Original Study

ACORN: Observational Study of Bevacizumab in Combination With First-Line Chemotherapy for Treatment of Metastatic Colorectal Cancer in the UK

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Abstract

Real-world data from 714 patients who received bevacizumab with first-line chemotherapy were collected to understand why survival in metastatic colorectal cancer is worse in the United Kingdom than in other countries. Shorter total chemotherapy duration (8.1 months) and less frequent use of bevacizumab provided after disease progression (13.9% of patients) may have contributed to the poorer overall survival (17.8 months) observed in the UK.

Introduction: Survival in metastatic colorectal cancer is worse than expected in the United Kingdom. Real-world data are needed to better understand UK-specific treatment practices that may explain this. **Patients and Methods:** The Avastin ColORectal Non-interventional (ACORN) study is a multicenter, prospective, UK-based, observational, phase 4 study (ClinicalTrials.gov, NCT01506167) that recruited patients with metastatic colorectal cancer scheduled to receive bevacizumab in combination with first-line chemotherapy as part of routine clinical practice. Primary end points included progression-free survival, overall survival (OS), serious adverse events (AEs), and grade 3 to 5 bevacizumab-related AEs. **Results:** A total of 714 patients were recruited between August 30, 2012, and February 4, 2014. Median follow-up was 16.4 months. Median first-line chemotherapy duration was 5.6 months, with capecitabine/oxaliplatin (265 [37.1%]) being the most common regimen. Median total chemotherapy duration was 8.1 months and did not vary by geographic location in the UK. Median progression-free survival (95% confidence interval) was 8.7 (8.2-9.1) months, and median OS was 17.8 (16.1-19.3) months. There was no significant difference in efficacy by chemotherapy regimen administered. Ninety-nine patients (13.9%) received bevacizumab after disease progression. The safety profile of bevacizumab was consistent with previous studies. **Conclusion:** ACORN provided evidence that there were no clear differences observed in outcomes between bevacizumab with capecitabine-based chemotherapy and fluorouracil-based regimens, and confirmed the safety profile of bevacizumab in a real-world UK-based population. The lower-than-expected OS is likely due to the short total chemotherapy duration, less frequent use of bevacizumab after disease progression, and higher rates of in-situ primary tumors.

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Introduction

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality, with an estimated 1.7 million cases and 832,000 deaths occurring worldwide in 2015.[1,2] It is the third most common type of cancer in men and the second most common in women.[1]

Patients presenting with early-stage CRC may be cured by surgery. However, almost 50% of patients will experience relapse and develop metastatic CRC (mCRC), and approximately 25% will present with metastases at the time of initial diagnosis.[3] Among metastatic patients, curative resection is only possible in a small proportion with limited disease.[3] For most patients, the predominant treatment modality is palliative systemic chemotherapy to improve overall survival (OS) while preserving quality of life (QoL).[3] The addition of antiangiogenic agents, epidermal growth factor inhibitors, and tyrosine kinase inhibitors to chemotherapy as well as the sequential use of all available treatments has contributed to incremental gains in survival, with median OS currently reaching 2 to 3 years.[3-8]

Bevacizumab is a recombinant humanized monoclonal antibody that was first approved for use in mCRC in 2004, in combination with fluoropyrimidine-based chemotherapy.[9] This angiogenesis inhibitor prevents binding of vascular endothelial growth factor A to its receptors, VEGFR-1 and VEGFR-2, leading to beneficial changes in tumor vasculature and ultimately inhibition of tumor growth.[10,11] First- and second-line bevacizumab plus chemotherapy improves progression-free survival (PFS) and OS in patients with advanced CRC or mCRC compared to chemotherapy alone.[12-14] Frequently reported adverse events (AEs) associated with bevacizumab include hypertension, proteinuria, impaired wound healing, gastrointestinal (GI) perforation, hemorrhage, and arterial thromboembolism.[3,10,12] Most AEs are generally considered manageable.[15]

In addition to randomized controlled trials, the evidence base supporting use of bevacizumab in combination with chemotherapy in first-line mCRC includes several observational studies that have provided real-world data. These include the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) study, the Bevacizumab Expanded Access Trial (BEAT), and the Avastin Registry—Investigation of Effectiveness and Safety (ARIES) study.[16-18] BRiTE and ARIES were conducted in the United States, whereas BEAT was conducted in 41 countries with ~ 5% of the patients recruited from the United Kingdom. Therefore, results from these studies may not be truly applicable to UK practice, where use of capecitabine-based chemotherapy is more common than in many other countries and survival in patients with CRC is consistently worse.[19-22] An estimated 1700 excess deaths occur in England each year compared to the best-performing European nations.[22]

The Avastin ColORectal Non-interventional (ACORN) study aimed to assess the outcomes and safety of bevacizumab in mCRC according to first-line chemotherapy regimen in a real-world setting in the UK, and to provide QoL data.

Patients and Methods

Study Design and Patients

ACORN is a real-world, multicenter, prospective, observational, phase 4 study (NCT01506167). Study centers were chosen to be representative of mCRC treatment across the UK; for center selection, feasibility was undertaken by the sponsor, and the centers were selected because of their ability to recruit and undertake the study. Given that the study was designed to provide real-world data, no adjustments to enrollment by baseline patient characteristics were made.

ACORN was designed to follow patients diagnosed with mCRC who were aged ≥ 18 years, who had provided written informed consent, and who had received no previous palliative systemic treatment for advanced disease. All patients had pathologic confirmation of CRC from either primary or metastatic sites. Patients were scheduled to receive bevacizumab in combination with a first-line standard-of-care chemotherapy regimen as part of routine clinical practice. Bevacizumab had to have been initiated at the same time as the first-line chemotherapy regimen or within 3 months, if delayed administration of bevacizumab was part of the standard of care or resulted from delayed access to bevacizumab. Patients were excluded if they were currently receiving bevacizumab treatment or were undergoing treatment with an investigational, first-line mCRC chemotherapy regimen. The treating physician was to adhere to the contraindications, warnings, and precautions for use of bevacizumab specified in the summary of product characteristics.[10] The study was overseen by a steering committee comprising 7 experts in the treatment of advanced CRC from different regions in the UK.

ACORN was conducted in accordance with the guidelines for Good Pharmacoepidemiology Practices and Good Clinical Practice, as well as the Declaration of Helsinki. It was approved by a central review board and local independent ethics committees.

Study End Points

A full list of study end points can be found in Supplemental Table 1 in the online version. Primary efficacy end points were PFS and OS. Primary safety end points were all serious AEs (SAEs) and bevacizumab-related grade 3 to 5 AEs. QoL was included as a secondary outcome end point (assessed by the 5-level EQ-5D questionnaire [EQ-5D-5L]). Secondary safety end points included AEs of special interest (AESI) for bevacizumab (all grades: GI perforation, fistulae and abscesses, thromboembolic events [arterial and venous], congestive heart failure, bleeding other than mucocutaneous hemorrhage, reversible posterior leukoencephalopathy syndrome, osteonecrosis of the jaw, neutropenia and febrile neutropenia, microangiopathic hemolytic anemia, hypersensitivity and infusion reaction, and ovarian failure). Other secondary safety end points were grade 2 to 5 AESIs (hypertension, wound healing complications, mucocutaneous bleeding, proteinuria); any-grade AEs leading to modification or discontinuation of treatment with bevacizumab; and hospitalizations for treatment-related AEs.

Other end points were as follows: treatment duration and reason for discontinuation of treatment with bevacizumab; first-line chemotherapy regimens used in combination with bevacizumab for the treatment of mCRC in the UK; and further treatments of mCRC and their outcomes.

Data Collection

Patient demographic data, disease characteristics before treatment, and clinical information during the study were extracted from

medical records and captured using an electronic data system. Data on QoL were collected using self-administered questionnaires every 3 to 4 months from start of treatment with chemotherapy and bevacizumab until 6 months (inclusive) after disease progression. These questionnaires were not mandatory and were subject to specific informed consent.

The duration of observation for each patient was from the initiation of bevacizumab therapy and first-line chemotherapy. No study-specific visits or evaluations were conducted. Evaluation for treatment outcomes was conducted according to the physician's standard practice (expected to be every 3 to 4 months) until disease progression. Nonserious AEs were documented by study personnel, while SAEs were reported to the study sponsor within 24 hours. All AEs and AESIs continued to be collected for $\geq$ 28 days and up to 6 months, respectively, after the last administration of bevacizumab.

Statistical Analyses

No predefined hypotheses were set for the magnitude of outcomes of any regimen, or for the frequency or severity of AEs. The sample size was set at approximately 700 patients to assess relatively uncommon safety events. It was based on appropriate comparisons with results from registration trials of bevacizumab in first-line mCRC and similar observational studies performed in other countries. Selection bias was minimized by the use of a large number of centers and minimal inclusion/exclusion criteria to give an accurate representation of mCRC treatment in the general UK population. In addition, collection of data from medical records was expected to minimize bias.

Summary statistics were used to describe baseline characteristics. PFS was defined as the time from the start of first-line therapy to investigator-assessed disease progression or death from any cause. If a patient had not had an event, PFS was censored at the date when the patient was last known to be free of disease progression. OS was defined as the time from the start of first-line therapy to death by any cause. If a patient had not died, OS was censored at the date they were last known to be alive. PFS and OS were summarized for the overall study population and concomitant mCRC first-line chemotherapy regimen for all enrolled patients and assessed by Kaplan-Meier methodology. There was no imputation for missing data. If, for example, a data point was missing when calculating a mean, then that mean was calculated using the remaining data points. A multivariable Cox proportional hazard regression model was used to model PFS and OS in terms of baseline and chemotherapy and bevacizumab administration covariates.

