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Network Meta-analysis of First-Line Systemic Treatment for Patients With Metastatic Colorectal Cancer

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Abstract

Purpose: To assess the relative efficacy and safety of first-line systemic therapies in patients with metastatic colorectal cancer.

Experimental Design: A comprehensive literature review was conducted including MEDLINE, Embase, and the Cochrane Central Registry of Controlled Trials for phase II or III randomized controlled trials (RCTs) published up to and including July 15, 2019. We included RCTs in which at least 1 intervention was either chemotherapeutic agents (such as fluorouracil, irinotecan, or oxaliplatin) or antibodies targeting angiogenesis (such as bevacizumab) or agents that act on the epidermal growth factor receptor pathway (such as cetuximab and panitumumab) or studies reported at least one of the following outcomes: overall survival (OS), progression-free survival (PFS), and/or Grade 3 + adverse events (AEs). Using a random effect model, we performed a Bayesian network meta-analysis to analyze the probability of optimal therapeutic regime obtained from direct comparisons with indirect evidences. We estimated hazard ratios for OS and PFS.

Results: A total of 30 RCTs comprising 12,146 mCRC patients with 25 different treatment strategies were included. The triple combination FOLFOXIRI [fluorouracil, leucovorin, oxaliplatin, and irinotecan] plus bevacizumab provided significant survival benefits with improved OS over all other treatments. The network meta-analysis also indicated a significant advantage of using FOLFOXIRI plus bevacizumab in comparison to other treatment strategies for PFS. Besides, FOLFOXIRI plus bevacizumab was associated with the well-tolerated adverse events.

Conclusions: Our study supported the use of FOLFOXIRI plus bevacizumab as the best first-line regimen and potentially effective and safe strategy for the management of patients with mCRC.

Introduction

Colorectal cancer (CRC) ranks third among all malignant neoplasms and continues to be the leading cause of cancer-associated mortality, worldwide.[1] Approximately, 25% of patients with CRC present with liver metastasis at the initial diagnosis or will develop liver metastasis during the course of their disease.[2] In spite of the emergence of highly effective chemotherapy and advances in surgical techniques, the pool of patients with liver- and/or lung-isolated metastasis has expanded, and for the majority of patients with metastatic CRC (mCRC), the treatment remains a clinical challenge.[3] Indeed, for many years, 5-fluorouracil (FU)–based regimens have been the backbone of systemic therapy for mCRC. Recent incremental advancements in the systemic therapy for mCRC have been significantly facilitated with the introduction of several new cytotoxic and biologic agents.

Systemic therapy includes combinations of chemotherapeutic agents (oxaliplatin, irinotecan, or fluorouracil) alone or in combination with monoclonal antibodies targeting epidermal growth factor receptor (EGFR; cetuximab and panitumumab) or vascular endothelial growth factor receptor (VEGFR; bevacizumab), thereby providing distinctly effective first-line therapeutic regimens for mCRC.[4] However, head-to-head randomized trials comparing these therapeutic regimens mentioned above are still lacking, thus there is no evidence to guide optimal regimen for patients' mCRC. To overcome these

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limitations, using a network meta-analysis (NMA) approach, we compared and evaluated the relative therapeutic efficacies of all possible combinations of treatments, by simultaneous integration of direct evidence from head-to-head trials and indirect evidence to rank the different treatments for mCRC.

Method

Literature Search

Literature screening was performed according to the method outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[5] Institutional review board approval was not required. We conducted a comprehensive literature search of electronic databases including MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (Central) databases from inception up to and including July 15, 2019. A combination of MeSH-terms and keywords strategy was applied as follows: "Advance or metastatic colon cancer," "hepatic metastases, liver metastases," and "immunotherapy and targeted therapy" (Supplemental sTable 1). Also, the references of the selected articles and reviews were manually retrieved to obtain all potentially relevant studies. Retrieved articles were screened and reviewed for their eligibility by 2 independent reviewers (SX and YBE). Differences in the determination of the study's eligibility were resolved by consensus or through discussion with a third adjudicator (AS). The language of publication was restricted to English.

Study Selection

We included phase II or III randomized controlled trials (RCTs) that met the following inclusion criteria: (a) the study subjects were patients with mCRC; (b) systemic therapy was used as first-line treatment for mCRC Patients; (c) at least one of the interventions compared in the trial was either chemotherapeutic agents (such as fluorouracil, irinotecan, or oxaliplatin) or antibodies targeting angiogenesis (such as bevacizumab) or agents that act on the EGFR-related pathway (such as, cetuximab and panitumumab); and (d) the primary outcome was overall survival (OS), progression-free survival (PFS), and/or adverse events (AEs) of greater than or equal to Grade 3 according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE).[6] We excluded studies that were not RCTs and had unavailable data.

Data Extraction and Risk of Bias Assessment

The data extraction from each included study was performed independently by 2 reviewers (SX and AS) and entered into a standardized, predesigned Microsoft Excel form. The following data were extracted: the first author, the year of publication, country, patient characteristics, treatment strategies, sample size, number of patients evaluated for response, dose and schedule, median cycles received, and outcomes (median OS and median PFS). For PFS and OS, we extracted the hazard ratio (HR) with a 95% confidence interval (95% CI) if available. However, when HRs and corresponding CIs were not reported, we estimated them by reconstructing individual patient data from published Kaplan–Meier curves with methods described by Guyot and colleagues.[6] Authors of included studies were contacted if important data were unclear or not reported. The risk of bias in randomized trials was assessed independently by the reviewers (SX and YBE) using the Cochrane Collaboration tool and the risk-of-bias (RoB 2.0) tool.[7] Any disagreements were resolved through consensus.

