Efficacy and Safety of Bevacizumab Combined With Fluoropyrimidine Monotherapy for Unfit or Older Patients With Metastatic Colorectal Cancer: A Systematic Review and Meta-Analysis

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Abstract

Whether bevacizumab represents a feasible option for the first-line treatment of unfit and elderly patients with metastatic colorectal cancer remains controversial. The present meta-analysis included data from 782 patients and provides evidence for the clinical benefit yielded in terms of progression-free survival and overall survival by the addition of bevacizumab to first-line fluoropyrimidine-based chemotherapy for these complex patients.

Background: Whether bevacizumab represents a feasible option for the first-line treatment of unfit and elderly patients with metastatic colorectal cancer (mCRC) remains controversial. The present systematic review and meta-analysis evaluated the efficacy and safety data of bevacizumab combined with first-line fluoropyrimidine monochemotherapy for these complex patients. **Patients and Methods:** A systematic search of the published data was conducted through May 31, 2016. The random-effects model was used to combine the effect estimates and the I^2 index to quantify the between-study heterogeneity unexplained by sampling error. **Results:** We included 3 randomized controlled trials, 4 single-arm phase II trials, and 1 prospective cohort study in the present meta-analysis (n = 782). The monochemotherapy administered was capecitabine in 531 patients (67.9%) and 5-fluorouracil in 251 (32.1%); 500 (63.9%) also received bevacizumab. The median age was 75 years, 441 patients (56.4%) were men, and the Eastern Cooperative Oncology Group performance status was 0 to 1 in 684 patients (87.7%). The combination with bevacizumab produced advantages in terms of both progression-free survival (hazard ratio, 0.52; 95% confidence interval, 0.43-0.64; $P < .00001$; $I^2 = 0\%$) and overall survival (HR, 0.79; 95% CI, 0.64-0.98; $P = .03$; $I^2 = 0\%$). The pooled effect estimates of the randomized controlled trials have been previously reported. As expected, all-grade hypertension (27% vs. 4.9%), bleeding (24% vs. 6.4%), thromboembolic events (10% vs. 5%), and proteinuria (25.6% vs. 8.2%) were more frequent in the bevacizumab combination group. **Conclusion:** Adding bevacizumab to first-line fluoropyrimidine monochemotherapy significantly improved progression-free and overall survival in unfit and elderly patients with mCRC, with a manageable safety profile and no unexpected toxicities.

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Introduction

With a median age of diagnosis of > 70 years and more than one third of all deaths occurring in patients aged > 80 years, colorectal cancer (CRC) is predominantly a disease of the elderly.[1] Although systemic treatment has markedly evolved in recent years, how to best approach geriatric or unfit populations remains a matter of debate, with specific guidelines lacking. A widespread use of the geriatric assessment has been advocated to improve patient selection; however, evidence of its value in the decision-making process is limited.[2] The results from 4 randomized trials (ie, Medical Research Council Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing [MRC FOCUS], CApecitabine, IRinotecan, Oxaliplatin [CAIRO], Fédération Francophone de Cancérologie Digestive 2000-05 [FFCD 2000-05], and Australasian Gastro-Intestinal Trials Group Mitomycin, Avastin, Xeloda [AGITG MAX]) have shown that in patients with advanced or metastatic CRC (mCRC), upfront combination chemotherapy (doublet) was not superior to sequential treatment beginning with 5-fluorouracil (5-FU) alone in terms of survival.[3-6] Hence, the upfront use of single-agent fluoropyrimidine, given either intravenously or orally,[7] can still be considered a valid option for frail, highly comorbid, or very old patients. Nevertheless, the upfront use of doublet chemotherapy with 5-FU coupled with irinotecan or oxaliplatin has been shown to be as effective for older patients as for younger subjects.[8,9] However, the prescription of a combination in clinical practice has been often restrained owing to the potential for an increased risk of toxicity.[10,11]

Bevacizumab, the first recombinant humanized monoclonal antibody to vascular endothelial growth factor, is commonly used in CRC in first- and second-line therapy and between treatment lines. A more rational use of the antiangiogenic strategy in the older or unfit population has also been proposed[12] based on results of community-based registries, phase II studies, and a large, randomized phase III trial.[13] Accordingly, subgroup analyses from randomized trials have suggested a similar benefit when adding bevacizumab to chemotherapy for older or younger patients and have not recommended using age alone as a specific criterion to exclude patients from antiangiogenic treatment. Similarly, frail or unfit patients with mCRC might still benefit from doublet chemotherapy regimens.[14] Notwithstanding this large body of evidence, both chemotherapy usage and biologic prescriptions decrease for patients of advanced age.[15,16]

The aim of the present trial-level meta-analysis was to evaluate the effect of adding bevacizumab to the most frequently used cytotoxic regimens for mCRC patients who had been judged unfit to receive an intense upfront treatment (because of age or frailty) and to estimate the magnitude of this effect.

Patients and Methods

Types of Studies, Participants, Interventions, and Outcomes

We included randomized controlled trials (RCTs) or prospective cohort studies of patients with advanced or metastatic CRC. We restricted the data to patients receiving monochemotherapy plus bevacizumab because of advanced age or comorbidity. Data on the following outcome measures were studied: objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Search Strategy and Selection Criteria

The PubMed and EMBASE databases were searched for RCTs and prospective cohort studies in May 31, 2016 with no language or publication status restrictions. The search query for PubMed was as follows: ("bevacizumab" [supplementary concept] OR "bevacizumab" [all fields]) AND ("colorectal neoplasms" [MeSH terms] OR ("colorectal" [all fields] AND "neoplasms" [all fields]) OR "colorectal neoplasms" [all fields] OR ("colorectal" [all fields] AND "cancer" [all fields]) OR "colorectal cancer" [all fields]) AND ("aged" [MeSH terms] OR "aged" [all fields] OR "elderly" [all fields] OR unfit [all fields]). For EMBASE, the query was "bevacizumab"/exp OR "bevacizumab" AND ("aged"/exp OR "aged" OR "elderly"/exp OR "elderly" OR "unfit") AND ("colorectal tumor"/exp OR "colorectal tumor" OR "colorectal carcinoma"/exp OR "colorectal carcinoma" OR "colorectal neoplasm"/exp OR "colorectal neoplasm" OR "colorectal cancer"/exp OR "colorectal cancer") AND [embase]/lim NOT [medline]/lim.

Ongoing studies and studies with < 10 patients per arm were excluded.

Data Extraction

Two investigators (V.T., L.P.) independently screened the titles and abstracts for inclusion. Full reports were retrieved for further assessment if the information in the abstract suggested that the study met all the prespecified criteria.

Two investigators (V.T., L.P.) were responsible for data assessment and extraction. Details on the study design, participants, setting, interventions, quality components, and efficacy and safety outcomes were recorded. Any inconsistency was resolved by discussion (F.P., G.M.).