Survival beyond progression was defined as the time from the date of first progression to death from any cause. Survival beyond progression according to whether bevacizumab was provided at or after progression was summarized for all patients with an available investigator-specified progression date and was assessed by Kaplan-Meier methodology.

The median total duration of chemotherapy was calculated for each treating center. The quartiles of these medians were computed as follows: quartile 1, $\leq$ 6.2 months; quartile 2, $>$ 6.2 to $\leq$ 8.4 months; quartile 3, $>$ 8.4 to $\leq$ 10.8 months; and quartile 4, $>$ 10.8 months. Centers were grouped according to the quartile in which their median duration fell: $\leq$ 25th percentile; $>$ 25th to $\leq$ 50th percentile; $>$ 50th to $\leq$ 75th percentile; and $>$ 75th percentile. Data from centers in the same quartile were pooled, and PFS and OS were calculated per quartile.

For EQ-5D-5L, responses of severity to each of the dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), the visual analog score, derived values for weighted index score, and crosswalk index score were summarized at baseline and then every 3 months.

AEs were coded according to the current Medical Dictionary for Regulatory Activities and were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0. A treatment-emergent AE (TEAE) was defined as one that started or worsened after the start of bevacizumab administration.

Statistical analysis was performed by SAS 9.2 (SAS Institute, Cary, NC). All statistical tests were performed assuming a significance level of $P < .05$.

The study database is owned by Roche Products Limited (Welwyn Garden City, UK). Statistical analysis was undertaken by Syne qua non Ltd (Diss, UK) on behalf of Roche Products Limited.

Results

Patient Enrollment

ACORN recruited 714 patients from across 42 centers in the UK between August 30, 2012, and February 4, 2014, with a minimum of 2 and a maximum of 95 patients per center. All enrolled patients were included in the analyses unless otherwise specified.

First-Line Chemotherapy Regimens

First-line chemotherapy regimens administered with bevacizumab were as follows: capecitabine/oxaliplatin (265 [37.1%]); fluorouracil/folinic acid/oxaliplatin (204 [28.6%]); capecitabine (107 [15.0%]); fluorouracil/folinic acid/irinotecan (101 [14.1%]); capecitabine/irinotecan (23 [3.2%]); fluorouracil with or without folinic acid (6 [0.8%]); and other (8 [1.1%]). Study results are presented for the overall patient population and the 4 most common first-line chemotherapy regimens.

Patient Cohort

Baseline demographics were consistent with previous observational trials of mCRC (Table 1).[16-18] A total of 424 patients (59.4%) had stage IV disease at first diagnosis. A total of 652 patients (91.3%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at study entry.

Older patients (those aged $>$ 75 years) tended to receive capecitabine alone. A total of 64 patients (59.8%) receiving capecitabine monotherapy were $>$ 75 years old (median age, 78.0 years), and 19 (17.8%) had a worse baseline ECOG PS of $\geq$ 2. A higher proportion of patients receiving fluorouracil/folinic acid/irinotecan had nonmetastatic disease at initial diagnosis than those receiving the other 3 most common chemotherapy regimens. In addition, more patients in this group had previously had their primary tumor resected and received previous systemic treatment in the neoadjuvant/adjuvant setting.

Most patients (436 [61.1%]) had ongoing medical conditions at baseline (Table 1 and Supplemental Table 2 in the online version). However, the proportion was higher for capecitabine/oxaliplatin

Table 1 Baseline Patient Demographics and Disease Characteristics, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Baseline Characteristic	Capecitabine, Oxaliplatin (N = 265)	Fluorouracil, Folinic Acid, Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil, Folinic Acid, Irinotecan (N = 101)	Overall (N = 714)
Age (y), median (range)	66.0 (26-85)	63.0 (31-82)	78.0 (40-89)	65.0 (30-80)	66.0 (26-89)
Age Group					
≤ 65 y	131 (49.4)	121 (59.3)	17 (15.9)	54 (53.5)	345 (48.3)
> 65 to ≤ 75 y	101 (38.1)	56 (27.5)	26 (24.3)	39 (38.6)	231 (32.4)
> 75 y	33 (12.5)	27 (13.2)	64 (59.8)	8 (7.9)	138 (19.3)
Sex					
Male	158 (59.6)	121 (59.3)	54 (50.5)	52 (51.5)	409 (57.3)
Female	107 (40.4)	83 (40.7)	53 (49.5)	49 (48.5)	305 (42.7)
ECOG PS					
0	127 (47.9)	86 (42.2)	26 (24.3)	48 (47.5)	302 (42.3)
1	123 (46.4)	104 (51.0)	61 (57.0)	42 (41.6)	350 (49.0)
≥ 2	15 (5.7)	14 (6.9)	19 (17.8)	10 (9.9)	60 (8.4)
Unknown	0	0	1 (0.9)	1 (1.0)	2 (0.3)
Race					
White	249 (94.0)	197 (96.6)	102 (95.3)	94 (93.1)	679 (95.1)
Black	8 (3.0)	5 (2.5)	2 (1.9)	1 (1.0)	16 (2.2)
Asian	5 (1.9)	2 (1.0)	2 (1.9)	4 (4.0)	13 (1.8)
Other	3 (1.1)	0	1 (0.9)	2 (2.0)	6 (0.8)
BMI (kg/m^2), median (range)	26.24 (14.8-56.5)	25.59 (15.5-47.0)	25.46 (17.8-47.8)	27.08 (16.4-39.9)	26.12 (14.8-56.5)
Stage IV disease at diagnosis[a]	173 (65.3)	142 (69.6)	60 (56.1)	33 (32.7)	424 (59.4)
Patients with previous systemic treatment for CRC	45 (17.0)	41 (20.1)	24 (22.4)	67 (66.3)	199 (27.9)
History of primary resection	71 (26.8)	61 (29.9)	25 (23.4)	45 (44.6)	215 (30.1)
History of colonic stents	0	3 (1.5)	0	1 (1.0)	4 (0.6)
History of arterial embolism or venous thromboembolism	18 (6.8)	13 (6.4)	15 (14.0)	9 (8.9)	57 (8.0)
Ongoing medical history of interest[b]					
Diabetes mellitus	18 (6.8)	3 (1.5)	6 (5.6)	2 (2.0)	30 (4.2)
Hypertension	66 (24.9)	50 (24.5)	36 (33.6)	21 (20.8)	181 (25.4)
Cardiac disorders	17 (6.4)	7 (3.4)	7 (6.5)	4 (4.0)	35 (4.9)
Respiratory, thoracic and mediastinal disorders	24 (9.1)	15 (7.4)	14 (13.1)	5 (5.0)	60 (8.4)
Endocrine disorders[c]	7 (2.6)	9 (4.4)	6 (5.6)	4 (4.0)	26 (3.6)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: BMI = body mass index; CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; PS = performance status.
[a]Disease assessment data not available for 3 patients.
[b]Most relevant ongoing medical history is included (preferred term). List of most commonly reported ongoing medical conditions (in ≥ 5% of patients) overall and for each of 4 most common first-line chemotherapy regiments is provided in Supplemental Table 2.
[c]Excluding diabetes mellitus.

(171 [64.5%]) and for capecitabine monotherapy (74 [69.2%]) compared to fluorouracil/folinic acid/irinotecan (50 [49.5%]) and fluorouracil/folinic acid/oxaliplatin (121 [59.3%]).

Treatment Patterns

At the final database lock (March 28, 2017), median patient follow-up was 16.4 months. A total of 170 patients (23.8%) were known to be alive, and 516 (72.3%) had died. The outcome for the remaining 28 patients (3.9%) was unknown, as they had withdrawn from the study for the following reasons: withdrawal of consent (n = 4), investigator decision (n = 3), or another reason (n = 7); or they had been lost to follow-up (n = 14).