Data Synthesis and Analysis

This study was implemented and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews.[8] All analyses were based on previous published studies, and no ethical approval or patient consent was required. The Bayesian NMA is as previously described.[9] We synthesized evidence for 3 outcomes: PFS, OS, and any Grade 3 + AEs. With regard to each outcome, we performed a Bayesian NMA with the help of Markov Chain Monte Carlo (MCMC) simulation technique with 100 000 iterations in each of the 3 chains. Non-informative priors (i.e., N[0, 10 000]) were selected as the effect parameters. We carried out a network plot for providing a visual representation of the evidence base, with different types of treatment expressed by nodes, while evidence weighted by lines connecting appropriate nodes. Each node represented a different treatment and its size depended on the number of patients that is directly examined. The nodes were joined by lines with different thickness which shows whether there was a direct relationship between treatments and the thickness was weighted according to the available direct evidence between them. What is more, we carried out the analysis under the fixed-effect model for the reason that only 1 trial has provided direct evidence for the majority of the treatment comparisons. However, a random-effects (RE) model was introduced as well as sensitivity analysis and model fits were compared using deviance information criteria (DIC).[10] In the comparison of any 2 models, suppose the DIC of 1 model was less than that of the other model by at least 5, it can be deemed as a better fit model. Heterogeneity in the network was assessed with the Cochrane Q ($\chi 2$) test and quantified in virtue of the I^2 statistic within each pairwise comparison when 2 or more trials were available for the comparison[11] and I^2 statistic whose values were 25%, 50%, and 75% indicated mild, moderate, and high heterogeneity, respectively. In our network, having both direct and indirect evidence for most comparisons is uncommon, we thus assume that our analysis is coherent (i.e., direct and indirect evidences, when both available for a given comparison, were statistically similar). In order to test the robustness of this assumption, node-splitting method was adopted so that incoherence in any

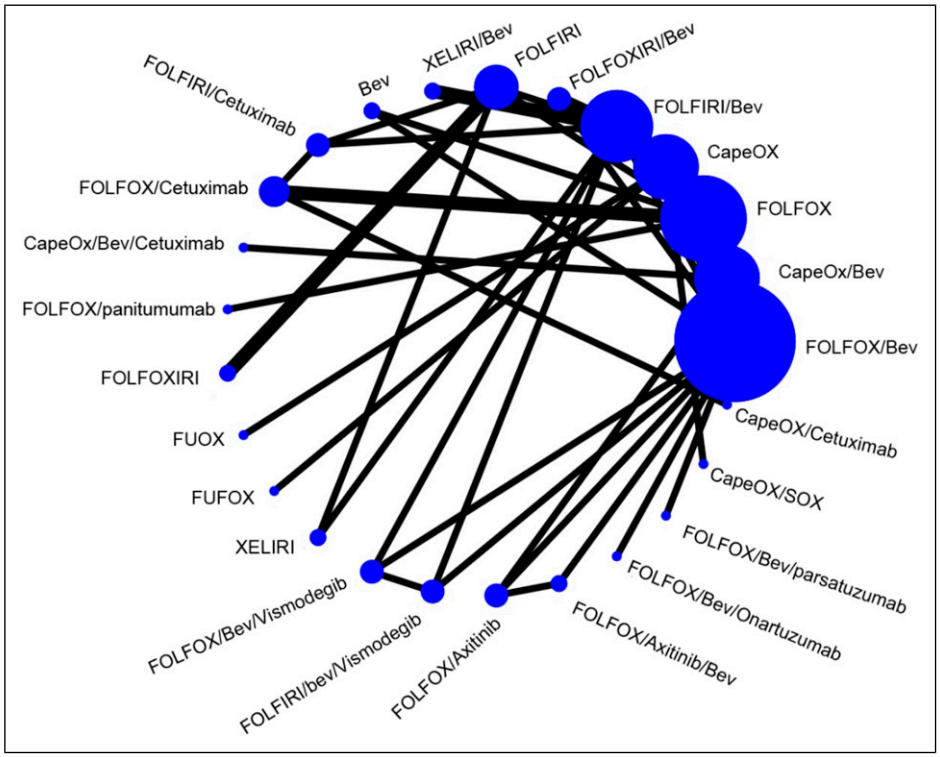

Figure 1. Network of the comparisons for the Bayesian network meta-analysis. XELIRI: CAPIRI, Irinotecan plus capecitabine, FOLFIRI: irinotecan plus fluorouracil plus leucovorin; BEV: bevacizumab; SOX: oxaliplatin; FUOX: high-dose fluorouracil plus oxaliplatin; FUFOX: fluorouracil plus folinic acid plus oxaliplatin; FOLFOX fluorouracil and leucovorin with oxaliplatin. CapeOX: XELOX, capecitabine plus oxaliplatin. Each node represented a different treatment and its size depended on the number of patients that is directly examined. The nodes were joined by lines with different thickness which shows whether there was a direct relationship between treatments and the thickness was weighted according to the available direct evidence between them.

closed loops can be assessed.[10,11] Relative effects of treatments are reported as HR for survival outcomes (PFS and OS) and as odds ratio (OR) for binary outcomes (AEs) along with corresponding 95% credible intervals (CrIs), the Bayesian equivalent of 95% CIs. Furthermore, through the calculation of the surface under the cumulative ranking curve (SUCRA), the overall ranks of treatments were estimated, respectively.[12] Notably, the SUCRA index ranges between 0 (or 0%) and 1 (or 100%), where the treatments with highest and lowest SUCRA are designated the best and worst treatments, respectively. Network meta-analysis was performed in WinBUGS software (version 1.4.3, MRC Biostatistics Unit) interfacing through R software.

Results

Overall Characteristics of Selected Studies and Quality of Evidence

The flowchart of included studies is presented in Supplemental sFigure 1 (shown in Supplemental Material). After the exclusion of duplicate studies, a total of 557 records were initially identified through our literature search. After a detailed assessment by the full-text review, 30 trials comprising 12 146 patients with mCRC were included in this meta-analysis (Figure 1). From this network figure, each node represented a different treatment and its size depended on the number of patients that is directly examined. The nodes were joined by lines with different thickness which shows whether there was a direct relationship between treatments and the thickness was weighted according to the available direct evidence between them. The characteristics of 30 RCTs included in the meta-analysis are summarized in Table 1. The study sample sizes ranged from 25 to 599. These studies were published between 2005 and 2019. The risk of bias and the quality assessment in all studies were presented in supplementary file (Supplemental sFigure 3), which indicated that the quality of the included studies was reliable. Moreover, according to the MCMC model, I^2 was estimated to be .00%. Therefore, there is no heterogeneity in the data, and the results of NMA are stable and reliable.

Overall Survival

Twenty-five trials comprising 11 175 patients with mCRC comparing 21 treatments were included in the OS analysis (Supplemental sFigure 2A; Supplemental sTable 2). The results indicated that the FOLFOXIRI/Bev treatment strategy was associated with improved OS benefits compared with all

Table 1. Study and patient population characteristics of included studies.