For studies included in > 1 publication, the data were extracted from all the publications. However, we considered the final or updated version of each trial as the primary reference. We included trials in which patients crossed-over to the other treatment arm at progression or received other treatment off-study and were analyzed according to the arm to which they had been originally randomized. We also extracted data from patient subgroups if these answered our original question.

Statistical Analysis

The measure of association for PFS and OS was expressed as the hazard ratio (HR). The measure of association for the ORR was the odds ratio (OR). The estimation of the median time to PFS and OS was calculated using the weighted average of the hazard rate with the weights calculated by the inverse variance approach. The hazard rate and its standard error were estimated using the median time as the denominator under the assumption of exponential distribution. The I^2 index was calculated to estimate the heterogeneity among trials. The random effects model was used for estimating and testing results in all analyses.

Although the efficacy analyses included data from RCTs, the safety analysis also incorporated data from cohort studies. The determination of toxicity (all National Cancer Institute Common Terminology Criteria for Adverse Events grades and grade 3-4) focused on the main class of toxicities involving chemotherapy and bevacizumab: hematologic, cardiovascular, and renal toxicity and

hypertension and bleeding. The quality of the RCTs was independently evaluated by 2 of us (V.T., L.P.) using the approach proposed by the Cochrane Collaboration for experimental studies; the most conservative rate was considered for each item. The meta-analysis was performed using Revman, version 5.2. The present work was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for the reporting of systematic reviews and meta-analyses.[17]

Results

Published Data Search Results and Study Population

The PubMed and EMBASE database search produced 1714 studies published until May 31, 2016. After exclusion of duplicates and irrelevant studies, 8 reports were deemed to be eligible for the meta-analysis (Figure 1).[13,18-24] Of the 8 studies, 3 were multicenter RCTs (n = 558)[13,18,19] and 5 were phase II or prospective series (n = 224).[20-24] The characteristics of the studies included are reported in Supplemental Table 1 (available in the online version). Patient age for inclusion was ≥70 or 75 years in 5 studies[13,20-23] and 2 studies,[18,24] respectively, and 65 years in 1 trial.[19] The major eligibility criteria are reported in Supplemental Table 2 (available in the online version). The baseline characteristics of all patients included in the analysis (n = 782) are listed in Table 1. Overall, 500 patients received capecitabine or 5-FU plus bevacizumab doublet therapy and 282 received monochemotherapy alone. 5-FU-based chemotherapy was the agent of choice for 251 patients, and all other subjects (n = 531) received capecitabine-based therapy. Almost all patients (87.7%) had an Eastern Cooperative Oncology Group performance status of 0 to 1 and primary colon and/or rectal cancer (primary site information was missing for only 18.3% of cases). The study population was not pretreated for metastatic disease, with approximately 77% of subjects not having received adjuvant therapy. Among all patients, 70.9% and 41.4% had liver and lung metastases, respectively, with 72.6% having already undergone primary tumor resection. The main comorbidities were hypertension (53.9%), diabetes (20%), hypercholesterolemia (18.8%), and atrial fibrillation (14.6%).

ORR, PFS, and OS

Overall, 6 trials provided data for the ORR.[13,19-23] The weighted pooled ORRs were 33.3% (95% confidence interval [CI], 21.7%-44.9%) for the bevacizumab arms (P for heterogeneity < .001; I^2 = 84%) and 12.1% (95% CI, 7%-17.1%) for the control arms (P for heterogeneity = .23; I^2 = 32%). In direct comparisons (2 RCTs),[13,19] bevacizumab added to chemotherapy (5-FU or capecitabine) doubled the ORR compared with monochemotherapy alone (OR, 2.05; 95% CI, 1.26-3.34; P = .004; P for heterogeneity = .84; I^2 = 0%; Figure 2A).

All trials provided data for PFS and OS.[13,18-24] The weighted pooled median PFS was 9.4 months (95% CI, 8.2-11.2 months) with the bevacizumab combinations (P for heterogeneity = .55; I^2 = 0%) and ranged from 5.1 to 5.5 months in the 2 control arms with data available.[13,19] Bevacizumab-based doublets reduced the risk of progression by approximately 50% compared with