Median duration of first-line chemotherapy was 5.6 months; median total duration was 8.1 months and appeared to be comparable between fluorouracil- and capecitabine-based combination regimens. Both first-line and total duration of chemotherapy were shorter among those receiving capecitabine monotherapy (Table 2). A total of 224 patients (31.4%) had a change from their starting chemotherapy regimen during first-line treatment. A higher proportion of patients receiving oxaliplatin changed from their starting

Table 2 Treatment Patterns, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Characteristic	Capecitabine, Oxaliplatin (N = 265)	Fluorouracil, Folinic Acid, Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil, Folinic Acid, Irinotecan (N = 101)	Overall (N = 714)
Duration of Bevacizumab Treatment (Mos), Median (Range)					
Total duration	5.1 (0.02-31.1)	5.0 (0.02-34.1)	4.4 (0.02-28.0)	5.6 (0.02-34.8)	5.1 (0.02-34.8)
First-line duration	4.9 (0.02-31.1)	4.8 (0.02-25.7)	4.1 (0.02-28.0)	5.6 (0.02-27.4)	4.9 (0.02-31.8)
Duration after progression	2.1 (0.02-17.4)	0.3 (0.02-7.8)	0.03 (0.02-4.2)	2.9 (0.02-24.0)	1.4 (0.02-24.0)
Patients receiving bevacizumab after progression	39 (14.7)	26 (12.7)	11 (10.3)	12 (11.9)	99 (13.9)
Reason for Bevacizumab Discontinuation					
Adverse event	32 (12.1)	45 (22.1)	18 (16.8)	19 (18.8)	122 (17.1)
Disease progression	84 (31.7)	58 (28.4)	41 (38.3)	30 (29.7)	235 (32.9)
Death	18 (6.8)	7 (3.4)	6 (5.6)	2 (2.0)	35 (4.9)
Patient decision	9 (3.4)	21 (10.3)	12 (11.2)	4 (4.0)	47 (6.6)
Investigator decision	78 (29.4)	52 (25.5)	22 (20.6)	36 (35.6)	190 (26.6)
Lost to follow-up	1 (0.4)	0	0	0	1 (0.1)
Other	43 (16.2)	21 (10.3)	8 (7.5)	10 (9.9)	84 (11.8)
Duration of Chemotherapy (Mos), Median (Range)					
Total duration	8.8 (0.2-41.4)	8.0 (0.9-46.9)	6.0 (0.02-33.3)	8.3 (0.8-34.3)	8.1 (0.02-46.9)
First-line duration	5.6 (0.2-31.6)	5.6 (0.1-26.6)	4.9 (0.02-33.3)	5.9 (0.8-29.7)	5.6 (0.02-33.3)
Duration after progression	5.2 (0.02-35.4)	4.6 (0.02-28.6)	4.7 (0.1-20.7)	4.7 (0.1-29.1)	4.9 (0.02-35.4)
Patients receiving postprogression chemotherapy	142 (53.6)	115 (56.4)	43 (40.2)	56 (55.4)	373 (52.2)
Duration of Chemotherapy by Age (Mos), Median (Range)					
Age $\leq$ 65 y					
Total duration	10.1 (0.4-41.4)	8.6 (0.1-46.9)	7.3 (1.3-33.3)	8.5 (1.0-34.3)	9.0 (0.1-46.9)
First-line duration	5.9 (0.4-26.6)	5.6 (0.1-26.6)	5.8 (1.3-33.3)	5.8 (0.8-25.8)	5.8 (0.1-33.3)
Duration after progression	6.1 (0.02-35.4)	4.3 (0.02-28.6)	2.4 (0.1-15.4)	4.6 (0.1-29.1)	5.1 (0.02-35.4)
Patients Receiving Postprogression Chemotherapy[a]	71 (54.2)	80 (66.1)	8 (47.1)	33 (61.1)	202 (58.6)
Age $>$ 65 to $\leq$ 75 y					
Total duration	7.9 (0.2-31.2)	6.7 (0.1-35.7)	5.4 (0.2-32.5)	8.3 (0.8-30.7)	7.7 (0.1-35.7)
First-line duration	5.6 (0.2-31.2)	5.6 (0.1-21.9)	3.7 (0.2-12.8)	6.0 (0.8-29.7)	5.6 (0.1-31.2)
Duration after progression	4.6 (0.1-22.2)	4.4 (0.02-28.6)	5.1 (0.1-20.7)	5.2 (0.6-17.8)	4.6 (0.02-28.6)
Patients Receiving Postprogression Chemotherapy[a]	52 (51.5)	22 (39.3)	10 (38.5)	19 (48.7)	107 (46.3)
Age $>$ 75 y					
Total duration	9.0 (0.3-36.2)	6.2 (0.1-30.7)	5.9 (0.02-28.4)	8.0 (1.3-25.5)	6.2 (0.02-41.7)
First-line duration	5.4 (0.3-31.6)	5.7 (0.1-18.7)	5.0 (0.02-28.4)	6.0 (0.8-15.1)	5.3 (0.02-31.6)
Duration after progression	3.1 (0.5-33.0)	5.1 (0.8-22.5)	4.9 (0.5-12.9)	4.1 (0.5-19.9)	4.1 (0.5-33.0)
Patients receiving postprogression chemotherapy[a]	19 (57.6)	13 (48.1)	25 (39.1)	4 (50.0)	64 (46.4)
Reason for First-Line Chemotherapy Discontinuation					
Adverse event	20 (7.5)	31 (15.2)	12 (11.2)	10 (9.9)	81 (11.3)
Disease progression	89 (33.6)	64 (31.4)	48 (44.9)	37 (36.6)	259 (36.3)
Death	21 (7.9)	10 (4.9)	6 (5.6)	2 (2.0)	41 (5.7)
Patient decision	12 (4.5)	21 (10.3)	12 (11.2)	5 (5.0)	53 (7.4)
Investigator decision	82 (30.9)	55 (27.0)	21 (19.6)	33 (32.7)	193 (27.0)
Lost to follow-up	2 (0.8)	0	1 (0.9)	0	3 (0.4)
Other	39 (14.7)	23 (11.3)	7 (6.5)	14 (13.9)	84 (11.8)

Data are presented as n (%) unless otherwise indicated.
[a]Percentage calculated based on total number of patients per age group.

regimen (capecitabine/oxaliplatin [41.9%], fluorouracil/folinic acid/oxaliplatin [36.8%]) compared to those who did not (capecitabine [5.6%], fluorouracil/folinic acid/irinotecan [16.8%]). The most common reasons for first-line chemotherapy discontinuation were disease progression (259 [36.3%]), investigator's decision (193 [27.0%]), and AEs (81 [11.3%]) (Table 2). The most commonly documented investigator's decision was completion of planned treatment course.

A total of 373 patients (52.2%) received chemotherapy after disease progression (median duration, 4.9 months). A slightly lower proportion of patients receiving capecitabine monotherapy received postprogression chemotherapy (40.2%) compared to other regimens. Total duration of chemotherapy appeared to decrease with increasing age, and patients aged $\leq$ 65 years were more likely to receive postprogression chemotherapy than those aged $>$ 65 years (Table 2).

Median duration of first-line bevacizumab was 4.9 months, and median total duration was 5.1 months; both appeared to be shorter in those receiving capecitabine monotherapy (Table 2). The most common reasons for bevacizumab discontinuation were progressive disease (235 [32.9%]), investigator's decision (190 [26.6%]), and AEs (122 [17.1%]). The most commonly documented investigator's decision was completion of the planned treatment course. Other frequently documented reasons included treatment holiday, toxicity, suspected progression, clinical deterioration, and awaiting consideration of surgery. A total of 99 patients (13.9%) received bevacizumab after disease progression; median duration of treatment after progression was 1.4 months.

Efficacy

PFS analysis included all patients except 3, for whom disease assessment data were unavailable (n = 711). Overall median PFS was 8.7 months (95% confidence interval, 8.2-9.1) (Figure 1A) in the 711 patients with available disease assessment data. Median PFS (95% confidence interval) for the 4 most common first-line chemotherapy regimens administered with bevacizumab were capecitabine/oxaliplatin 9.2 (8.4-9.7) months, fluorouracil/folinic acid/oxaliplatin 8.5 (7.1-9.3) months, capecitabine 7.9 (5.7-9.0) months, and fluorouracil/folinic acid/irinotecan 8.7 (7.2-9.8) months (Figure 1B). Corresponding values for OS were 17.8 (16.1-19.3) months overall (Figure 1C); and 19.6 (17.4-22.1) months, 16.5 (13.6-21.2) months, 15.1 (12.8-16.9) months, and 18.7 (14.7-23.3) months, respectively (Figure 1D). No statistically significant between-group differences were observed for PFS ($P = .35$) or OS ($P = .21$).

Cox regression analyses were used to evaluate the effect of baseline characteristics on PFS and OS (Supplemental Tables 3 and 4 in the online version). A worse baseline ECOG PS and a history of colonic stents were associated with a significantly increased risk of progression, whereas a change from planned bevacizumab treatment was associated with a reduced risk ($P < .05$). A change from planned bevacizumab treatment included dose modifications, interruptions, and delay but not discontinuation (with the exception of 1 case where insufficient information was available to interpret what was meant by change in bevacizumab treatment). A worse baseline ECOG PS and a history of colonic stents were associated with a significantly increased risk of death, whereas previous systemic treatment and a change from planned bevacizumab treatment were associated with a reduced risk ($P < .05$).

In an exploratory post hoc analysis conducted in 554 patients with an available investigator-specified disease progression date, median survival after progression was 8.4 months. Survival after progression was longer in the 99 patients who received bevacizumab at or after progression compared to the 455 patients who did not: median (95% CI) 12.6 (10.0, 15.5) months versus 7.6 (6.7, 8.4) months, respectively (hazard ratio 0.7, $P = .0012$; Figure 2). The median age of patients receiving bevacizumab at or after progression was 64 (range, 31-84) years, with 60 male (61%), compared to median age 66 (range, 26-85) years and 257 male (57%) in those who did not receive it. The first dose of bevacizumab provided at or after progression was administered with chemotherapy in 83 patients (84%). Bevacizumab was provided within a median of 10 days of the progression date (range, 0-125 days), with 82 patients (83%) receiving bevacizumab within 28 days of progression. Among those receiving bevacizumab at or after progression, 24% were in quartile 1 ($\leq$ 6.2 months) for the total duration of chemotherapy, 17% were in quartile 2 ($>$ 6.2 to $\leq$ 8.4 months), 32% were in quartile 3 ($>$ 8.4 to $\leq$ 10.8 months), and 26% were in quartile 4 ($>$ 10.8 months) compared to 29%, 28%, 25%, and 18%, respectively, in those not receiving bevacizumab after progression.

