to 1.41)	<.0001[b]	1,588/1,882	1.40 (1.31 to 1.50)	<.0001[b]
BRAF-MT	480/527	1.94 (1.76 to 2.14)	<.0001[b]	472/527	2.15 (1.95 to 2.38)	<.0001[b]

Abbreviations: HR, hazard ratio; MT, mutated; OS, overall survival; PFS, progression-free survival; WT, wild type.
[a]Stratified type 3 likelihood-ratio *P* value.
[b]Covariate Wald *P* value; stratified by arm within trial.

TABLE A3. Additional Multivariable Models

	PFS				OS			
Variable	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]
All patients								
Middle adjusted model[b]								
50 years or older	4,077/4,413	8.3 (8.1 to 8.5)	Reference		3,600/4,420	19.9 (19.4 to 20.6)	Reference	
Younger than 50 years	670/744	8.5 (7.8 to 9.0)	1.00 (0.92 to 1.08)	.9118	568/745	22.4 (20.6 to 23.9)	0.90 (0.82 to 0.98)	.0177
Middle adjusted model w/ biomarkers[c]								
50 years or older	2,981/3,252	8.0 (7.8 to 8.3)	Reference		2,661/3,258	19.1 (18.2 to 19.6)	Reference	
Younger than 50 years	424/475	7.7 (7.3 to 8.6)	1.02 (0.92 to 1.13)	.6890	365/476	20.6 (17.8 to 22.8)	0.89 (0.80 to 1.00)	.0512
Fully adjusted model[d]								
50 years or older	2,298/2,407	7.0 (6.7 to 7.4)	Reference		2,001/2,412	16.7 (16.2 to 17.1)	Reference	
Younger than 50 years	249/264	6.9 (6.2 to 8.3)	0.98 (0.86 to 1.12)	.7787	209/265	18.3 (14.7 to 22.0)	0.84 (0.73 to 0.98)	.0214
Fully adjusted model w/ biomarkers[e]								
50 years or older	1,963/2,053	6.9 (6.6 to 7.4)	Reference		1,732/2,057	16.5 (15.8 to 17.0)	Reference	
Younger than 50 years	207/217	6.6 (6.1 to 8.2)	0.97 (0.84 to 1.12)	.6592	181/218	15.7 (13.4 to 19.9)	0.89 (0.76 to 1.05)	.1638
Chemotherapy alone								
Middle adjusted model[b]								
50 years or older	1,350/1,434	6.2 (6.0 to 6.3)	Reference		1,221/1,435	16.4 (15.7 to 17.0)	Reference	
Younger than 50 years	139/152	5.8 (5.6 to 6.7)	1.06 (0.89 to 1.27)	.4866	124/152	15.7 (12.6 to 21.3)	0.88 (0.73 to 1.07)	.1963
Middle adjusted model w/ biomarkers[c]								
50 years or older	1,206/1,287	6.2 (6.1 to 6.4)	Reference		1,104/1,288	16.3 (15.5 to 16.9)	Reference	
Younger than 50 years	125/137	5.8 (5.6 to 6.7)	1.04 (0.86 to 1.25)	.7094	115/137	13.3 (12.3 to 19.6)	0.92 (0.75 to 1.12)	.3961
Fully adjusted model[d]								
50 years or older	1,263/1,294	6.2 (6.0 to 6.3)	Reference		1,111/1,295	16.2 (15.3 to 16.9)	Reference	
Younger than 50 years	129/134	5.8 (5.5 to 6.5)	1.05 (0.87 to 1.26)	.5933	110/134	15.3 (12.6 to 20.6)	0.88 (0.72 to 1.08)	.2243
Fully adjusted model w/ biomarkers[e]								
50 years or older	1,119/1,147	6.2 (6.1 to 6.4)	Reference		994/1,148	16.0 (15.1 to 16.7)	Reference	
Younger than 50 years	115/119	5.8 (5.6 to 6.5)	1.02 (0.84 to 1.24)	.8378	101/119	13.3 (12.3 to 19.6)	0.93 (0.76 to 1.15)	.5110
Bev + chemotherapy								
Middle adjusted model[b]								
50 years or older	1,318/1,437	10.6 (10.2 to 11.0)	Reference		1,072/1,440	24.9 (23.7 to 26.0)	Reference	
Younger than 50 years	291/320	10.7 (9.5 to 11.5)	1.04 (0.91 to 1.18)	.5926	230/320	25.6 (24.1 to 28.0)	0.99 (0.85 to 1.14)	.8683