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Hochster, 2008[19]	71	FOLFOX+ BEV	**Colon:** 65% **Rectum:** 17% **Colon/Rectum:** 17% **Others:** 1%	-	**Live:** 73% **Lung:** 42% **Other:** 42%	-	-	64	OS AE
	72	CapeOx + BEV	**Colon:** 69% **Rectum:** 7% **Colon/Rectum:** 24% **Others:** 0%		**Live:** 83% **Lung:** 44% **Other:** 33%			62	
	49	FOLFOX	**Colon:** 55% **Rectum:** 18% **Colon/Rectum:** 27% **Others:** 0%	-	**Live:** 76% **Lung:** 47% **Other:** 55%	-	-	62	
	48	CapeOX	**Colon:** 75% **Rectum:** 6% **Colon/Rectum:** 19% **Others:** 0%	-	**Live:** 65% **Lung:** 50% **Other:** 65%	-	-	62.5	
Cremolini, 2015[14]	256	FOLFIRI + BEV	**Colon:** 24% **Rectum: -** **Colon/Rectum:** 70% **Others:** 6%	**Yes:** 65% **No:** 35%	—	—	**0 :** 89% **1-2:** 11%	60	OS PFS
	252	FOLFOXIRI + BEV	**Colon:** 35% **Rectum: -** **Colon/Rectum:** 60% **Others:** 5%	**Yes:** 69% **No:** 31%	-	-	**0 :** 90% **1-2:** 10%	60.5	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Fuchs, 2007[20]	144	FOLFIRI	**Colon:** 69.4% **Rectum: -** **Colon/Rectum:** 30.6% **Others:** - **Rectum:**				**0 :** 52.1% **1-2:** 47.9%	61	OS PFS
	57	FOLFIRI + BEV	**Colon:** 61.4% **Rectum: -** **Colon/Rectum:** 38.6% **Others:** -				**0 :** 54.4% **1-2:** 45.6%	59	
Ducreux, 2013[21]	72	XELIRI +BEV	**Colon:** 65% **Rectum: 35%** **Colon/Rectum:** - **Others:** -	—	—	**1:** 46% **≥2:**54%	**0 :** 92% **1-2:** 8%	61	OS PFS AE
	73	FOLFIRI + BEV	**Colon:** 79% **Rectum:** 21% **Colon/Rectum:** - **Others:** -	—	—	**1:** 44% **≥2**:56%	**0** : 90% **1-2**: 10%	61	
Pectasides, 2012[22]	143	XELIRI + BEV	**Colon:** 68% **Rectum:** 25% **Colon/Rectum:** - **Others:** 4%	**Yes:** 80% **No:** 20%	**Live:** 72% **Lung:** 36% **Other:** 38%	**1:** 59% **≥2**:41%	**0 :** 64% **1-2:** 36%		OS PFS
	142	FOLFIRI +BEV	**Colon:** 60% **Rectum:** 31% **Colon/Rectum:** - **Others:** 3%	**Yes:** 87% **No:** 13%	**Live:** 71% **Lung:** 28% **Other:** 43%	**1:** 60% **≥2**:40%	**0 :** 66% **1-2:** 34%		