Centers that had a lower total duration of chemotherapy (within quartile 1) were associated with shorter OS (Supplemental Table 5 in the online version). No clear relationship was observed between geographic location (North vs. Midlands and East vs. London vs. South) and the total duration of chemotherapy received (Table 3).

Safety

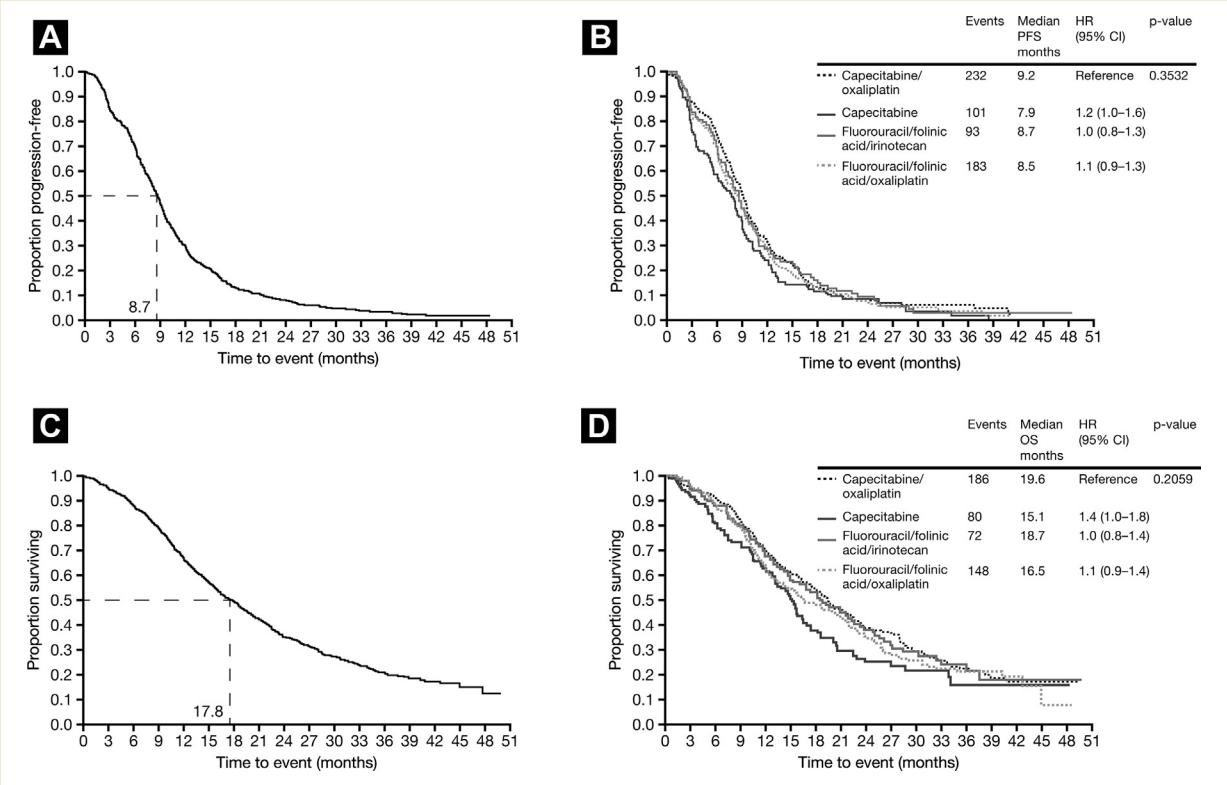
Most patients (703 [98.5%]) had at least 1 TEAE, with 307 (43.0%) and 125 (17.5%) experiencing TEAEs that led to hospitalization and bevacizumab discontinuation, respectively (Table 4). The incidence of TEAEs was comparable across the 4 most common first-line chemotherapy regimens, though the number of TEAEs per patient was numerically lower for capecitabine. Most patients (512 [71.7%]) had at least 1 TEAE (of any grade) deemed to be probably or possibly related to bevacizumab. A total of 210 patients (29.4%) experienced grade 3 to 5 bevacizumab-related TEAEs.

A total of 336 patients (47.1%) experienced serious TEAEs, most commonly GI disorders, including diarrhea, vomiting and abdominal pain, and pyrexia (Table 4). Patients receiving bevacizumab in combination with single-agent capecitabine had a lower number of serious TEAEs than those receiving bevacizumab in combination with each of the other 3 most common chemotherapy regimens.

Twenty-one patients (2.9%) had a TEAE that led to death, with one third (n = 7) of deaths due to GI perforations (Table 5). A higher proportion of patients receiving capecitabine/oxaliplatin experienced a TEAE that led to death (12 [4.5%]) than each of the other 3 most common chemotherapy regimens. Pneumonia and cardiac events were mainly responsible for the increased death rate observed.

Overall, 299 patients (41.9%) experienced AESIs (Supplemental Table 6 in the online version). The most frequently reported AESIs were hypertension, pulmonary embolism (PE), venous thromboembolic disease, and neutropenia (reported by $>$ 5% of patients

Figure 1 Kaplan-Meier Survival Estimates. (A) PFS for All Evaluable Patients (65/711, 9.1%, Censored) and (B) by Each of 4 Most Common First-line Chemotherapy Regimens Provided With Bevacizumab. (C) OS (198/714, 27.7%, Censored) for All Patients. (D) OS for Each of 4 Most Common First-line Chemotherapy Regimens Provided With Bevacizumab



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

overall). Hypertension rates appeared to be lower with first-line fluorouracil/folinic acid/irinotecan.

Quality of Life

Although no formal statistical analysis was conducted, no apparent differences in QoL, as assessed by EQ-5D-5L, were observed between treatments or over time (Supplemental Figure 1 in the online version). Mean EQ-5D-5L weighted index scores were similar at baseline (0.82) and month 15 (0.85) (Supplemental Table 7 in the online version). Questionnaire response rates decreased over time, from 75.1% at baseline to < 12% beyond month 15 (Supplemental Table 8 in the online version).

Discussion

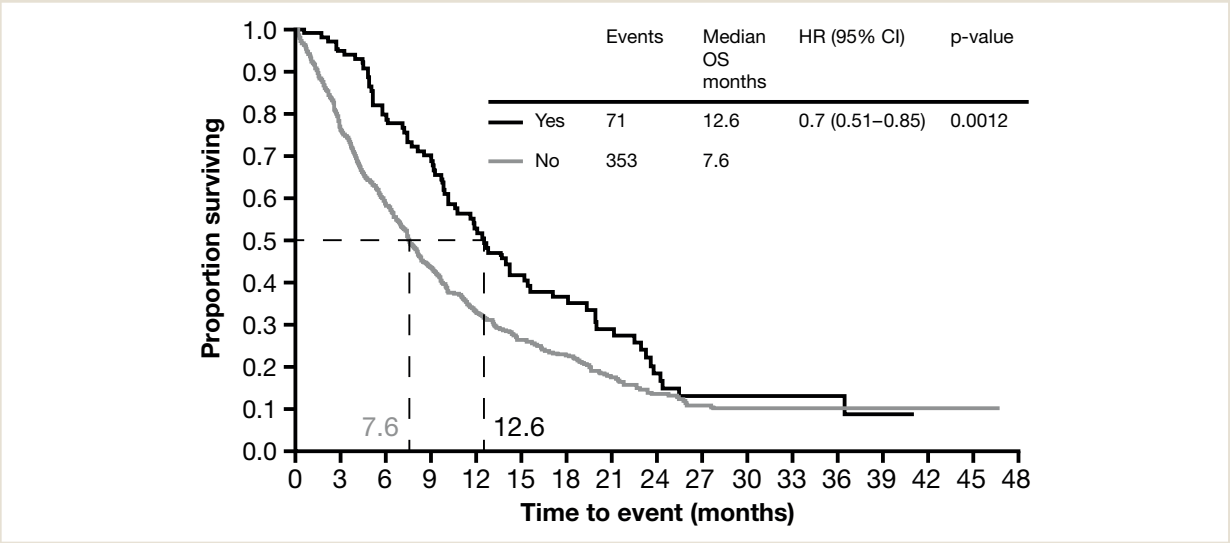
This prospective observational multicenter study provided a comprehensive analysis of treatment patterns, efficacy, safety, and QoL of first-line mCRC chemotherapy provided in combination with bevacizumab in a real-world setting in the UK. The median PFS (8.7 months) is similar to that reported in other published observational studies (9.9 months in BRiTE, 10.8 months in BEAT, and 10.2 months in ARIES), although it is numerically shorter.[16-18] In contrast, median OS was considerably shorter in ACORN (17.8 months) compared to BRiTE (22.9 months), BEAT (22.7 months), and ARIES (23.2 months), suggesting that treatment provided after progression affected the differences seen. However, there are likely to be multifactorial reasons for the reduced efficacy of treatment observed in ACORN.

In ACORN, patients who had already begun therapy with bevacizumab were excluded, whereas in ARIES and BRiTE, patients could have initiated bevacizumab therapy within 4 months or ≤ 3 months before study enrollment, respectively. Therefore, compared to ACORN, these studies may have inadvertently recruited patients who had a higher propensity to tolerate, and perhaps respond to, chemotherapy.