Figure 1 Flow Diagram of Systematic Published Data Search

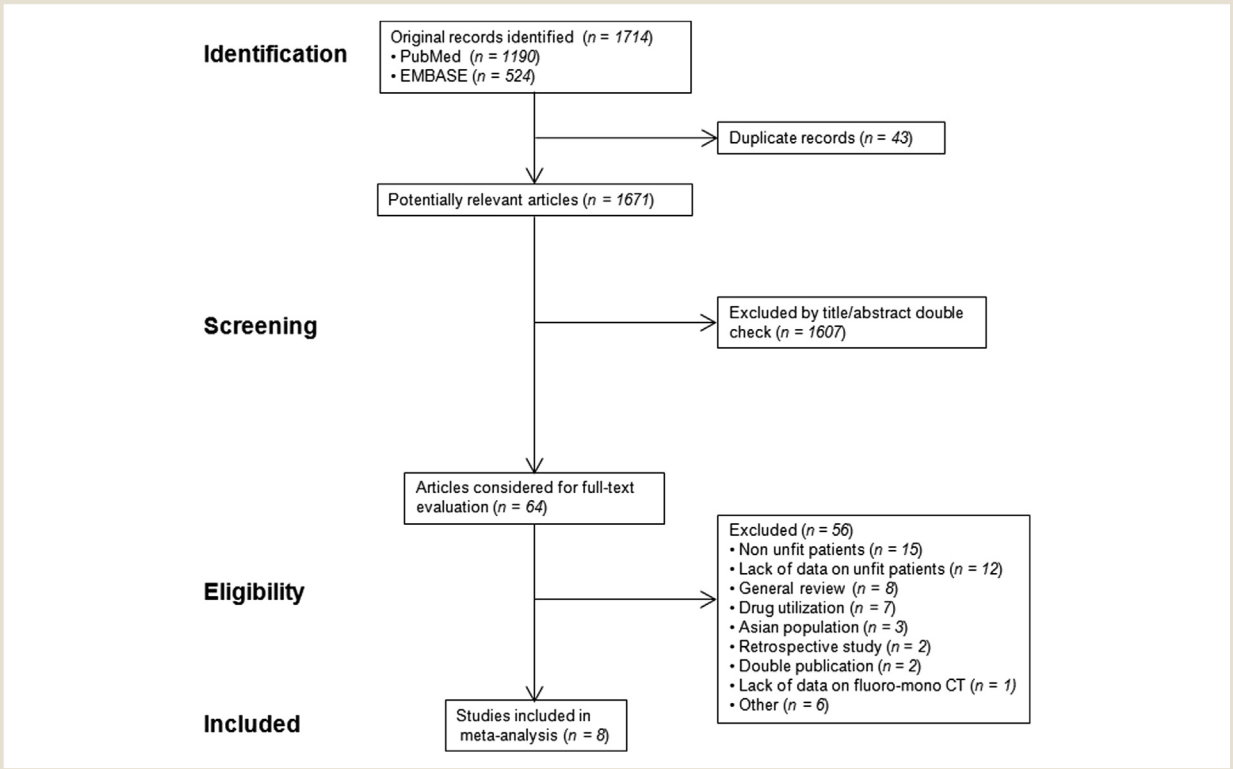
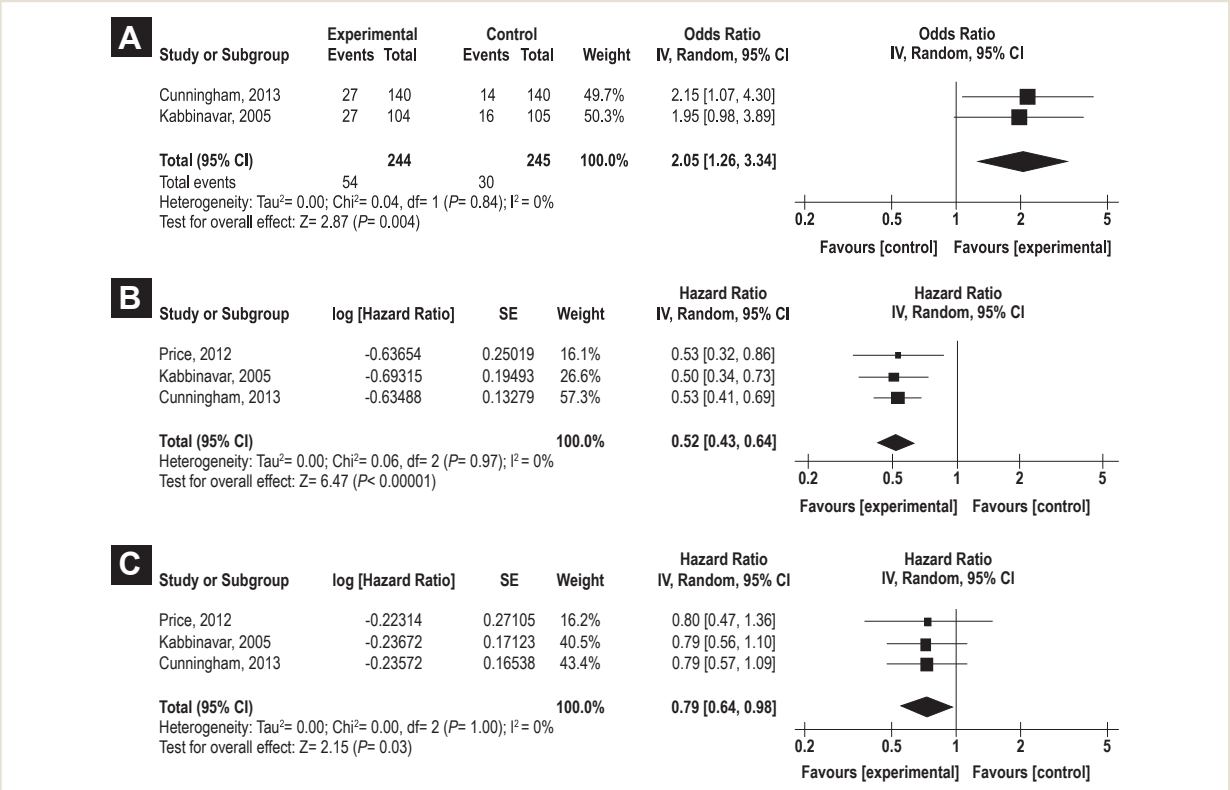


Table 1 Baseline Patient Characteristics of Overall Population and Stratified by Study Design

Characteristic	RCTs (n = 558)	Not Controlled (n = 224)	All Patients (n = 782)
Age (years) (assumption of normality)	75	77	75
Male gender	325 (58.2)	116 (50.8)	441 (56.4)
ECOG PS			
0-1	505 (90.8)	179 (79.9)	684 (87.7)
>1	51 (9.2)	45 (20.1)	96 (12.3)
Missing data	2 (0.4)	0 (0)	2 (0.3)
Primary site			
Rectum	117 (24.5)	31 (19.3)	148 (23.2)
Colon	319 (66.7)	119 (73.9)	438 (68.5)
Rectum and colon	42 (8.9)	11 (6.8)	53 (8.3)
Missing data	80 (14.3)	63 (28.1)	143 (18.3)
Metastatic site number			
1	70 (34.7)	102 (63)	172 (47.3)
>1	132 (65.3)	60 (37)	192 (52.7)
Missing data	356 (63.8)	62 (27.7)	418 (53.5)
Metastatic site			
Liver	236/349 (67.6)	159/208 (76.4)	395/557 (70.9)
Lung	149/349 (42.7)	80/208 (38.5)	229/557 (41.4)
Previous treatment			
Adjuvant CT			
Yes	111 (22.7)	48 (21.4)	159 (22.3)
No	378 (77.3)	176 (78.6)	554 (77.7)
Missing data	69 (12.4)	0 (0)	69 (8.8)
RT			
Yes	55 (11.2)	11 (7.6)	66 (10.4)
No	434 (88.8)	134 (92.4)	568 (89.6)
Missing data	69 (12.4)	79 (35.3)	148 (18.9)
Primary tumor resection			
Yes	249 (71.3)	34 (82.9)	283 (72.6)
No	100 (28.7)	7 (17.1)	107 (27.4)
Missing data	209 (37.5)	183 (81.7)	392 (50.1)
Comorbidities			
Hypertension	186/349 (53.3)	56/100 (56)	242/449 (53.9)
Myocardial infarction	24/349 (6.9)	NR	24/349 (6.9)
Thromboembolic events	12/280 (4.3)	NR	12/280 (4.3)
Diabetes	13/69 (18.8)	9/41 (22)	22/110 (20)
Angina pectoris	6/69 (8.7)	NR	6/69 (8.7)
Hypercholesterolemia	13/69 (18.8)	NR	13/69 (18.8)
Atrial fibrillation	NR	6/41 (14.6)	6/41 (14.6)
CVI or stroke	11/349 (3.2)	NR	11/349 (3.2)
Transient ischemic attack	3/69 (4.3)	NR	3/69 (4.3)
Neurologic disorders	16/280 (5.7)	NR	16/280 (5.7)
Administered CT			
Capecitabine	349 (62.5)	182 (81.2)	531 (67.9)
5-FU/LV	209[a] (37.5)	42[b] (18.8)	251 (32.1)

Data presented as median or frequency (n or n/total number of patients evaluated [%]).
Abbreviations: 5-FU = 5-fluorouracil; CT = chemotherapy; CVI = cerebrovascular infarction; ECOG PS = Eastern Cooperative Oncology Group performance status; LV = leucovorin; NR = not reported; RCTs = randomized controlled trials; RT = radiotherapy.
[a]Data from Tebbutt et al.[5]
[b]Data from Kim[10] (assuming a 2:1 ratio of 5-FU to capecitabine).