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Giantonio, 2007[23]	286	FOLFOX + BEV			**Live:** 73.4% **Lung:** 55.5% **Other:** -		**0 :** 48.9% **1-2:** 51.1%	62	OS PFS AE
	291	FOLFOX	—	—	**Live:** 75.9% **Lung:** 51.2% **Other:** -		**0 :** 51.2% **1-2:** 58.8%	60	
			—	—		—			
	243	BEV			**Live:** 70.8% **Lung:** 59.7%		**0 :** 48.6% **1-2:** 41.4%	59.6	
			—	—	**Other:** -	—			
Cutsem, 2011[24]	599	FOLFIRI + cetuximab	-	-	**Live:** 20.2% **Lung:** - **Other:** -	-	**0 :** 55.1% **1-2:** 44.9%	61	OS PFS AE
	599	FOLFIRI	-	-	**Live:** 22.4% **Lung:** - **Other:** -	-	**0 :** 53.1% **1-2:** 46.9%	61	
Bokemeyer, 2008[26]	169	FOLFOX + cetuximab	**Colon:** 54% **Rectum:** 46% **Colon/Rectum:** 1% **Others:** -	**Yes:** 81% **No:** 19%	**Live:** 88% **Lung:** 38% **Other:** 15%	**1:** 43% **≥2:**57%	**0 :** 39% **1-2:** 61%	62	PFS AE
	168	FOLFOX	**Colon:** 53% **Rectum:** 47% **Colon/Rectum:** 0% **Others:** -	**Yes:** 91% **No:** 9%	**Live:** 87% **Lung:** 39% **Other:** 16%	**1:** 41% **≥2:**59%	**0 :** 45% **1-2:** 55%	60	
Tol, 2009[27]	368	CapeOx + BEV	**Colon:** 44.6% **Rectum:** 29.3% **Colon/Rectum: -** **Others:** 26.1	—	—	**1:** 45.4% **≥2:**54.6%	**0 :** 59.5% **1-2:** 40.5%	62	OS PFS AE
	368	CapeOx + BEV+ cetuximab	**Colon:** 46.7% **Rectum:** 25.5% **Colon/Rectum: -** **Others:** 27.7	—	—	**1:** 44.3% **≥2:**55.7%	**0 :** 65.2% **1-2:** 34.8%	62	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Douillard, 2014[28]	593	FOLFOX + panitumumab	**Colon:** 66% **Rectum:** 34% **Colon/Rectum:** - **Others:** -	-	**Live:** 19% **Lung:** - **Other:** 12%	**1:** 21% **≥2:**79%	**0 :** 94% **1-2:** 6%	62.5	OS PFS AE
	590	FOLFOX	**Colon:** 65% **Rectum:** 35% **Colon/Rectum:** - **Others:** -	-	**Live:** 17% **Lung:** - **Other:** 14%	**1:** 21% **≥2:**79%	**0 :** 96% **1-2:** 4%	61	
Souglakos, 2006[29]	146	FOLFIRI	**Colon:** 75% **Rectum:** 25% **Colon/Rectum:** - **Others:** -	—	**Live:** 70% **Lung:** 32% **Other:** 43%	**1:** 40% **≥2:**60%	**0 :** 38% **1-2:** 62%	66	OS
	137	FOLFOXIRI	**Colon:** 73% **Rectum:** 27% **Colon/Rectum:** - **Others:** -	—	**Live:** 72% **Lung:** 31% **Other:** 46%	**1:** 40% **≥2:**60%	**0 :** 36% **1-2:** 64%	66	
Falcone, 2007[30]	122	FOLFOXIRI	**Colon:** 66% **Rectum:** 34% **Colon/Rectum:** - **Others:** -	—	**Live:** 32% **Lung:** - **Other:** -	**1:** 53% **≥2:**47%	**0 :** 61% **1-2:** 39%	64	OS PFS
	122	FOLFIRI	**Colon:** 78% **Rectum:** 22% **Colon/Rectum:** - **Others:** -	—	**Live:** 34% **Lung:** - **Other:** -	**1:** 55% **≥2:**45%	**0 :** 61% **1-2:** 39%	62	
Colucci, 2005[31]	178	FOLFIRI	**Colon:** 66% **Rectum:** 34% **Colon/Rectum:** - **Others:** -	—	**Live:** 72% **Lung:** 28% **Other:** -	**1:** 56% **≥2:**44%	**0 :** 60% **1-2:** 40%	62	OS AE
	182	FOLFOX	**Colon:** 68% **Rectum:** 32% **Colon/Rectum:** - **Others:** -	—	**Live:** 73% **Lung:** 25% **Other:** -	**1:** 54% **≥2:**46%	**0 :** 58% **1-2:** 42%	62	
Díaz-Rubio, 2007[32]	171	CapeOX	**Colon:** 64% **Rectum:** 29% **Colon/Rectum:** 7% **Others:** -	**Yes:** 81% **No:** 19%	**Live:** 75% **Lung:** 32% **Other:** 11%	—	**0 :** 89% **1-2:** 11%	64	OS
	171	FUOX	**Colon:** 68% **Rectum:** 29% **Colon/Rectum:** 3% **Others:** -	**Yes:** 83% **No:** 17%	**Live:** 83% **Lung:** 29% **Other:** 8%	-	**0 :** 90% **1-2:** 10%	65	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Porschen, 2007[33]	241	CapeOX	—	**Yes:** 92% **No:** 8%	—	**1:** 49%≥**2:** 51%	**0 :** 91%**1-2:** 9%	66	OS PFS
	233	FUFOX	—	**Yes:** 95% **No:** 5%	—	**1:** 49% ≥**2**:51%	**0 :** 93% **1-2:** 7%	64	
Ducreux, 2011[34]	156	CapeOX	**Colon:** 60% **Rectum:** 24% **Colon/Rectum:** 16% **Others:** -	—	—	—	**0 :** 92% **1-2:** 8%	66	OS PFS
	150	FOLFOX	**Colon:** 63% **Rectum:** 25% **Colon/Rectum:** 11% **Others:** -	—	—	—	**0 :** 93% **1-2:** 7%	64	
Cassidy, 2011[35]	317	FOLFOX	**Colon:** 63% **Rectum:** 32% **Colon/Rectum:** 5% **Others:** -	—	—	**1:** 37.2% ≥**2**:62.8%	**0 :** 51% **1-2:** 49%	62	OS AE
	317	CapeOX	**Colon:** 64% **Rectum:** 26% **Colon/Rectum:** 9% **Others:** -	—	—	**1:** 40.1% ≥**2**:59.9%	**0 :** 50% **1-2:** 50%	61	
	349	FOLFOX +BEV	**Colon:** 64% **Rectum:** 28% **Colon/Rectum:** 8% **Others:** -	—	—	**1:** 43% ≥**2**:57%	**0 :** 57% **1-2:** 43%	60	
	350	CapeOX + BEV	**Colon:** 67% **Rectum:** 23% **Colon/Rectum:** 9% **Others:** -			**1:** 38.3% ≥**2**: 61.7%	**0 :** 59% **1-2:** 41%	61	
Bokemeyer, 2011[36]	168	FOLFOX	—	**Yes:** 91% **No:** 9%	**Live:** 23% **Lung:** - **Other:** -	**1:** 41% ≥**2**:59%	**0 :** 45% **1-2:** 55%	60	OS PFS AE
	169	FOLFOX + cetuximab	—	**Yes:** 81% **No:** 19%	**Live:** 30% **Lung:** -**Other:** -	**1:** 44% ≥**2**:56%	**0 :** 39% **1-2:** 61%	62	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Heinemann, 2014[37]	297	FOLFIRI + cetuximab	**Colon:** 57% **Rectum:** 39% **Colon/Rectum:** 3% **Others:** 2%	**Yes:** 84% **No:** 16%	**Live:** 81% **Lung:** - **Other:** -	**1:** 40% ≥**2**:60%	**0 :** 52% **1-2:** 48%	64	OS PFS AE
	295	FOLFIRI +BEV	**Colon:** 60% **Rectum:** 36% **Colon/Rectum:** 4% **Other:** -	**Yes:** 85% **No:** 15%	**Live:** 81% **Lung:** - **Other:** -	**1:** 42% ≥**2**:58%	**0 :** 54% **1-2:** 46%	65	
Infante, 2013[38]	39	FOLFOX + axitinib	—	**Yes:** 92.9% **No:** 7.1%	—	—	**0 :** 40.5% **1-2:** 59.5%	61	OS PFS
	43	FOLFOX + BEV	—	**Yes:** 93% **No:** 7%	—	—	**0 :** 46.5% **1-2:** 53.5%	64	
	41	FOLFOX + BEV + axitinib	—	**Yes:** 97.6% **No:** 2.4%	—	—	**0 :** 61% **1-2:** 39%	59	
Bendell, 2017[39]	97	FOLFOX +BEV +onartuzumab	**Colon:** 81.4% **Rectum:** 18.6% **Colon/Rectum:** - **Others:** -	—	**Live:** 13.4% **Lung:** - **Other:** -	**1:** 24.7% ≥**2**:75.3%	**0 :** 67% **1-2:** 33%	60	OS PFS AE
	97	FOLFOX + BEV	**Colon:** 87.6% **Rectum:** 12.4% **Colon/Rectum:** - **Others:** -	—	**Live:** 18.6% **Lung:** - **Other:** -	**1:** 24.7% ≥**2**:75.3%	**0 :** 56.7% **1-2:** 43.3%	62	
Carbonero, 2017[40]	63	FOLFOX+ BEV + parsatuzumab	—	—	—	—	**0 :** 52.% **1-2:** 48%	62	OS PFS
	62	FOLFOX + BEV	—	—	—	—	**0 :** 52% **1-2:** 48%	62	
Kim, 2014[41]	172	CapeOX	**Colon:** 63% **Rectum:** 37% **Colon/Rectum:** - **Others:** -	—	**Live:** 65% **Lung:** - **Other:** 35%	**1:** 29% ≥**2**:77.1%	**0 :** 98% **1-2:** 2%	62	OS PFS
	168	CapeOX +S-1 + SOX	**Colon:** 65% **Rectum:** 35% **Colon/Rectum:** - **Others:** -	—	**Live:** 63% **Lung:** - **Other:** 37%	**1:** 39% ≥**2**:61%	**0 :** 98% **1-2:** 2%	61	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Loupakis, 2014[18]	256	FOLFIRI + BEV	**Colon:** 23.8% **Rectum: -Colon/ Rectum** 70% **Others:** -	**Yes:** 61.3% **No:** 38.7%	**Live:** 18% **Lung:** - **Other:** -	**1:** - ≥**2**:82%	**0 :** 89.5% **1-2:** 10.5%	60	OS PFS AE
	252	FOLFOXIRI + BEV	**Colon:** 34.9% **Rectum:** - **Colon/Rectum:** 60.3% **Others:** -	**Yes:** 69.4% **No:** 30.6%	**Live:** 23.4% **Lung:** - **Other:** -	**1:** - ≥**2**:76.6%	**0 :** 90.1% **1-2:** 9.9%	60.5	
Souglakos, 2012[41]	159	XELIRI + BEV	**Colon:** 80% **Rectum:** 20% **Colon/Rectum:** - **Others:** -	—	**Live:** 38% **Lung:** - **Other:** -	**1:** 49% ≥**2**:51%	**0 :** 30% **1-2:** 70%	—	PFS AE
	160	FOLFIRI + BEV	**Colon:** 74% **Rectum:** 26% **Colon/Rectum:** - **Others:** -	—	**Live:** 37% **Lung:** - **Other:** -	**1:** 49% ≥**2**:51%	**0 :** 31% **1-2:** 69%	—	
Folprecht, 2014[42]	56	FOLFOX + cetuximab	**Colon:** 60.7% **Rectum:** 37.5% **Colon/Rectum:** - **Others:** 1.8%	—	—	—	—	—	OS
	55	FOLFIRI + cetuximab	**Colon:** 49% **Rectum:** 50.9% **Colon/Rectum: -Others:** .1%	—	—	—	—	—	PFS
Hurwitz, 2019[43]	95	FOLFOX + BEV	**Colon:** 81% **Rectum:** 18% **Colon/Rectum: -Others:** 1%	**Yes:** 64% **No:** 36%	—	—	**0 :** 54% **1-2:** 46%	58	OS PFS AE
	92	FOLFOXIRI + BEV	**Colon:** 73% **Rectum:** 26% **Colon/Rectum: -Others:** .1%	**Yes:** 60% **No:** 40%	—	—	**0 :** 67% **1-2:** 33%	58	
Giuliani, 2008[44]	20	FOLFIRI	—	—	—	—	—	—	PFS
	34	XELIRI	—	—	—	—	—	—	