As expected, in ACORN a worse baseline ECOG PS predicted shorter PFS and OS. However, PS (PS0, 42.3-49.1%; PS1, 42.2-49.0%) and median age (59-66 years) were similar among all 4 observational studies, with the notable exception that in BEAT, patients with ECOG PS ≥ 2 were not included. Therefore, it is unlikely that age and ECOG PS contributed to inferior efficacy outcomes in ACORN. However, other baseline patient characteristics could have potentially contributed. For example, in BRiTE and ARIES, patients with locally advanced disease were recruited in addition to those with mCRC, whereas in ACORN (and BEAT) only patients with mCRC were enrolled onto the study.

The primary tumor resection rate was substantially lower at baseline in ACORN (30.1%) compared to other observational studies (BRiTE, 84.4%; BEAT, 87%; ARIES, 80.8%). This

Figure 2 Kaplan-Meier Survival Estimate According to Receipt of Bevacizumab At or After Disease Progression. Shown Is Estimate for Survival Beyond Progression for All Evaluable Patients (n = 554) by Whether or Not Bevacizumab Was Administered at or After Progression



Abbreviations: HR = hazard ratio; OS = overall survival.

difference is noteworthy, as retrospective analyses have found a survival advantage for CRC patients with synchronous metastases who underwent resection of their primary tumor compared to those who did not.[23,24] Although to our knowledge no formal randomized controlled trials addressing this question have been reported, such trials are currently ongoing and may provide further insight in the near future.[25,26]

Recently a study confirmed inferior survival in England and suggested that this may be partly due to more conservative selection of patients for surgery.[27] The authors reported that patients > 75 years old in England were less likely to undergo curative resection of their primary tumor compared to Scandinavian countries. Therefore, there are likely to be country-specific treatment practices that influence survival outcomes.

Interestingly, in ACORN, Cox regression analysis of PFS by baseline characteristics showed that the presence of a colonic stent was associated with a shorter PFS. This result suggests that patients with colonic stents may be more likely to experience complications that affect efficacy. Therefore, palliative surgery may play a role in avoiding this outcome in symptomatic patients with adequate ECOG PS. We acknowledge that the small patient numbers for this analysis preclude firm conclusions from being drawn.

In the Cox regression analysis of OS by baseline characteristics in ACORN, receiving previous systemic treatment for CRC was a statistically significant predictor for longer OS. It may therefore be relevant that a higher proportion of patients in BRiTE (36.4%) and BEAT (35.5%) had received previous systemic treatment (adjuvant chemotherapy) compared to ACORN (27.9%). However, the proportion of patients with prior adjuvant therapy was lower in ARIES (24.8%).

In ACORN, the median total duration of chemotherapy (8.1 months) was lower than expected compared to 11.1 months in BRiTE and 12.2 months in ARIES (unknown in BEAT). Considering the fact that in ACORN centers that had a short total duration of chemotherapy (ie, within the first quartile) had a shorter median OS, this is likely to have been a major contributor to the poorer efficacy observed in the UK. It remains uncertain why the total chemotherapy duration was shorter than anticipated in the UK. Although intermittent chemotherapy was not proven to be noninferior to continuous chemotherapy in the randomized phase 3 MRC COIN trial,[28] given that there was minimal survival difference between the 2 groups and there was an improvement in QoL in the intermittent chemotherapy arm, it is possible that in the context of palliative chemotherapy, where maintaining QoL is

Table 3 Total Duration of Chemotherapy by Geographic Location of Treating Center

Geographic Location	No. of Recruiting Centers (N = 42)	No. of Subjects (N = 714)	Mean Total Chemotherapy Duration (Months)	Median Total Duration of Chemotherapy (Months)	Total Duration of Chemotherapy (Months), Range
South	10	161	8.4	8.3	3.8-14.1
London	7	192	9.0	7.5	5.3-17
Midlands and East	14	255	8.9	8.3	4.2-15.9
North	11	106	9.7	9.3	6.0-15.5

Table 4 TEAEs, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab[a]

Treatment-Emergent Adverse Event	Capecitabine, Oxaliplatin (N = 265)	Fluorouracil, Folinic Acid, Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil, Folinic Acid, Irinotecan (N = 101)	Overall (N = 714)
Patients with any TEAE	260 (98.1)	202 (99.0)	106 (99.1)	99 (98.0)	703 (98.5)
Highest NCI CTCAE Grade					
1	27 (10.2)	15 (7.4)	16 (15.0)	5 (5.0)	64 (9.0)
2	82 (30.9)	56 (27.5)	44 (41.1)	29 (28.7)	224 (31.4)
3	120 (45.3)	103 (50.5)	41 (38.3)	51 (50.5)	333 (46.6)
4	19 (7.2)	22 (10.8)	4 (3.7)	12 (11.9)	61 (8.5)
5	12 (4.5)	6 (2.9)	1 (0.9)	2 (2.0)	21 (2.9)
Patients with any TEAE requiring bevacizumab discontinuation	34 (12.8)	45 (22.1)	19 (17.8)	19 (18.8)	125 (17.5)
Patients with any TEAE requiring hospitalization	108 (40.8)	95 (46.6)	34 (31.8)	50 (49.5)	307 (43.0)
Patients with any serious TEAE	120 (45.3)	106 (52.0)	36 (33.6)	53 (52.5)	336 (47.1)
Serious TEAEs Reported in ≥ 2% of Patients Overall					
Gastrointestinal disorder	58 (21.9)	32 (15.7)	11 (10.3)	25 (24.8)	134 (18.8)
Diarrhea	21 (7.9)	5 (2.5)	1 (0.9)	10 (9.9)	41 (5.7)
Vomiting	17 (6.4)	4 (2.0)	1 (0.9)	6 (5.9)	29 (4.1)
Abdominal pain	10 (3.8)	10 (4.9)	2 (1.9)	3 (3.0)	28 (3.9)
Infections and infestation	36 (13.6)	41 (20.1)	9 (8.4)	23 (22.8)	114 (16.0)
Lower respiratory tract infection	6 (2.3)	7 (3.4)	5 (4.7)	3 (3.0)	21 (2.9)
Neutropenic sepsis	4 (1.5)	6 (2.9)	0	3 (3.0)	15 (2.1)
Sepsis	5 (1.9)	5 (2.5)	1 (0.9)	4 (4.0)	15 (2.1)
General disorders and administration site conditions	24 (9.1)	18 (8.8)	8 (7.5)	8 (7.9)	62 (8.7)
Pyrexia	14 (5.3)	13 (6.4)	2 (1.9)	7 (6.9)	40 (5.6)
Respiratory, thoracic and mediastinal disorder	18 (6.8)	10 (4.9)	4 (3.7)	10 (9.9)	46 (6.4)
Pulmonary embolism	7 (2.6)	5 (2.5)	2 (1.9)	7 (6.9)	25 (3.5)
Blood and lymphatic system disorder	3 (1.1)	11 (5.4)	1 (0.9)	2 (2.0)	21 (2.9)
Neutropenia	3 (1.1)	7 (3.4)	1 (0.9)	1 (1.0)	14 (2.0)
Vascular disorder	3 (1.1)	10 (4.9)	2 (1.9)	5 (5.0)	21 (2.9)
Cardiac disorder	10 (3.8)	2 (1.0)	3 (2.8)	3 (3.0)	20 (2.8)
Nervous system disorder	7 (2.6)	5 (2.5)	2 (1.9)	2 (2.0)	17 (2.4)
Investigation	4 (1.5)	10 (4.9)	0	1 (1.0)	15 (2.1)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event.
[a]Reported in ≥ 2% of patients in overall group.

important, clinicians and patients in some UK centers may have been more likely to consider a treatment break. Another possible explanation for the shorter total chemotherapy duration is late diagnosis, with patients having a higher level of metastatic disease burden at presentation.[29] However, there are no confirmatory data from ACORN to support this, as the number and sites of metastases were not collected, and neither was the rate of metastasectomy with curative intent. Although late diagnosis may also affect survival in CRC,[30] this has not been replicated across all studies,[31,32] perhaps reflecting the inconsistent definitions of diagnostic delay.

In ACORN, the median duration of first-line chemotherapy (5.6 months) was similar to that in other studies (5.8 months in ARIES and 5.7 months in BRiTE). Capecitabine/oxaliplatin was the most frequently administered first-line chemotherapy backbone (37.1%). This was in contrast with the other 3 observational studies, where the most common regimens were fluorouracil/folinic acid/oxaliplatin in BRiTE (56%), BEAT (29%), and ARIES (62.5%), with capecitabine/oxaliplatin provided in only 5%, 18%, and 8.6% of patients, respectively.[16-18] Overall, the increased use of capecitabine does not seem to have contributed to worse survival outcomes, as no difference in OS was observed between the different therapy regimens.