Figure 2 Meta-Analysis Results for (A) Objective Response Rate, (B) Progression-Free Survival and (C) Overall Survival for Unfit or Elderly Patients With Metastatic Colorectal Cancer Treated With Bevacizumab Plus Fluoropyrimidine-Based Monochemotherapy (Experimental Arm) or Monochemotherapy Alone (Control Arm). Data Presented as Forest Plot Showing Odds Ratios and 95% Confidence Intervals (CI)



Abbreviation: SE = standard error.

chemotherapy alone (HR, 0.52; 95% CI, 0.43-0.64; $P < .00001$; P for heterogeneity = .97; $I^2 = 0\%$; Figure 2B). In contrast, the weighted pooled median OS in the bevacizumab arms was 20.4 months (95% CI, 17.3-24.8 months; P for heterogeneity = .85; $I^2 = 0\%$) and ranged from 12.9 to 16.8 months in the 2 control arms with data available.[13,19] The addition of bevacizumab to chemotherapy reduced the risk of death by approximately 20% (HR, 0.79; 95% CI, 0.64-0.98; $P = .03$; P for heterogeneity = 1.00, $I^2 = 0\%$; Figure 2C).

Compliance and Safety

The treatment regimens are reported in Supplemental Table 3 (available in the online version). The reasons for discontinuation in the bevacizumab arms were mainly disease progression (48.2%), toxicity (21.2%), and refusal (11.4%).[13,20,22,24] In the control arms, the corresponding values were 66.2%, 9.8%, and 6.8%.[13] Toxicity was reported as the reason for treatment discontinuation in the bevacizumab arms for 25.4% of the patients in the non-randomized studies[20,22,24] and 17.6% of those in the randomized trials.[13]

In the safety analysis (Table 2), which included 75% of all patients (6 trials),[13,19-23] the main all-grade toxicities were hand-foot syndrome (57.4%), diarrhea (42.1%), and hypertension (27%) in the bevacizumab arms and hand-foot syndrome (38.6%), diarrhea (34.3%), and nausea (26.4%) in the monochemotherapy-alone arms. Among the severe toxicities (grade 3-4; Table 3), the more frequent were hand-foot syndrome (16.3%), diarrhea (15.7%), and venous thrombosis (7.4%) in the bevacizumab arms and diarrhea (19.5%), hand-foot syndrome (6.4%), and venous thrombosis (4.3%) in control arms. The rates of grade 3-4 hypertension were greater among the bevacizumab-treated patients (6.9% vs. 2%).

The adverse events typically observed with bevacizumab therapy, such as bleeding and proteinuria (all grades), were also more frequent with bevacizumab than with chemotherapy alone (24.3% vs. 6.4% and 25.6% vs. 8.2%, respectively). Grade 3 to 4 hematologic toxicity was rare.

Modification of the chemotherapy was reported rarely. In the largest phase III trial (Avastin With Xeloda in the Elderly [AVEX]),[13] the capecitabine dose modification rate was 54% and 43% in the experimental and control arms, respectively. The dose intensity for the combination arms was generally good when reported, for both chemotherapy (range, 84%-94%) and bevacizumab (99%) in the 5 arms with data available.[13,18,19,21,22] A similar dose intensity was reported in the 3 fluoropyrimidine arms.[13,18,19]

Table 2 All-Grade Toxicities Reported Stratified by Study Design and Treatment Arm

All-Grade Toxicity	RCTs		Not Controlled		All	
	Patients (n)	Point Estimate (95% CI)	Patients (n)	Point Estimate (95% CI)	Patients (n)	Point Estimate (95% CI)
Bevacizumab arm						
Hypertension	58/244	23.8 (18.6-29.6)	35/100	35 (25.6-44.4)	93/344	24 (22.3-31.7)
Venous thrombosis	16/140	11.4 (6.2-16.7)	9/100	9 (3.4-14.6)	25/240	10.4 (6.5-14.3)
Arterial thrombosis	16/244	6.6 (3.5-9.7)	3/75	4 (0-8.4)	19/319	6 (3.4-8.6)
MI	ND	NA	0/59	0 (0-5.9)	0/59	0 (0-5.9)
GI perforation	3/244	1.2 (0-2.6)	1/16	6.3 (0-18.1)	4/260	1.5 (0-3)
Bleeding	34/140	24.3 (17.2-31.4)	ND	NA	34/140	24.3 (17.2-31.4)
Proteinuria	48/244	19.7 (14.7-24.7)	25/41	61 (46-75.9)	73/285	25.6 (20.6-30.7)
Neutropenia	7/140	5 (1.4-8.6)	18/145	12.4 (7.1-17.8)	25/285	8.8 (5.8-12.7)
Thrombocytopenia	ND	NA	32/145	22.1 (15.3-28.8)	32/145	22.1 (15.3-28.8)
Mucositis	20/140	14.3 (8.5-20.1)	38/145	26.2 (19.1-33.4)	58/285	20.4 (15.7-25)
Anemia	ND	NA	32/145	22.1 (15.3-28.8)	32/145	22.1 (15.3-28.8)
Diarrhea	54/140	38.6 (30.5-46.6)	66/145	45.5 (37.4-53.6)	120/285	42.1 (36.4-47.8)
Hand-foot syndrome	66/140	47.1 (38.9-55.4)	90/145	62.1 (54.2-70)	156/285	57.4 (49-60.5)
Nausea	32/140	22.9 (15.9-29.8)	36/145	24.8 (17.8-31.9)	68/285	23.9 (18.9-28.8)
Neurotoxicity	ND	NA	ND	NA	ND	NA
Control arm						
Hypertension	12/245	4.9 (2.2-7.6)	NA	NA	12/245	4.9 (2.2-7.6)
Venous thrombosis	7/140	5 (1.4-8.6)	NA	NA	7/140	5 (1.4-8.6)
Arterial thrombosis	8/245	3.3 (1-5.5)	NA	NA	8/245	3.3 (1-5.5)
MI	ND	NA	NA	NA	ND	NA
GI perforation	0/245	0 (0-1.2)	NA	NA	0/245	0 (0-1.2)
Bleeding	9/140	6.4 (2.4-10.5)	NA	NA	9/140	6.4 (2.4-10.5)
Proteinuria	20/245	8.2 (4.7-11.6)	NA	NA	20/245	8.2 (4.7-11.6)
Neutropenia	1/140	0.7 (0-2.1)	NA	NA	1/140	0.7 (0-2.1)
Thrombocytopenia	ND	NA	NA	NA	ND	NA
Mucositis	11/140	7.9 (3.4-12.3)	NA	NA	11/140	7.9 (3.4-12.3)
Anemia	ND	NA	NA	NA	ND	NA
Diarrhea	48/140	34.3 (26.4-42.3)	NA	NA	48/140	34.3 (26.4-42.3)
Hand-foot syndrome	54/140	38.6 (30.5-46.6)	NA	NA	54/140	38.6 (30.5-46.6)
Nausea	37/140	26.4 (19.1-33.7)	NA	NA	37/140	26.4 (19.1-33.7)
Neurotoxicity	ND	NA	NA	NA	ND	NA

Data presented as the number of patients experiencing a specific adverse event/total number of patients evaluated, along with the point estimate (95% CI).
Abbreviations: CI = confidence interval; GI = gastrointestinal; MI = myocardial infarction; NA = not applicable; ND = not determined; RCT = randomized controlled trial.