(continued)

Table 1. (continued)

Author/years	Sample size (n)	Intervention	Primary tumor site	Primary tumor surgical resection	Metastases location	Metastases sites	ECOG performance status	Median age	Outcomes
Berlin, 2013[45]	64	FOLFOX + BEV	**Colon:** 75% **Rectum:** 25% **Colon/Rectum:** **-Others:** -	—	—	—	**0 :** 55% **1-2:** 45%		PFS AE
	60	FOLFOX + BEV +vismodegib	**Colon:** 82% **Rectum:** 18% **Colon/Rectum:** **-Others:** -	—	—	—	**0 :** 48% **1-2:** 52%	—	
	37	FOLFIRI + BEV	**Colon:** 81% **Rectum:** 19% **Colon/Rectum:** **-Others:** -	—	—	—	**0 :** 60% **1-2:** 40%	—	
	38	FOLFIRI + BEV + vismodegib	**Colon:** 87% **Rectum:** 13% **Colon/Rectum:** **-Others:** -	—	—	—	**0 :** 58% **1-2:** 42%	—	
Soda, 2015[46]	37	FOLFOX + cetuximab	**Colon:** 48.6% **Rectum:** 51.4% **Colon/Rectum:** **-Others:** -	—	**Live:** 78.4% **Lung:** 27.0% **Other:** 5.4%	—	**0 :** 89.2% **1-2:** 10.8%	—	PFS
	25	CapeOX + cetuximab	**Colon:** 32% **Rectum:** 68% **Colon/Rectum:** **-Others:** -	—	**Live:** 72% **Lung:** 20% **Other:** 24%	—	**0 :** 88% **1-2:** 12%	—	

ECOG: Eastern Cooperative Oncology Group; XELIRI: CAPIRI, Irinotecan plus capecitabine, FOLFIRI: irinotecan plus fluorouracil plus leucovorin; BEV: bevacizumab; SOX: oxaliplatin; FUOX: high-dose fluorouracil plus oxaliplatin; FUFOX: fluorouracil plus folinic acid plus oxaliplatin; FOLFOX fluorouracil and leucovorin with oxaliplatin; CapeOX: XELOX, capecitabine plus oxaliplatin; -: Not reported.