ACORN provides further evidence for capecitabine monotherapy in combination with bevacizumab as a viable mCRC treatment strategy, particularly for elderly patients with a poorer baseline ECOG PS. Median PFS (7.9 months) and median OS (15.1 months) were not significantly different to the other 3 most common chemotherapy regimens ($P = .35$ and $P = .21$, respectively). These results are similar to the Avastin in the Elderly with Xeloda (AVEX) study involving patients with previously untreated mCRC,

Table 5 TEAEs Resulting in Death, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Treatment-Emergent Adverse Event	Capecitabine/ Oxaliplatin (N = 265)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Overall (N = 714)
Patients with any TEAE leading to death	12 (4.5)	1 (0.9)	2 (2.0)	6 (2.9)	21 (2.9)
GI perforation[a,b]	3 (1.1)	1 (0.9)	0	3 (1.5)	7 (1.0)
Pneumonia	4 (1.5)	0	1 (1.0)	0	5 (0.7)
Cardiac arrest	2 (0.8)	0	0	0	2 (0.3)
Tumor perforation[a]	0	0	0	1 (0.5)	1 (0.1)
Lower GI hemorrhage[a]	0	0	0	1 (0.5)	1 (0.1)
Neutropenic sepsis[a]	1 (0.4)	0	0	0	1 (0.1)
Myocardial infarction	1 (0.4)	0	0	0	1 (0.1)
General physical health deterioration	1 (0.4)	0	0	0	1 (0.1)
Head injury	0	0	0	1 (0.5)	1 (0.1)
Thrombosis[a]	0	0	1 (1.0)	0	1 (0.1)

Data are presented as n (%).
Abbreviations: GI = gastrointestinal; TEAE = treatment-emergent adverse event.
[a]TEAEs considered to be of special interest.
[b]Large intestine, intestinal, or GI perforation.

in which capecitabine with bevacizumab resulted in a median PFS of 9.1 months.[33] The proportion of patients receiving further chemotherapy after progression was lowest for those commencing capecitabine monotherapy (40.2%) in the first-line setting compared to the other 3 most common regimens (53.6-56.4%). This is unsurprising, given the higher proportion of elderly patients with worse ECOG PS at baseline who received capecitabine alone as first-line chemotherapy, for whom further chemotherapy may not have been appropriate.

In ACORN, 52.2% of patients had further chemotherapy after disease progression. In ARIES, 67.9% of patients in the first-line chemotherapy cohort received second-line therapy. It is unclear whether this figure included patients who had switched chemotherapy without disease progression. Given that sequential therapy is known to improve OS in mCRC,[34] the relatively low proportion of patients receiving further chemotherapy should be taken into consideration when interpreting the OS findings in ACORN.

Despite the short median duration of bevacizumab therapy after disease progression (1.4 months), receipt of bevacizumab at or after first progression was still associated with significantly longer survival after disease progression in ACORN (12.6 vs. 7.6 months for no bevacizumab, $P = .0012$). Total median chemotherapy duration was similar between those who received bevacizumab at or after progression and those who did not, so this factor alone cannot account for the difference. Only 13.9% of patients received bevacizumab after disease progression in ACORN compared to 44.4% in BRiTE[35] and 40.5% in ARIES. Consistent with the findings in ACORN, median postprogression survival was higher in patients receiving bevacizumab after progression (19.2 months in BRiTE and 14.4 months in ARIES)[36] compared to those receiving postprogression treatment without bevacizumab (9.5 months in BRiTE and 10.6 months in ARIES) or no postprogression treatment (3.6 months in BRiTE). The degree of survival difference between those receiving postprogression treatment with or without bevacizumab was not replicated to the same extent in randomized controlled trials[37,38] but still remained statistically significant, favoring bevacizumab after progression. This raises important questions that have long been debated about the use of antiangiogenics beyond first disease progression.

The safety profile of bevacizumab in combination with first-line chemotherapy was generally as expected. However, direct safety comparisons between ACORN, BRiTE, BEAT, and ARIES are difficult to make because of the differences in data collection methods. All AEs and SAEs were collected in ACORN and BEAT. In contrast, protocol-specified AEs suspected to be associated with bevacizumab and/or those commonly observed in the general mCRC population were collected in ARIES; prespecified bevacizumab-related AEs or SAEs suspected to be possibly related to bevacizumab were collected in BRiTE. These differences are reflected in the lower overall SAE rate of 10.9% in ARIES compared to ACORN (serious TEAEs 47.1%) and BEAT (33%). Serious AESI rates were generally similar in ACORN (15.7%) and BEAT (11%).

Sixteen patients (2.2%) experienced a GI perforation that led to death in 7 cases. Despite the higher proportion of primary tumors in situ in ACORN, the perforation rate was similar to those seen in BRiTE (1.9%), ARIES (1.2%), and BEAT (2%). The rate of PEs in ACORN (7.7%) was higher than that observed in the landmark first-line randomized controlled trial (3.6%), in which the chemotherapy backbone was fluorouracil/folinic acid/irinotecan.[39] The difference in these PE rates can probably be explained by the stringent eligibility criteria required for randomized controlled trials compared to observational studies like ACORN, which include a less selected population. Reassuringly, PE was a manageable AE and was not documented as having accounted for any of the 21 (2.9%) TEAEs leading to death.

In addition to PE, hypertension and neutropenia were among the most frequently reported AESIs in ACORN. Hypertension was more common in ACORN (11.3%) than in BEAT (5.3%) and ARIES (8.6%). Other recognized bevacizumab-related AEs that are of concern to treating oncologists, including hemorrhage and

arterial thromboembolic events, appeared to be similar in ACORN to those reported in other observational studies, with the exception of BEAT, in which the bleeding rate was much higher (31%).[17] TEAEs leading to death occurred in 2.9% patients in ACORN, which is similar to the 60-day mortality rates of 3% in BEAT and 2.1% in BRiTE.

QoL data from ACORN should be interpreted with caution, given the decline in response rate over time and the nonmandatory requirement for questionnaire completion that inevitably introduced bias. Regardless of these clear limitations, there appeared to be no difference in QoL between treatments or over time. The fact that treatment did not have a negative impact on QoL is reassuring.

Limitations of this study include its observational design and the frequency of assessments for PFS (every 3-4 months), which may have led to the duration of this end point being overestimated. In addition, there was no independent central review of scans, as data were derived directly from individual centers. Because of the captured data, unfortunately, there was no provision to provide a detailed description of treatment paths after first-line mCRC. Finally, the results of ACORN are exclusively from mCRC patients based in the UK, which limits the broader generalizability of the findings.

Conclusion

ACORN confirmed the safety profile of bevacizumab in a real-world UK-based population without raising any new concerns. Unlike previous bevacizumab-related observational studies, capecitabine-based chemotherapy was the preferred chemotherapy backbone in ACORN. Although PFS was generally similar to that reported in other studies, it is disappointing that OS was much lower. A shorter-than-expected median total chemotherapy duration is likely to have contributed to this. Of note, however, is the fact that total duration of chemotherapy was similar among different regions in the UK, and therefore this is an issue that applies across the UK as opposed to specific areas. Other plausible explanations include less frequent use of bevacizumab beyond disease progression and higher rates of in situ primary tumor. Alternative explanations that were not examined in this study may include the adoption of chemotherapy holidays in some UK centers, differing access to health system resources such as radiology services, and barriers to surgical management of potentially resectable metastatic cancer. However, it is worth noting that differences in study design and study populations may also have played a role, and therefore direct median OS comparisons should be interpreted with caution. An in-depth analysis exploring reasons for the short observed median total chemotherapy duration in UK centers is needed.

Clinical Practice Points

- Previous observational studies have provided real-world data on the use of bevacizumab in CRC in many countries, but none has included an exclusively UK-based population.
- Survival outcomes in patients with CRC in the UK are consistently worse than in other European countries.
- This study aimed to assess real-world data on bevacizumab in mCRC in an exclusively UK-based population to better understand treatment practices that may explain the worse survival outcomes in the UK compared to other European countries.
- This study demonstrated that there was no difference in outcomes for bevacizumab with capecitabine-based chemotherapy (the most commonly used regimen in the UK) compared to bevacizumab with fluorouracil-based regimens.
- A shorter OS was reported in this trial compared to similar observational trials (17.8 vs. 22.9-23.2 months), possibly due to a shorter total duration of chemotherapy (8.1 vs. 11.1-12.2 months), less frequent provision of bevacizumab after progression (13.9% vs. 40.5-44.4%), and higher rates of in-situ primary tumors.
- Median survival after disease progression was longer in patients who received bevacizumab provided after progression compared to those who did not (12.6 vs. 7.6 months), raising important questions about the use of antiangiogenics beyond first progression.
- The safety profile of bevacizumab and first-line chemotherapy was generally as expected.
- An in-depth analysis exploring reasons for the short observed median total chemotherapy duration in UK centers is needed.

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Supplemental Data

Supplemental figure and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.07.003.