Risk of Bias Assessment

The risk of bias was evaluated on the PFS endpoint, which was less accurate than the OS endpoint. A selection bias could not be excluded in 1 of the 3 RCTs because of inadequate reporting.[18] For the same reason, an attrition bias could not be excluded in 2 of the 3 RCTs.[18,19] All review authors (V.T., L.P., F.P., G.M.) independently assessed a high risk of detection bias for each RCT because of the absence of blinding[13,18] or inadequate reporting of applied statistical methods.[19] Details regarding the risk of bias are shown in Figure 3.

Discussion

We performed the present analysis in the attempt to understand the feasibility, safety, and efficacy of the combination of bevacizumab with fluoropyrimidines in elderly or unfit patients with mCRC. The treatment of these patients is a common challenge in clinical practice, because a worldwide accepted therapeutic standard is still lacking. It is well known that elderly and unfit patients are generally excluded or underrepresented in RCTs.[25] Furthermore, the elderly patients included in clinical trials are typically a selected group of subjects with favorable clinical features; therefore, they are not fully representative of the patients seen in real-world clinical practices. Moreover, elderly and unfit patients are a heterogeneous group of subjects with as yet undefined rigorous criteria for age cutoffs and comorbidity assessments. Therefore, elderly patients are commonly treated with a very conservative approach for the fear of excessive toxicities or complications related to medical therapies.[26] To date, monochemotherapy combined with fluoropyrimidines (5-FU or capecitabine) is one of the most commonly used

Table 3 Grade 3 to 4 Toxicities Reported Stratified by Study Design and Treatment Arm

Grade 3-4 Toxicity	RCTs		Not Controlled		All	
	Patients (n)	Point Estimate (95% CI)	Patients (n)	Point Estimate (95% CI)	Patients (n)	Point Estimate (95% CI)
Bevacizumab arm						
Hypertension	19/244	7.8 (4.4-11.2)	9/161	5.6 (2.0-9.1)	28/405	6.9 (4.4-9.4)
Venous thrombosis	11/140	7.9 (3.4-12.3)	10/145	6.9 (2.8-11)	21/285	7.4 (4.3-10.4)
Arterial thrombosis	3/140	2.1 (0-4.5)	1/104	1 (0-2.8)	4/244	1.6 (0-3.2)
MI	ND	NA	1/104	1 (0-2.8)	1/104	1 (0-2.8)
GI perforation	0/140	0 (0-2.1)	2/45	4.4 (0-10.5)	2/185	1.1 (0-2.6)
Bleeding	5/244	2 (0.3-3.8)	1/45	2.2 (0-6.5)	6/289	2.1 (0.4-3.7)
Proteinuria	3/244	1.2 (0-2.6)	3/86	3.5 (0-7.4)	6/330	1.8 (0.4-3.3)
Neutropenia	1/140	0.7 (0-2.1)	3/120	2.5 (0-5.3)	4/260	1.5 (0-3)
Thrombocytopenia	ND	NA	2/75	2.7 (0-6.3)	2/75	2.7 (0-6.3)
Mucositis	0/140	0.7 (0-2.1)	6/161	3.7 (0.8-6.7)	6/301	2 (0.4-3.6)
Anemia	ND	NA	1/75	1.3 (0-3.9)	1/75	1.3 (0-3.9)
Diarrhea	48/240	20 (14.9-25.1)	8/166	4.8 (1.6-8.1)	56/356	15.7 (11.9-19.5)
Hand-foot syndrome	21/140	15 (9.1-20.9)	28/161	17.4 (11.5-23.3)	49/301	16.3 (12.1-20.5)
Nausea	1/140	0.7 (0-2.1)	2/120	1.7 (0-4)	3/260	1.2 (0-2.5)
Neurotoxicity	ND	NA	ND	NA	ND	NA
Control arm						
Hypertension	5/245	2 (0.3-3.8)	NA	NA	5/245	2 (0.3-3.8)
Venous thrombosis	6/140	4.3 (0.9-7.6)	NA	NA	6/140	4.3 (0.9-7.6)
Arterial thrombosis	1/140	0.7 (0-2.1)	NA	NA	1/140	0.7 (0-2.1)
MI	ND	4.3 (0.9-7.6)	NA	NA	ND	4.3 (0.9-7.6)
GI perforation	0/140	0 (0-2.1)	NA	NA	0/140	0 (0-2.1)
Bleeding	3/245	1.2 (0-2.6)	NA	NA	3/245	1.2 (0-2.6)
Proteinuria	0/245	0 (0-1.2)	NA	NA	0/245	0 (0-1.2)
Neutropenia	1/140	0.7 (0-2.1)	NA	NA	1/140	0.7 (0-2.1)
Thrombocytopenia	ND	NA	NA	NA	ND	NA
Mucositis	1/140	0.7 (0-2.1)	NA	NA	1/140	0.7 (0-2.1)
Anemia	ND	NA	NA	NA	ND	NA
Diarrhea	47/241	19.5 (14.5-24.5)	NA	NA	47/241	19.5 (14.5-24.5)
Hand-foot syndrome	9/140	6.4 (2.4-10.5)	NA	NA	9/140	6.4 (2.4-10.5)
Nausea	0/140	0 (0-2.1)	NA	NA	0/140	0 (0-2.1)
Neurotoxicity	ND	NA	NA	NA	ND	NA

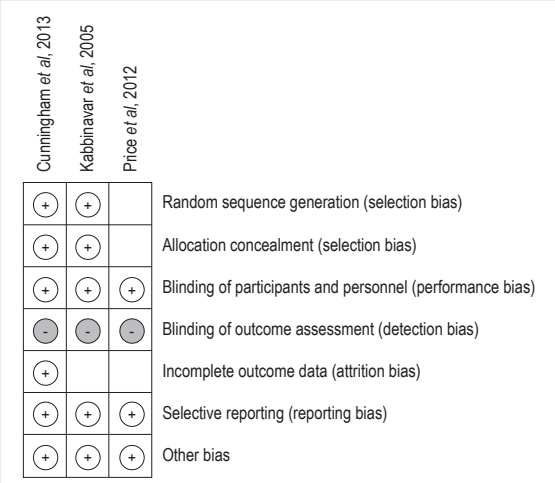
Data presented as number of patients experiencing a specific adverse event/total number of patients evaluated and point estimate (95% CI).
Abbreviations: CI = confidence interval; GI = gastrointestinal; MI = myocardial infarction; NA = not applicable; ND = not determined; RCT = randomized controlled trial.

treatments.[27] Retrospective data have shown that in elderly or unfit patients, the use of bevacizumab is usually limited compared with that use in a younger population. This is mainly because clinicians are concerned about possible cardiovascular toxicities, although several trials have indicated the significant benefit afforded by the addition of bevacizumab to fluoropyrimidines compared with fluoropyrimidines alone.[16,28]

Therefore, the aim of the present meta-analysis was to only select trials reporting data for elderly or unfit patients treated with a backbone chemotherapy of fluoropyrimidines alone combined with bevacizumab. Our results demonstrated clinically meaningful improvements in terms of activity and efficacy provided by the addition of bevacizumab to fluoropyrimidines. The weighted ORR was 33.3%. Also, by pooling the data from the RCTs, the OR for progression was 2.05 in favor of bevacizumab ($P = .004$). The overall-weighted PFS was 9.4 months. By pooling the data from the RCTs, the HR for progression was 0.52 in favor of bevacizumab ($P < .001$). Finally, the weighted OS was 20.4 months; by pooling the RCT data, the HR for death was 0.64 in favor of bevacizumab ($P = .03$). We believe these findings are not only statistically significant but also relevant from a clinical viewpoint for this population of patients with unfavorable medical features.