A

Overall survival

FOLFOX/ Bev																								
0.94 (0.76-1.16)	**CapeOx/ Bev**																							
0.81 (0.67-0.99)	0.86 (0.68-1.09)	**FOLFOX**																						
0.85 (0.67-1.11)	0.9 (0.71-1.16)	1.05 (0.86-1.28)	**CapeOX**																					
0.96 (0.63-1.48)	1.02 (0.65-1.63)	1.19 (0.77-1.84)	1.13 (0.7-1.8)	**FOLFIRI/ Bev**																				
1.03 (0.69-1.52)	1.09 (0.7-1.68)	1.26 (0.83-1.9)	1.2 (0.76-1.86)	1.07 (0.84-1.34)	**FOLFOXIRI/ Bev**																			
0.66 (0.39-1.12)	0.7 (0.41-1.22)	0.81 (0.49-1.36)	0.77 (0.45-1.35)	0.68 (0.45-1.04)	0.64 (0.41-1.03)	**FOLFIRI**																		
0.96 (0.6-1.54)	1.03 (0.61-1.7)	1.19 (0.73-1.92)	1.13 (0.67-1.88)	1.01(0.8-1.22)	0.94 (0.69-1.28)	1.48 (0.9-2.27)	**XELIRI/ Bev**																	
0.82 (0.64-1.04)	0.86 (0.68-1.11)	1 (0.78-1.28)	0.95 (0.71-1.27)	0.85 (0.53-1.36)	0.79 (0.51-1.26)	1.23 (0.7-2.14)	0.84 (0.51-1.43)	**Bev**																
0.75 (0.48-1.17)	0.79 (0.5-1.3)	0.92 (0.59-1.45)	0.88 (0.54-1.42)	0.78 (0.58-1.05)	0.73 (0.52-1.06)	1.14 (0.86-1.49)	0.77 (0.54-1.14)	0.92 (0.57-1.51)	**FOLFIRI/ Cetuximab**															
0.79 (0.55-1.14)	0.84 (0.57-1.25)	0.97 (0.7-1.34)	0.92 (0.64-1.35)	0.82 (0.53-1.27)	0.77 (0.5-1.21)	1.2 (0.73-1.95)	0.82 (0.5-1.34)	0.97 (0.66-1.45)	1.06 (0.7-1.58)	**FOLFOX/ Cetuximab**														
0.84 (0.57-1.22)	0.89(0.64-1.22)	1.03 (0.69-1.52)	0.98 (0.66-1.45)	0.87 (0.49-1.51)	0.81 (0.47-1.4)	1.27 (0.66-2.39)	0.86 (0.47-1.58)	1.02 (0.69-1.52)	1.12 (0.62-1.97)	1.06 (0.63-1.75)	**CapeOx/Bev/ Cetuximab**													
0.68 (0.47-0.98)	0.72 (0.48-1.07)	0.84 (0.6-1.14)	0.79 (0.54-1.15)	0.7 (0.41-1.2)	0.66 (0.39-1.13)	1.03 (0.55-1.86)	0.7 (0.39-1.26)	0.83 (0.55-1.25)	0.9 (0.52-1.54)	0.85 (0.54-1.34)	0.81 (0.49-1.35)	**FOLFOX/ Panitumumab**												
0.46 (0.24-0.9)	0.49 (0.25-0.98)	0.57 (0.3-1.11)	0.54 (0.28-1.08)	0.48 (0.27-0.85)	0.45 (0.25-0.84)	0.7 (0.47-1.05)	0.48 (0.26-0.9)	0.57 (0.29-1.14)	0.62 (0.38-1.01)	0.58 (0.31-1.11)	0.55 (0.26-1.19)	0.68 (0.33-1.43)	**FOLFOXIRI**											
0.7 (0.45-1.11)	0.75 (0.47-1.17)	0.86 (0.56-1.32)	0.82 (0.57-1.2)	0.73 (0.4-1.34)	0.68 (0.38-1.25)	1.06 (0.54-2.08)	0.73 (0.39-1.39)	0.86 (0.53-1.39)	0.93 (0.51-1.72)	0.89 (0.52-1.52)	0.84 (0.48-1.46)	1.04 (0.61-1.77)	1.52 (0.68-3.29)	**FUOX**										
0.76 (0.52-1.13)	0.81 (0.55-1.2)	0.94 (0.65-1.36)	0.9 (0.66-1.21)	0.79 (0.45-1.38)	0.74 (0.44-1.28)	1.16 (0.62-2.14)	0.79 (0.44-1.45)	0.93 (0.62-1.42)	1.02 (0.58-1.79)	0.96 (0.59-1.55)	0.91 (0.55-1.51)	1.13 (0.7-1.82)	1.67 (0.77-3.42)	1.09 (0.68-1.75)	**FUFOX**								
0.95 (0.49-1.82)	1.01 (0.52-1.95)	1.17 (0.61-2.23)	1.12 (0.57-2.18)	0.99 (0.45-2.12)	0.92 (0.44-1.97)	1.45 (0.63-3.22)	0.99 (0.44-2.18)	1.17 (0.63-2.14)	1.27 (0.58-2.72)	1.21 (0.58-2.48)	1.14 (0.55-2.36)	1.4 (0.67-2.89)	2.08 (0.82-5.05)	1.36 (0.62-2.94)	1.25 (0.6-2.61)	**FOLFOX/ Axitinib**							
0.77 (0.4-1.48)	0.82 (0.43-1.57)	0.95 (0.49-1.82)	0.9 (0.46-1.75)	0.81 (0.37-1.72)	0.76 (0.35-1.6)	1.19 (0.51-2.64)	0.8 (0.36-1.79)	0.95 (0.52-1.73)	1.04 (0.47-2.2)	0.98 (0.47-2.01)	0.93 (0.45-1.92)	1.15 (0.55-2.36)	1.68 (0.66-4.1)	1.11 (0.51-2.36)	1.02 (0.48-2.08)	0.81 (0.34-1.93)	**FOLFOX/ Axitinib/Bev**						
0.96 (0.58-1.6)	1.02 (0.59-1.79)	1.19 (0.68-2.03)	1.13 (0.63-1.99)	1 (0.51-1.93)	0.94 (0.5-1.79)	1.46 (0.69-3.03)	1 (0.5-2.01)	1.19 (0.67-2.08)	1.28 (0.64-2.51)	1.22 (0.65-2.27)	1.15 (0.61-2.18)	1.43 (0.75-2.69)	2.1 (0.9-4.76)	1.38 (0.69-2.75)	1.26 (0.66-2.41)	1.01 (0.44-2.32)	1.25 (0.55-2.86)	**FOLFOX/Bev/ Onartuzumab**					
0.96 (0.44-2.12)	1.02 (0.46-2.32)	1.19 (0.53-2.66)	1.13 (0.5-2.59)	1.01 (0.4-2.44)	0.94 (0.39-2.27)	1.48 (0.56-3.78)	1 (0.39-2.51)	1.19 (0.52-2.69)	1.3 (0.52-3.19)	1.22 (0.52-2.94)	1.16 (0.49-2.8)	1.43 (0.59-3.39)	2.1 (0.75-5.75)	1.38 (0.55-3.46)	1.27 (0.53-3.03)	1.01 (0.36-2.83)	1.25 (0.45-3.42)	1 (0.39-2.56)	**FOLFOX/Bev /Parsatuzumab**				
0.98 (0.62-1.45)	1.07 (0.76-1.54)	1.25 (0.9-1.72)	1.19 (0.92-1.52)	1.05 (0.62-1.8)	0.99 (0.59-1.67)	1.54 (0.83-2.8)	1.05 (0.59-1.88)	1.25 (0.85-1.82)	1.35 (0.79-2.32)	1.28 (0.81-2.01)	1.21 (0.76-1.95)	1.49 (0.95-2.36)	2.2 (1.05-4.48)	1.45 (0.91-2.27)	1.32 (0.9-1.95)	1.06 (0.52-2.18)	1.31 (0.64-2.69)	1.05 (0.57-1.95)	1.05 (0.44-2.51)	**CapeOX/ SOX**		