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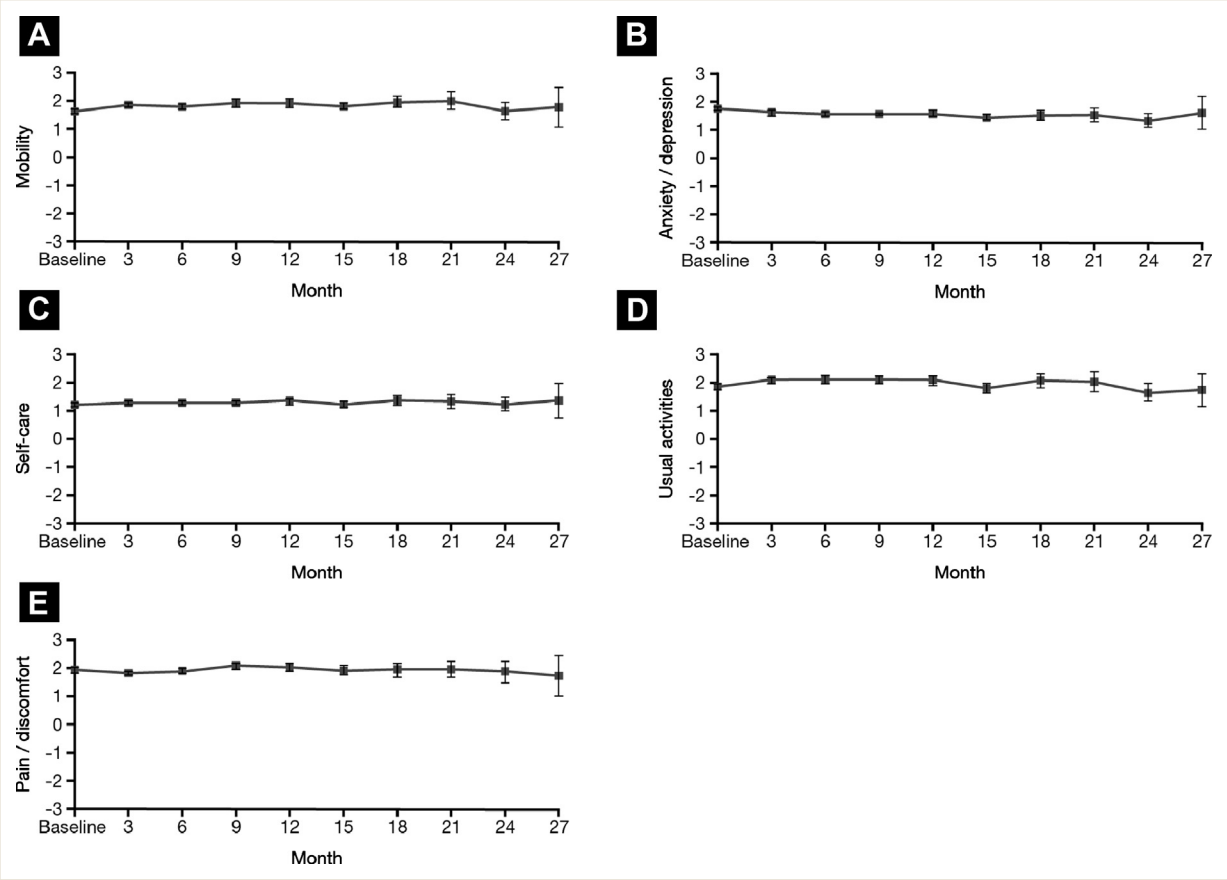
Supplemental Data

Supplemental Figure 1 Mean EQ-5D-5L Questionnaire Dimension Scores Over Time. Scores for (A) Mobility, (B) Anxiety/Depression, (C) Self-Care, (D) Usual Activities, and (E) Pain/Discomfort for All Patients



Supplemental Table 1	List of Study End Points
Primary End Points	
Outcomes	Progression-free survival (defined as time period from start of first-line therapy to investigator-assessed disease progression or death from any cause).
	Overall survival (defined as time period from start of first-line therapy to death by any cause).
Safety	All serious EEs observed during first-line treatment of mCRC.
	Bevacizumab related grade 3-5 AEs observed during first-line treatment of mCRC.
Secondary End Points	
Outcomes	Quality of life as assessed by EQ-5D 5L questionnaire self-administered to patients every 3-4 months from start of treatment with chemotherapy and bevacizumab until 6 months (inclusive) after disease progression.
	Burden of illness as assessed by short questionnaire self-administered to patients every 3-4 months from start of treatment with chemotherapy and bevacizumab until 6 months (inclusive) after disease progression.
Safety	AEs of special interest for bevacizumab. All grades: gastrointestinal perforation, fistulae and abscesses, arterial and venous thromboembolic events, bleeding other than mucocutaneous bleeding, congestive heart failure, reversible posterior leukoencephalopathy syndrome, osteonecrosis of jaw, neutropenia and febrile neutropenia, microangiopathic hemolytic anemia, hypersensitivity and infusion reaction, and ovarian failure; grade 2-5: hypertension, wound healing complications, mucocutaneous bleeding, proteinuria.
	AEs of any grade leading to modification or discontinuation of treatment with bevacizumab.
	Hospitalizations for treatment-related AEs
Other	Dosage, schedule (including duration of infusion), duration and reason for discontinuation of treatment with bevacizumab
	Composition of first line chemotherapy regimens
	All recorded deviations from bevacizumab Summary of Product Characteristics

Abbreviations: AE = adverse event; EQ-5D 5L = EuroQoL-5 Dimensions-5 Levels questionnaire; mCRC = metastatic colorectal cancer.

Supplemental Table 2 List of Most Commonly Reported Ongoing Medical Conditions (in ≥ 5% of Patients), Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

System Organ Class	Capecitabine/ Oxaliplatin (N = 265)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Overall (N = 714)
Patients with any ongoing medical history	171 (64.5)	121 (59.3)	74 (69.2)	50 (49.5)	436 (61.1)
Vascular disorders	75 (28.7)	50 (24.5)	39 (36.4)	22 (21.8)	195 (27.3)
Hypertension	66 (24.9)	50 (24.5)	36 (33.6)	36 (33.6)	181 (25.4)
Metabolism and nutrition disorders	43 (16.2)	22 (10.8)	24 (22.4)	10 (9.9)	103 (14.4)
Type 2 diabetes mellitus	15 (5.7)	10 (4.9)	9 (8.4)	5 (5.0)	40 (5.6)
Diabetes mellitus	18 (6.8)	3 (1.5)	6 (5.6)	2 (2.0)	30 (4.2)
Neoplasm benign, malignant and unspecified[a]	33 (12.5)	27 (13.2)	9 (8.4)	7 (6.9)	80 (11.2)
Gastrointestinal disorders	23 (8.7)	23 (11.3)	9 (8.4)	6 (5.9)	66 (9.2)
Respiratory, thoracic and mediastinal disorders	24 (9.1)	15 (7.4)	14 (13.1)	5 (5.0)	60 (8.4)
Cardiac disorders	17 (6.4)	7 (3.4)	7 (6.5)	4 (4.0)	35 (4.9)
Musculoskeletal and connective tissue disorders	10 (3.8)	11 (5.4)	9 (8.4)	2 (2.0)	35 (4.9)
Nervous system disorders	14 (5.3)	5 (2.5)	5 (4.7)	6 (5.9)	35 (4.9)
Neuropathy peripheral	3 (1.1)	3 (1.5)	2 (1.9)	5 (5.0)	15 (2.1)
Endocrine disorders[b]	7 (2.6)	9 (4.4)	6 (5.6)	4 (4.0)	26 (3.6)

Data are presented as n (%).
[a]Including cysts and polyps.
[b]Excluding diabetes mellitus.

Supplemental Table 3 Cox Regression Analysis of Progression-Free Survival for All Enrolled Patients

Baseline Characteristic	Parameter Estimate	Standard Error	*P*	HR	HR 95% CI
Age Group			.7956		
> 65 to ≤ 75 y	0.059	0.089		1.061	0.890-1.264
> 75 y	0.008	0.106		1.008	0.819-1.241
Previous systemic treatment	−0.085	0.087	.3315	0.919	0.774-1.090
ECOG PS			< .0001		
1	0.259	0.083		1.296	1.101-1.525
2	0.900	0.150		2.460	1.832-3.302
3	2.902	0.593		18.206	5.701-58.141
History of primary resection	0.036	0.085	.6721	1.037	0.877-1.226
History of anticoagulant	1.415	1.003	.1584	4.117	0.576-29.404
History of stents	1.021	0.503	.0422	2.776	1.037-7.433
History of hypertension	0.009	0.089	.9190	1.009	0.848-1.201
History of arterial embolism or venous thromboembolism	0.244	0.144	.0894	1.276	0.963-1.691
Any change from planned treatment[a]	−0.669	0.085	< .0001	0.512	0.433-0.606
Age and ECOG PS interaction			.8879		
Age and primary resection			.6063		

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PS = performance status.
[a]Includes dose modifications and dose interruptions.

Supplemental Table 4 Cox Regression Analysis of Overall Survival for All Enrolled Patients

Baseline Characteristic	Parameter Estimate	Standard Error	*P*	HR	HR 95% CI
Age Group			.4990		
> 65 to ≤ 75 y	0.117	0.099		1.124	0.925-1.365
> 75 y	0.041	0.120		1.042	0.824-1.317
Previous systemic treatment	−0.213	0.100	.0328	0.808	0.665-0.983
ECOG PS			< .0001		
1	0.233	0.094		1.262	1.050-1.517
2	1.150	0.157		3.157	2.322-4.292
3	0.034	0.711		1.035	0.257-4.172
History of primary resection	0.070	0.095	.4613	1.073	0.890-1.293
History of anticoagulant	0.690	1.001	.4911	1.993	0.280-14.187
History of stents	1.390	0.504	.0058	4.014	1.496-10.769
History of hypertension	−0.002	0.099	.9803	0.998	0.822-1.211
History of arterial embolism or venous thromboembolism	0.173	0.158	.2733	1.189	0.873-1.619
Any change from planned treatment[a]	−0.476	0.093	< .0001	0.622	0.518-0.746
Age and ECOG PS interaction			.8338		
Age and primary resection			.8051		

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PS = performance status.
[a]Includes dose modifications and dose interruptions.