The safety profile seems acceptable and manageable. The increase in all-grade toxicities was not surprising, and the incidence of grade 3-4 toxicity was only slightly increased by the addition of bevacizumab. In particular, the frequency of clinically harmful toxicities (eg, arterial thrombosis, myocardial infarction, gastrointestinal perforation, and bleeding) ranged from 1% to 2%. Furthermore, no

Figure 3 Risk of Bias Assessment, Evaluated on Progression-Free Survival Endpoint, of the 3 Randomized Controlled Trials Included in the Meta-Analysis



trial reported unexpected toxicities. These results compare well with published data for younger patients.[29]

Our analysis had several limitations. First, our study was not a pooled analysis of raw data from individual patients but a meta-analysis of summary statistics of published data. Therefore, the heterogeneity of trial design, patient inclusion criteria, and treatment administration should be considered as potential biases. However, to limit this problem, we decided to carefully select the trials to be included in our analysis. In particular, we selected only prospective trials reporting data from elderly or unfit patients treated in first-line with monochemotherapy with 5-FU or capecitabine with or without bevacizumab. Also, we excluded trials of Asian patients. A second limitation lies in the quality of published data in this setting. Despite our careful selection, the criteria for patient accrual were often poorly defined ("patient deemed unsuitable for combination therapy"). Also, the reported data on comorbidity assessment and treatment modulation and discontinuation were sometime incomplete. Once more, in this scenario, it would only be possible to have more robust data by increasing the number of patients analyzed (782 in our pooled analysis). Finally, we reported data derived from the analysis of published trials; therefore, some degree of patient selection was present (ie, Eastern Cooperative Oncology Group performance status was > 1 for only 13% of patients). However, the median age of the subjects included in the analysis was relatively old (75 years), and the frequency of comorbidities was considerable (hypertension in 54%, cardiomyopathy in 30%, diabetes in 20%, vascular accidents in 11%), suggesting that our studied population was the target population as we had planned.

The present analysis showed that bevacizumab added to first-line fluoropyrimidine chemotherapy for elderly or unfit patients with mCRC provides statistically significant and clinically meaningful advantages in ORR, PFS, and OS. Currently, only few data are available regarding upfront treatment of elderly or unfit patients with mCRC using anti-endothelial growth factor receptor agents as monotherapy.[30] The available data from retrospective analyses or small phase II trials[31,32] are intriguing; however, their results are difficult to translate into daily practice. A randomized study of elderly or unfit patients with mCRC and RAS/BRAF wild-type tumors would be desirable to formally confirm the efficacy of anti-endothelial growth factor receptor agents as single-agent first-line therapy. We believe the optimal selection of first-line treatment in this population is particularly important, because of the limited use of subsequent lines of therapy (the rate of second-line therapies ranged from 37% to 50% in the trials we analyzed). Although the overall incidence of adverse events was slightly increased by the addition of bevacizumab, the safety profile of the treatment did not differ significantly from that of younger patients. Therefore, older age or the presence of some comorbidities should not be considered as an absolute contraindication for the addition of bevacizumab to fluoropyrimidine-based chemotherapy. Moreover, it should be noted that concomitant anticoagulant therapy, if indicated, could be safely administered with bevacizumab.[33] Nevertheless, a careful assessment of the patient's medical history with the identification of clinically relevant comorbidities (in particular, cardiovascular events $\leq$ 6 months before treatment start) and potential risk factors (eg, uncontrolled hypertension, unstable angina, and arrhythmia requiring treatment) is necessary to minimize treatment-related toxicities and increase the therapeutic ratio of treatment.

The strength of our results are potentially limited by the overall quality of the trials conducted in elderly and unfit patients, which was generally quite low owing to several factors, including the relatively low patient number, the equivocal criteria used for the definition of "elderly," and the variable assessment of comorbidities. Further efforts to conduct high-quality prospective trials with elderly or unfit mCRC patients is needed, and it is highly recommended that these trials include a comprehensive geriatric assessment and the evaluation of important endpoints such as changes in functional, mental, and comorbid status and quality of life. In particular, a formal comparison between 5-FU or capecitabine plus bevacizumab and dose-adapted doublet chemotherapy in the geriatric population is warranted. Similarly, it would be interesting to address the comparison between capecitabine plus bevacizumab versus capecitabine and oxaliplatin plus bevacizumab, although the latter combination seems feasible.[34] These comparisons should be prospectively tested in randomized trials, which could include evaluations of the quality of life and pharmacoeconomics aspects. The results of these studies are eagerly awaited by the oncologic community.

Conclusion

The addition of bevacizumab to first-line fluoropyrimidine-based chemotherapy in elderly or unfit patients with mCRC is feasible without particular safety concerns and provides relevant results in terms of both activity and efficacy. This combination should therefore represent an important treatment option for this complex group of patients.

Clinical Practice Points

- A therapeutic standard for elderly and unfit patients with mCRC is still lacking.

- The present meta-analysis tested bevacizumab with fluoropyrimidines as first-line therapy.
- PFS and OS were significantly increased with the combination of bevacizumab and a fluoropyrimidine.
- The safety profile was acceptable, without particular concerns.
- First-line bevacizumab with fluoropyrimidines is feasible for these complex patients.

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Disclosure

The authors declare that they have no competing interests.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clcc.2016.08.006.