B

Progression-free survival

FOLFOX/ Bev																								
0.75 (0.47-1.22)	**CapeOx/ Bev**																							
0.78 (0.58-1.04)	1.04 (0.67-1.6)	**FOLFOX**																						
0.66 (0.42-1.05)	0.88 (0.6-1.28)	0.85 (0.58-1.23)	**CapeOX**																					
1.03 (0.73-1.43)	1.38 (0.77-2.39)	1.32 (0.88-1.97)	1.55 (0.9-2.64)	**FOLFIRI/ Bev**																				
1.38 (0.94-1.99)	1.84 (1.01-3.32)	1.77 (1.12-2.77)	2.08 (1.16-3.71)	1.34 (0.93-1.93)	**FOLFOXIRI/ Bev**																			
0.83 (0.43-1.49)	1.11 (0.5-2.25)	1.07 (0.54-1.93)	1.26 (0.58-2.48)	0.8 (0.44-1.39)	0.6 (0.3-1.14)	**FOLFIRI**																		
1.06 (0.66-1.72)	1.42 (0.73-2.75)	1.36 (0.8-2.32)	1.62 (0.85-3.06)	1.03 (0.74-1.46)	0.77 (0.47-1.28)	1.28 (0.68-2.59)	**XELIRI/ Bev**																	
0.59 (0.41-0.88)	0.79 (0.54-1.16)	0.76 (0.53-1.08)	0.9 (0.58-1.38)	0.57 (0.35-0.94)	0.43 (0.25-0.73)	0.71 (0.37-1.48)	0.55 (0.3-1.02)	**Bev**																
0.97 (0.61-1.49)	1.3 (0.68-2.34)	1.26 (0.77-1.92)	1.48 (0.79-2.56)	0.94 (0.63-1.36)	0.71 (0.42-1.14)	1.17 (0.77-1.8)	0.91 (0.53-1.48)	1.65 (0.92-2.77)	**FOLFIRI/ Cetuximab**															
0.9 (0.62-1.38)	1.21 (0.72-2.03)	1.16 (0.85-1.62)	1.36 (0.84-2.25)	0.88 (0.57-1.4)	0.66 (0.4-1.11)	1.09 (0.61-2.08)	0.85 (0.49-1.49)	1.54 (0.96-2.44)	0.93 (0.61-1.49)	**FOLFOX/ Cetuximab**														
0.61 (0.33-1.09)	0.82 (0.53-1.26)	0.79 (0.53-1.46)	0.93 (0.53-1.65)	0.59 (0.3-1.22)	0.44 (0.21-0.94)	0.68 (0.32-1.42)	0.58 (0.28-1.27)	1.04 (0.58-1.86)	0.68 (0.31-1.38)	0.68 (0.34-1.35)	**CapeOx/Bev/ Cetuximab**													
0.62 (0.37-1.05)	0.83 (0.45-1.55)	0.8 (0.52-1.25)	0.94 (0.53-1.68)	0.6 (0.33-1.13)	0.45 (0.24-0.86)	0.75 (0.36-1.67)	0.58 (0.3-1.17)	1.05 (0.59-1.86)	0.64 (0.35-1.25)	0.69 (0.4-1.19)	1.01 (0.48-2.18)	**FOLFOX/ Panitumumab**												
1.14 (0.54-2.25)	1.52 (0.64-3.85)	1.48 (0.7-2.89)	1.73 (0.75-3.71)	1.11 (0.55-2.14)	0.8 (0.39-1.7)	1.38 (0.98-1.93)	1.07 (0.5-2.2)	1.93 (0.86-4.06)	1.17 (0.68-2.01)	1.27 (0.6-2.46)	1.86 (0.72-4.53)	1.84 (0.77-4.06)	**FOLFOXIRI**											
0.86 (0.29-1.08)	0.79 (0.41-1.38)	0.72 (0.39-1.31)	0.84 (0.53-1.35)	0.54 (0.27-1.14)	0.07 (0.19-0.86)	0.67 (0.29-1.67)	0.53 (0.24-1.16)	0.95 (0.5-1.8)	0.57 (0.28-1.26)	0.62 (0.31-1.22)	0.9 (0.44-1.92)	0.9 (0.42-1.9)	0.49 (0.2-1.28)	**FUOX**										
0.97 (0.3-3.06)	0.76 (0.42-1.34)	0.73 (0.41-1.28)	0.85 (0.55-1.31)	0.55 (0.28-1.12)	0.41 (0.2-0.84)	0.68 (0.3-1.65)	0.53 (0.25-1.16)	0.95 (0.52-1.77)	0.58 (0.29-1.23)	0.63 (0.32-1.21)	0.91 (0.45-1.88)	0.9 (0.46-1.88)	0.49 (0.21-1.28)	1.01 (0.54-1.92)	**FUFOX**								
0.61 (0.27-1.3)	0.82 (0.32-1.92)	0.79 (0.34-1.67)	0.92 (0.38-2.14)	0.59 (0.27-1.22)	0.446 (0.19-0.97)	0.73 (0.45-1.2)	0.57 (0.28-1.27)	1.03 (0.42-2.32)	0.63 (0.33-1.2)	0.68 (0.3-1.43)	0.99 (0.39-2.59)	0.98 (0.38-2.32)	0.53 (0.3-0.96)	1.09 (0.39-2.86)	1.08 (0.39-2.77)	**XELIRI**							
0.76 (0.43-1.35)	1.02 (0.48-2.14)	0.98 (0.51-1.88)	1.15 (0.55-2.39)	0.74 (0.38-1.46)	0.55 (0.28-1.12)	0.92 (0.41-2.16)	0.72 (0.34-1.51)	1.28 (0.64-2.56)	0.79 (0.39-1.67)	0.84 (0.41-1.7)	1.25 (0.52-2.92)	1.22 (0.55-2.66)	0.67 (0.28-1.7)	1.36 (0.57-3.29)	1.35 (0.58-3.19)	1.26 (0.49-3.39)	**FOLFOX/Bev/ Vismodegib**						
0.9 (0.42-1.88)	1.2 (0.49-2.83)	1.15 (0.52-2.51)	1.36 (0.57-3.16)	0.87 (0.44-1.7)	0.65 (0.3-1.39)	1.08 (0.46-2.64)	0.84 (0.39-1.79)	1.52 (0.66-3.39)	0.92 (0.43-2.03)	0.99 (0.44-2.2)	1.46 (0.54-3.82)	1.45 (0.58-3.49)	0.79 (0.31-2.03)	1.6 (0.59-4.18)	1.58 (0.61-4.06)	1.48 (0.54-4.1)	1.17 (0.45-3.03)	**FOLFIRI/Bev/ Vismodegib**					
0.64 (0.24-1.72)	0.85 (0.32-1.29)	0.83 (0.31-2.2)	0.97 (0.36-2.66)	0.63 (0.23-1.75)	0.47 (0.17-1.34)	0.77 (0.25-2.46)	0.6 (0.2-1.79)	1.08 (0.44-2.69)	0.66 (0.23-1.93)	0.71 (0.25-1.97)	1.05 (0.36-3.06)	1.03 (0.35-3)	0.57 (0.17-1.88)	1.15 (0.38-3.46)	1.14 (0.38-3.39)	1.05 (0.31-3.67)	0.84 (0.27-2.64)	0.71 (0.21-2.46)	**FOLFOX/ Axitinib**				
0.88 (0.37-2.12)	1.17 (0.49-2.83)	1.14 (0.48-2.69)	1.34 (0.54-3.25)	0.85 (0.34-2.16)	0.64 (0.25-1.67)	1.06 (0.38-3.13)	0.83 (0.31-2.2)	1.49 (0.68-3.29)	0.9 (0.35-2.41)	0.97 (0.39-2.44)	1.43 (0.54-3.78)	1.4 (0.54-3.78)	0.77 (0.26-2.39)	1.57 (0.57-4.31)	1.55 (0.58-4.22)	1.45 (0.46-4.66)	1.15 (0.41-3.29)	0.98 (0.31-3.06)	1.36 (0.41-4.66)	**FOLFOX/ Axitinib/Bev**			
0.75 (0.44-1.28)	1 (0.49-2.03)	0.97 (0.52-1.77)	1.14 (0.55-2.27)	0.73 (0.39-1.39)	0.55 (0.29-1.05)	0.9 (0.41-2.12)	0.7 (0.34-1.45)	1.27 (0.65-2.46)	0.77 (0.39-1.6)	0.84 (0.43-1.62)	1.22 (0.53-2.77)	1.21 (0.57-2.53)	0.66 (0.28-1.67)	1.35 (0.58-3.1)	1.32 (0.58-3.03)	1.23 (0.49-3.32)	0.99 (0.44-2.18)	0.84 (0.33-2.12)	1.17 (0.39-3.63)	0.86 (0.3-2.36)	**FOLFOX/Bev/ Onartuzumab**		
1.17 (0.62-2.2)	1.37 (0.71-3.39)	1.51 (0.75-3)	1.77 (0.82-3.86)	1.14 (0.56-2.32)	0.86 (0.41-1.79)	1.42 (0.6-3.46)	1.09 (0.5-2.41)	1.97 (0.95-4.1)	1.2 (0.57-2.68)	1.3 (0.61-2.69)	1.92 (0.77-4.66)	1.88 (0.83-4.26)	1.02 (0.41-2.69)	2.1 (0.84-5.16)	2.08 (0.86-5.05)	1.92 (0.73-5.42)	1.54 (0.65-3.63)	1.31 (0.49-3.53)	1.82 (0.57-5.87)	1.32 (0.45-3.86)	1.55 (0.68-3.6)	**FOLFOX/Bev/ Parsatuzumab**	
0.81 (0.47-1.43)	1.08 (0.66-1.8)	1.05 (0.63-1.73)	1.23 (0.89-1.72)	0.79 (0.42-1.52)	0.59 (0.31-1.14)	0.98 (0.45-2.27)	0.76 (0.38-1.57)	1.38 (0.79-2.36)	0.9 (0.40-44.1.68)	0.9 (0.49-1.62)	1.32 (0.69-2.53)	1.31 (0.66-2.56)	0.71 (0.31-1.77)	1.46 (0.81-2.59)	1.45 (0.84-2.48)	1.34 (0.54-3.49)	1.06 (0.48-2.41)	0.9 (0.37-2.29)	1.27 (0.44-3.63)	0.92 (0.35-2.41)	1.08 (0.5-2.36)	0.7 (0.3-1.62)	**CapeOX/ SOX**	
0.84 (0.29-1.03)	0.72 (0.41-1.28)	0.7 (0.39-1.25)	0.82 (0.53-1.27)	0.53 (0.26-1.07)	0.39 (0.19-0.82)	0.65 (0.29-1.6)	0.51 (0.24-1.09)	0.91 (0.5-1.7)	0.55 (0.28-1.2)	0.6 (0.31-1.15)	0.88 (0.43-1.82)	0.87 (0.42-1.8)	0.47 (0.2-1.25)	0.96 (0.52-1.84)	0.96 (0.52-1.77)	0.89 (0.35-2.46)	0.71 (0.3-1.67)	0.61 (0.23-1.6)	0.84 (0.28-2.51)	0.62 (0.23-1.68)	0.72 (0.32-1.65)	0.46 (0.19-1.11)	0.66 (0.39-1.14)	**CapeOx/ Cetuximab**