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TABLE A3. Additional Multivariable Models (continued)

	PFS				OS			
Variable	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]	Events/Total	Median (95% CI)	HR (95% CI)	*P*[a]
Middle adjusted model w/ biomarkers[c]								
50 years or older	681/759	11.1 (10.6 to 11.9)	Reference		530/761	26.3 (25.2 to 28.7)	Reference	
Younger than 50 years	133/149	10.3 (9.2 to 11.2)	1.14 (0.94 to 1.38)	.1713	98/149	26.1 (23.6 to 32.8)	1.05 (0.84 to 1.31)	.6878
Fully adjusted model[d]								
50 years or older	365/400	9.4 (8.8 to 10.0)	Reference		284/401	19.7 (17.5 to 22.0)	Reference	
Younger than 50 years	44/50	10.4 (9.1 to 12.9)	0.92 (0.66 to 1.26)	.5887	31/50	23.0 (18.4 to 36.1)	0.76 (0.52 to 1.11)	.1527
Fully adjusted model w/ biomarkers[e]								
50 years or older	182/203	10.6 (9.4 to 12.6)	Reference		139/203	21.3 (17.5 to 25.4)	Reference	
Younger than 50 years	16/19	11.7 (9.1 to 20.7)	0.86 (0.50 to 1.46)	.5756	12/19	19.9 (14.7 to NE)	0.97 (0.52 to 1.82)	.9313
EGFRi + chemotherapy								
Middle adjusted model[b]								
50 years or older	1,409/1,542	8.1 (7.9 to 8.5)	Reference		1,307/1,545	19.7 (18.9 to 20.8)	Reference	
Younger than 50 years	240/272	9.1 (8.2 to 10.0)	0.90 (0.78 to 1.04)	.1460	214/273	23.2 (19.4 to 27.7)	0.81 (0.70 to 0.94)	.0064
Middle adjusted model w/ biomarkers[c]								
50 years or older	1,094/1,206	7.9 (7.5 to 8.3)	Reference		1,027/1,209	18.5 (17.1 to 19.6)	Reference	
Younger than 50 years	166/189	8.9 (7.6 to 9.5)	0.93 (0.79 to 1.10)	.4104	152/190	22.8 (18.2 to 27.4)	0.80 (0.67 to 0.95)	.0105
Fully adjusted model[d]								
50 years or older	670/713	7.8 (7.1 to 8.3)	Reference		606/716	16.5 (14.9 to 17.6)	Reference	
Younger than 50 years	76/80	8.9 (7.1 to 10.0)	0.89 (0.69 to 1.14)	.3526	68/81	22.0 (14.3 to 27.7)	0.80 (0.62 to 1.03)	.0877
Fully adjusted model w/ biomarkers[e]								
50 years or older	662/703	7.8 (7.1 to 8.2)	Reference		599/706	16.5 (14.9 to 17.4)	Reference	
Younger than 50 years	76/79	8.9 (6.6 to 10.0)	0.89 (0.69 to 1.14)	.3638	68/80	19.7 (14.3 to 27.4)	0.81 (0.62 to 1.05)	.1131

Abbreviations: Bev, bevacizumab; EGFRi, epithelial growth factor receptor inhibitor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

[a]Covariate Wald *P* value; adjusted Kaplan-Meier methods (direct adjustment method) stratified by arm within trial.

[b]Adjusted for sex, performance score, sidedness, liver and lung metastatic sites, No. of metastatic sites, and chemotherapy backbone.

[c]Adjusted for sex, performance score, sidedness, liver and lung metastatic sites, No. of metastatic sites, chemotherapy backbone, *KRAS*, and *BRAF* status.

[d]Adjusted for sex, performance score, sidedness, prior primary tumor surgery/resection, prior metastatic surgery/resection, liver, lung, peritoneal, and lymph node metastatic sites, No. of metastatic sites, and chemotherapy backbone.

[e]Adjusted for sex, performance score, sidedness, prior primary tumor surgery/resection, prior metastatic surgery/resection, liver, lung, peritoneal, and lymph node metastatic sites, No. of metastatic sites, chemotherapy backbone, *KRAS*, and *BRAF* status.