Supplemental Table 5 OS by Center Group Based on Median Total Duration of Chemotherapy, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Quartile (Median Total Duration of Therapy in Months)	Characteristic	Capecitabine/ Oxaliplatin (N = 265)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Overall (N = 714)
Q1 (≤ 6.2)	Patients in group, n (%)	83 (31.3)	76 (37.3)	24 (22.4)	26 (25.7)	212 (29.7)
	OS (mos), median (95% CI)	13.2 (10.5-18.8)	12.5 (11.0-15.7)	13.7 (7.8-20.4)	16.7 (12.5-22.3)	13.2 (12.0-15.8)
Q2 (> 6.2 to ≤ 8.4)	Patients in group, n (%)	82 (30.9)	30 (14.7)	24 (22.4)	38 (37.6)	182 (25.5)
	OS (mos), median (95% CI)	21.6 (17.4-32.2)	20.3 (10.2-30.8)	20.5 (14.4—NC)	16.8 (10.9—NC)	19.4 (16.4-23.4)
Q3 (> 8.4 to ≤ 10.8)	Patients in group, n (%)	30 (11.3)	75 (36.8)	42 (39.3)	23 (22.8)	186 (26.1)
	OS (mos), median (95% CI)	28.0 (15.1-36.4)	22.9 (15.4-26.1)	13.4 (7.5-16.5)	18.1 (10.0-25.6)	18.5 (15.1-21.5)
Q4 (> 10.8)	Patients in group, n (%)	70 (26.4)	23 (11.3)	17 (15.9)	14 (13.9)	134 (18.8)
	OS (mos), median (95% CI)	21.7 (18.3-24.5)	16.7 (12.0-22.1)	15.3 (3.5-28.8)	27.7 (14.9-36.1)	21.4 (18.3-23.7)

Abbreviations: CI = confidence interval; NC = not calculable; OS = overall survival; Q = quartile.

Supplemental Table 6 AESIs, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Adverse Event of Special Interest	Capecitabine/ Oxaliplatin (N = 265)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Overall (N = 714)
Total no. of AESIs	158	141	49	60	438
Patients with any AESI	108 (40.8)	88 (43.1)	40 (37.4)	43 (42.6)	299 (41.9)
Hypertension	34 (12.8)	24 (11.8)	13 (12.1)	6 (5.9)	81 (11.3)
Pulmonary embolism	22 (8.3)	12 (5.9)	6 (5.6)	9 (8.9)	55 (7.7)
Venous thromboembolic disease[a]	15 (5.7)	20 (9.8)	6 (5.6)	7 (6.9)	53 (7.4)
Neutropenia	9 (3.4)	18 (8.8)	1 (0.9)	10 (9.9)	41 (5.7)
Proteinuria	9 (3.4)	3 (1.5)	5 (4.7)	6 (5.9)	24 (3.4)
Non-GI hemorrhage[b]	8 (3.0)	4 (2.0)	4 (3.7)	1 (1.0)	21 (2.9)
GI hemorrhage[c]	7 (2.6)	3 (1.5)	2 (1.9)	3 (3.0)	17 (2.4)
GI perforation[d]	6 (2.3)	5 (2.5)	3 (2.8)	2 (2.0)	16 (2.2)
Neutrophil count decreased	4 (1.5)	8 (3.9)	0	0	12 (1.7)
Hypersensitivity and infusion reaction	6 (2.3)	0	0	1 (1.0)	7 (1.0)
Cardiac failure including congestive	2 (0.8)	0	1 (0.9)	2 (2.0)	5 (0.7)
Cerebrovascular accident	2 (0.8)	0	1 (0.9)	1 (1.0)	4 (0.6)
Fistulae[e]	2 (0.8)	2 (1.0)	0	0	4 (0.6)
Neutropenic sepsis	2 (0.8)	1 (0.5)	0	0	4 (0.6)
Wound infection	2 (0.8)	1 (0.5)	0	0	3 (0.4)
Impaired healing	0	1 (0.5)	1 (0.9)	0	2 (0.3)
Skin ulcer	1 (0.4)	0	1 (0.9)	0	2 (0.3)
Tumor perforation	0	2 (1.0)	0	0	2 (0.3)
Osteonecrosis of jaw	1 (0.4)	0	0	0	1 (0.1)
Patients with any AESI related to bevacizumab	88 (33.2)	67 (32.8)	36 (33.6)	32 (31.7)	242 (33.9)
Total no. of serious AESIs	42	39	13	25	130
Patients with serious AESIs	37 (14.0)	35 (17.2)	12 (11.2)	20 (19.8)	112 (15.7)

Data are presented as n (%).
Abbreviations: AESI = adverse event of special interest; GI = gastrointestinal.
[a]Deep vein thrombosis, venous thrombosis, embolism, thrombosis, or subclavian vein thrombosis.
[b]Epistaxis, hematuria, or vaginal hemorrhage.
[c]Rectal, GI, small intestinal, or stoma site hemorrhage.
[d]Large intestine, intestinal, GI, small intestinal, or rectal perforation.
[e]Anal or enterovesical fistula.

Supplemental Table 7 EQ-5D-5L Questionnaire Weighted Index Score Over Time, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Month	Capecitabine/ Oxaliplatin (N = 265)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Overall (N = 714)
0 (Baseline)					
n	204	161	73	70	536
Mean score (SD)	0.84 (0.14)	0.82 (0.18)	0.79 (0.20)	0.82 (0.18)	0.82 (0.17)
Median score (range)	0.87 (0.08 to 1.00)	0.87 (0.05 to 1.00)	0.85 (0.09 to 1.00)	0.87 (0.05 to 1.00)	0.87 (0.03 to 1.00)
3					
n	140	121	56	54	387
Mean score (SD)	0.82 (0.17)	0.82 (0.18)	0.79 (0.19)	0.82 (0.19)	0.81 (0.18)
Median score (range)	0.85 (−0.28 to 1.00)	0.87 (0.11 to 1.00)	0.84 (0.11 to 1.00)	0.87 (0.14 to 1.00)	0.86 (−0.28 to 1.00)
6					
n	115	80	42	34	289
Mean score (SD)	0.82 (0.15)	0.83 (0.17)	0.82 (0.22)	0.86 (0.11)	0.82 (0.17)
Median score (range)	0.84 (0.09 to 1.00)	0.83 (0.14 to 1.00)	0.84 (−0.28 to 1.00)	0.87 (0.62 to 1.00)	0.84 (−0.28 to 1.00)
9					
n	84	71	28	28	221
Mean score (SD)	0.82 (0.14)	0.79 (0.18)	0.84 (0.12)	0.78 (0.18)	0.80 (0.18)
Median score (range)	0.86 (0.34 to 1.00)	0.82 (0.21 to 1.00)	0.85 (0.58 to 1.00)	0.80 (0.21 to 1.00)	0.84 (−0.06 to 1.00)
12					
n	62	48	27	20	163
Mean score (SD)	0.79 (0.18)	0.80 (0.19)	0.79 (0.18)	0.81 (0.14)	0.80 (0.18)
Median score (range)	0.82 (0.00 to 1.00)	0.85 (0.19 to 1.00)	0.83 (0.30 to 1.00)	0.83 (0.50 to 1.00)	0.83 (0.00 to 1.00)
15					
n	48	37	21	24	135
Mean score (SD)	0.83 (0.13)	0.84 (0.17)	0.88 (0.11)	0.85 (0.15)	0.85 (0.14)
Median score (range)	0.84 (0.42 to 1.00)	0.89 (0.28 to 1.00)	0.89 (0.67 to 1.00)	0.83 (0.46 to 1.00)	0.87 (0.28 to 1.00)

Abbreviation: SD = standard deviation.

Supplemental Table 8 EQ-5D-5L Questionnaire Response Rates Over Time, Overall and for Each of 4 Most Common First-Line Chemotherapy Regimens Provided With Bevacizumab

Month	Capecitabine/ Oxaliplatin (N = 265)	Fluorouracil/Folinic Acid/Oxaliplatin (N = 204)	Capecitabine (N = 107)	Fluorouracil/Folinic Acid/Irinotecan (N = 101)	Overall (N = 714)
0 (Baseline)	204 (77.0)	161 (78.9)	73 (68.2)	70 (69.3)	536 (75.1)
3	140 (52.8)	121 (59.3)	56 (52.3)	54 (53.5)	387 (54.2)
6	115 (43.4)	80 (39.2)	42 (39.3)	34 (33.7)	289 (40.5)
9	84 (31.7)	71 (34.8)	28 (26.2)	28 (27.7)	221 (31.0)
12	62 (23.4)	48 (23.5)	27 (25.2)	20 (19.8)	163 (22.8)
15	48 (18.1)	37 (18.1)	21 (19.6)	24 (23.8)	135 (18.9)
18	22 (8.3)	28 (13.7)	18 (16.8)	11 (10.9)	84 (11.8)
21	16 (6.0)	14 (6.9)	6 (5.6)	3 (3.0)	41 (5.7)
24	9 (3.4)	9 (4.4)	2 (1.9)	4 (4.0)	26 (3.6)
27	4 (1.5)	3 (1.5)	0	1 (1.0)	8 (1.1)

Data are presented as n (%).