References

1. Siegel R, DeSantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin* 2014; 64:104-17.
2. Puts MTE, Hardt J, Monette J, Girre V, Springall E, Alibhai SMH. Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J Natl Cancer Inst* 2012; 104:1133-63.
3. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370: 143-52.
4. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; 370:135-42.
5. Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group randomized phase III MAX study. *J Clin Oncol* 2010; 28:3191-8.
6. Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011; 12:1032-44.
7. Biganzoli L, Lichtman S, Michel JP, et al. Oral single-agent chemotherapy in older patients with solid tumours: a position paper from the International Society of Geriatric Oncology (SIOG). *Eur J Cancer* 2015; 51:2491-500.
8. Folprecht G, Seymour MT, Saltz L, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. *J Clin Oncol* 2008; 26:1443-51.
9. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 2006; 24:4085-91.
10. Kim JH. Chemotherapy for colorectal cancer in the elderly. *World J Gastroenterol* 2015; 21:5158-66.
11. Landre T, Uzzan B, Nicolas P, et al. Doublet chemotherapy vs. single-agent therapy with 5FU in elderly patients with metastatic colorectal cancer. a meta-analysis. *Int J Colorectal Dis* 2015; 30:1305-10.
12. Aprile G, Fontanella C, Lutrino ES, et al. Angiogenic inhibitors for older patients with advanced colorectal cancer: does the age hold the stage? *World J Gastroenterol* 2013; 19:2131-40.
13. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14:1077-85.
14. Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet* 2011; 377:1749-59.
15. Doat S, Thiébaut A, Samson S, Ricordeau P, Guillemot D, Mitry E. Elderly patients with colorectal cancer: treatment modalities and survival in France. National data from the ThInDiT cohort study. *Eur J Cancer* 2014; 50:1276-83.
16. Parakh S, Wong H, Rai R, et al. Patterns of care and outcomes for elderly patients with metastatic colorectal cancer in Australia. *J Geriatr Oncol* 2015; 6: 387-94.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151:264-9.
18. Price TJ, Zannino D, Wilson K, et al. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of capecitabine, bevacizumab and mitomycin C. *Ann Oncol* 2012; 23:1531-6.
19. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; 23:3697-705.
20. Naeim A, Ward PR, Wang HJ, et al. A phase II trial of frontline capecitabine and bevacizumab in poor performance status and/or elderly patients with metastatic colorectal cancer. *J Geriatr Oncol* 2013; 4:302-9.
21. Vrdoljak E, Omrčen T, Boban M, Hrabar A. Phase II study of bevacizumab in combination with capecitabine as first-line treatment in elderly patients with metastatic colorectal cancer. *Anticancer Drugs* 2011; 22:191-7.
22. Feliu J, Safont MJ, Salud A, et al. Capecitabine and bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer. *Br J Cancer* 2010; 102:1468-73.
23. Puthillath A, Mashtare T, Wilding G, et al. A phase II study of first-line biweekly capecitabine and bevacizumab in elderly patients with metastatic colorectal cancer. *Crit Rev Oncol Hematol* 2009; 71:242-8.
24. Hofheinz R, Petersen V, Kindler M, et al. Bevacizumab in first-line treatment of elderly patients with metastatic colorectal cancer: German community-based observational cohort study results. *BMC Cancer* 2014; 14:761.
25. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003; 21:1383-9.
26. Quipourt V, Jooste V, Cottet V, Faivre J, Bouvier AM. Comorbidities alone do not explain the undertreatment of colorectal cancer in older adults: a French population-based study. *J Am Geriatr Soc* 2011; 59:694-8.
27. Seal BS, Sullivan SD, Ramsey SD, et al. Systemic therapy for colorectal cancer: patterns of chemotherapy and biologic therapy use in nationally representative US claims database. *BioDrugs* 2014; 28:229-36.
28. Fu AZ, Tsai HT, Marshall JL, Freedman AN, Potosky AL. Utilization of bevacizumab in US elderly patients with colorectal cancer receiving chemotherapy. *J Oncol Pharm Pract* 2014; 20:332-40.
29. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. *BMC Cancer* 2012; 12:89.
30. Rosati G, Aprile G, Cardellino GG, Avallone A. A review and assessment of currently available data of the EGFR antibodies in elderly patients with metastatic colorectal cancer. *J Geriatr Oncol* 2016; 7:134-41.
31. Pietrantonio F, Cremolini C, Aprile G, et al. Single-agent panitumumab in frail elderly patients with advanced RAS and BRAF wild-type colorectal cancer: challenging drug label to light up new hope. *Oncologist* 2015; 20:1261-5.
32. Sastre J, Massuti B, Pulido G, et al. First-line single-agent panitumumab in frail elderly patients with wild-type KRAS metastatic colorectal cancer and poor prognostic factors: a phase II study of the Spanish Cooperative Group for the treatment of digestive tumours. *Eur J Cancer* 2015; 51:1371-80.
33. Leighl NB, Bennouna J, Yi J, Moore N, Hambleton J, Hurwitz H. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. *Br J Cancer* 2011; 104:413-8.
34. Feliu J, Salud A, Safont MJ, et al. First-line bevacizumab and capecitabine—oxaliplatin in elderly patients with mCRC: GEMCAD phase II BECOX study. *Br J Cancer* 2014; 111:241-8.
35. Petrelli N, Douglass HO Jr, Herrera L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial—Gastrointestinal Tumor Study Group. *J Clin Oncol* 1989; 7:1419-26.

Supplemental Table 1 Characteristics of 8 Studies Included in the Meta-Analysis

Investigator	Year	Controlled	Design	International	Geographic Area			Recruitment		Patients (n)	
					USA	Europe	Other	Start	End	Bevacizumab	Control
Cunningham et al,[13] 2013	2013	Yes	RCT, phase III, multicenter	Yes	No	Yes	Canada, Mexico, South Korea	July 2007	December 2010	140	140
Price et al,[18] 2012	2012	Yes	RCT, phase II/III, multicenter	Yes	No	Yes	Australia, New Zealand	July 2005	June 2007	32	37
Kabbinavar et al,[19] 2005	2005	Yes	RCT, phase II, multicenter	Yes	Yes	No	Australia, New Zealand	August 2000	July 2002	104	105
Naeim et al,[20] 2013	2013	No	Phase II, multicenter	No	Yes	No	None	October 2005	February 2009	45	-
Vrdoljak et al,[21] 2011	2011	No	Phase II, single center	No	No	Yes	None	June 2007	November 2008	41	-
Feliu et al,[22] 2010	2010	No	Phase II, multicenter	No	No	Yes	None	August 2006	January 2008	59	-
Puthillath et al,[23] 2009	2009	No	Phase II, single center	No	Yes	No	None	December 2004	April 2007	16	-
Hofheinz et al,[24] 2014	2014	No	Prospective cohort, multicenter	No	No	Yes	None	January 2005	June 2009	63	-

Abbreviation: RCT = randomized controlled trial.

Supplemental Table 2 Major Eligibility Criteria for Included Studies

Investigator	Baseline Characteristics				Clinical Characteristics		Previous Treatment	
	Patient Age (Years)	ECOG PS	Life Expectancy at Enrollment (mo)	Judgement of Treating Investigator	mCRC Diagnosis	Measurable Disease	Metastatic Disease	Early Disease
Cunningham et al,[13] 2013	≥70	0-2	≥3	Not candidate for combination CT with IRI or OXA or curative resection of metastatic lesions	Cytologically or histologically proven CA of colon or rectum, or both	≥1 Measurable lesion; evaluable disease according to RECIST, version 1.0	No previous CT for mCRC	Adjuvant (neoadjuvant) CT completed >6 mo before start of study treatment; no adjuvant anti-VEGF treatment
Price et al,[18] 2012	≥75	0-2	≥3	Considered suitable for capecitabine monotherapy	Histologically proven colorectal ACA	Measurable or nonmeasurable unresectable metastatic disease	No previous CT for mCRC	Adjuvant CT completed >6 mo before disease relapse
Kabbinavar et al,[19] 2005	≥65[a]	1-2[a]	NR	Not candidate for first-line IRI-containing therapy	Histologically proven mCRC	Measurable metastatic disease	Untreated mCRC; previous RT to abdomen or pelvis[a]	NR
Naeim et al,[20] 2013	>18 or >70[b]	2 or 1[b]	NR	NR	Histologically proven ACA of colon	≥1 Measurable lesion according to RECIST, version 1.0	No previous CT for mCRC	Adjuvant CT completed >6 mo before diagnosis of metastatic disease
Vrdoljak et al,[21] 2011	≥70	0-2	≥3	NR	Cytologically or histologically proven colorectal ACA	≥1 Lesion unidimensionally measurable by computed tomography (RECIST, version 1.0)	No previous CT for mCRC	Adjuvant CT completed >6 mo before trail enrollment
Feliu et al,[22] 2010	≥70	0-2	≥3	Unsuitable for receiving combination OXA or IRI CT	Histologically proven mCRC	≥1 Lesion unidimensionally measurable by computed tomography (RECIST, version 1.0)	No previous CT for mCRC; earlier RT for mCRC permitted if completed ≥6 wk before study inclusion and if untreated measurable disease remained	Disease free ≥6 mo after adjuvant/neoadjuvant CT completion
Puthillath et al,[23] 2009	≥70	0-2	≥3	NR	Histologically proven mCRC	Measurable disease, defined as ≥1 lesion >20 mm on conventional computed tomography or >10 mm on spiral computed tomography scan	No previous CT for mCRC	Only previous 5-FU/LV adjuvant CT allowed, provided it was completed >6 mo before metastatic disease development
Hofheinz et al,[24] 2014	≥75	NR	NR	NR	mCRC diagnosis	NR	No previous CT for mCRC	NR

Abbreviations: 5-FU = 5-fluorouracil; ACA = adenocarcinoma; CA = carcinoma; CT = chemotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; IRI = irinotecan; LV = leucovorin; mCRC = metastatic colorectal cancer; NR = not reported; OXA = oxaliplatin; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; VEGF = vascular endothelial growth factor.

[a]At least 1 of these characteristics was required.

[b]Both conditions requested (ie, age > 18 years and ECOG PS 2 or age > 70 years and ECOG PS 1).

Supplemental Table 3 Treatment Regimen, Compliance, and Second-Line Therapy in 8 Included Studies

Investigator	Treatment Arm	Regimen	Median Duration; Median Dose Intensity	Patients Receiving Modified Dose[a]	Patients Administered Second-Line Therapy	
					Overall	Bevacizumab Only
Cunningham et al,[13] 2013	Experimental	Capecitabine (1000 mg/m^2 p.o. twice daily on days 1-14); bevacizumab (7.5 mg/kg I.V. on day 1), every 3 wk	5.8 mo; 9 cycles; capecitabine, 85.2%[b]; bevacizumab, 99.1%[b]	72/134 (54)	52/140 (37.1)	8/140 (5.7)
	Control	Capecitabine (1000 mg/m^2 p.o. twice daily on days 1-14), given every 3 wk	4.2 mo; 6 cycles; capecitabine, 89.6%[b]	59/136 (43)	52/140 (37.1)	11/140 (7.9)
Price et al,[18] 2012	Experimental	Capecitabine (1.25 g/m^2 twice daily on days 1-14 every 3 wk); investigators could nominate a lower starting dosage (ie, 1 g/m^2 twice daily) for patients considered at risk of toxicity; bevacizumab (7.5 mg/kg on day 1) every 3 wk	8 cycles; capecitabine, 85.6%; bevacizumab, 99.3%	NR	NR	NR
	Control	Capecitabine (1.25 g/m^2 twice daily on days 1-14 every 3 wk); investigators could nominate a lower starting dosage (ie, 1 g/m^2 twice daily) for patients considered at risk of toxicity	7 cycles; capecitabine, 93.2%	NR	NR	NR
Kabbinavar et al,[19] 2005	Experimental	5-FU/LV regimen: LV 500 mg/m^2 over 2 h and 5-FU 500 mg/m^2 as a bolus midway through LV infusion (Roswell Park regimen[c]), administered weekly for first 6 wk of each 8-wk cycle; total administration, 96 wk; bevacizumab, 5 mg/kg every 2 wk	31 wk; 5-FU: 84%; bevacizumab, NR	NR	52/104 (50)	NR
	Control	5-FU/LV regimen: LV 500 mg/m^2 over 2 h and 5-FU 500 mg/m^2 as bolus midway through LV infusion (Roswell Park regimen[c]), administered weekly for first 6 wk of each 8-wk cycle; total administration, 96 wk; placebo	23 wk; 5-FU, 92%; bevacizumab, NR	NR	52/105 (50)	NR
Naeim et al,[20] 2013	Experimental	Capecitabine (1000 mg/m^2 p.o. twice daily for 2 wk, followed by 1 wk of rest); bevacizumab (7.5 mg/kg I.V., every 3 wk)	6 cycles; NR	13/45 (28.9)	NR	NR
Vrdoljak et al,[21] 2011	Experimental	Capecitabine (1000 mg/m^2 twice daily for 2 wk, followed by 1 week of rest); bevacizumab (7.5 mg/kg on the first day of each 3-wk cycle)	12 cycles; capecitabine, 94%; bevacizumab, NR	24/41 (58.5)	11/41 (26.8)	NR
Feliu et al,[22] 2010	Experimental	Capecitabine (1250 mg/m^2 twice daily if CrCl >50 mL/min; 950 mg/m^2 twice daily if CrCl 30-50 mL/min); capecitabine administered for 2 wk, followed by 1 wk of rest; bevacizumab (7.5 mg/kg on first day of each 3-wk cycle)	7.1 cycles[b]; capecitabine, 94.2%[b]; bevacizumab, 99.0%[b]	NR	NR	NR
Puthillath et al,[23] 2009	Experimental	Capecitabine (1500 mg/m^2 p.o. twice daily for 7 days every 2 wk); bevacizumab (5 mg/kg I.V., every 2 wk)	12 cycles; NR	NR	13/16 (81.3)	NR
Hofheinz et al,[24] 2014	Experimental	Capecitabine or 5-FU at physician discretion; bevacizumab 5-10 mg/kg every 2 wk or 7.5-15 mg/kg every 3 wk at physician discretion	NR	NR	NR	NR

Abbreviations: 5-FU = 5-fluorouracil; CrCl = creatinine clearance; I.V. = intravenous; LV = leucovorin; NR = not reported; p.o. = orally.
[a]Regimen (eg, capecitabine plus bevacizumab, only capecitabine).
[b]Mean value.
[c]Petrelli et al.[35]