C

Grade 3 + Adverse Events

CapeOx/Bev/ Cetuximab																								
1.02 (0.71,1.46)	**FOLFOX/Bev**																							
1.05 (0.74,1.49)	1.03 (0.77,1.38)	**FOLFOX/ Cetuximab**																						
0.58 (0.35,0.95)	0.57 (0.35,0.92)	0.55 (0.34,0.89)	**FOLFOX/Bev/ Onartuzumab**																					
0.97 (0.66,1.42)	0.95 (0.63,1.42)	0.92 (0.62,1.37)	1.67 (1.00,2.79)	**FOLFIRI/ Cetuximab**																				
1.02 (0.73,1.43)	1.01 (0.70,1.44)	0.98 (0.69,1.38)	1.77 (1.11,2.83)	1.06 (0.75,1.49)	**FOLFOXIRI**																			
0.93 (0.64,1.36)	0.91 (0.65,1.30)	0.89 (0.63,1.25)	1.61 (1.10,2.36)	0.96 (0.64,1.44)	0.91 (0.64,1.29)	**FOLFIRI/Bev/ Vismodegib**																		
1.65 (1.13,2.41)	1.62 (1.08,2.42)	1.57 (1.06,2.33)	2.85 (1.70,4.78)	1.71 (1.14,2.56)	1.61 (1.13,2.29)	1.77 (1.18,2.66)	**Bev**																	
1.02 (0.68,1.53)	1.00 (0.70,1.45)	0.97 (0.68,1.39)	1.77 (1.11,2.81)	1.06 (0.68,1.63)	1.00 (0.68,1.47)	1.10 (0.82,1.47)	0.62 (0.40,0.96)	**XELIRI/Bev**																
1.18 (0.81,1.73)	1.16 (0.81,1.67)	1.13 (0.79,1.61)	2.04 (1.48,2.82)	1.22 (0.82,1.83)	1.15 (0.82,1.62)	1.27 (1.04,1.56)	0.72 (0.48,1.07)	1.16 (0.83,1.62)	**FOLFIRI**															
1.18 (0.83,1.67)	1.16 (0.79,1.68)	1.12 (0.78,1.62)	2.03 (1.23,3.38)	1.22 (0.82,1.81)	1.15 (0.81,1.63)	1.26 (0.86,1.87)	0.71 (0.48,1.06)	1.15 (0.76,1.75)	1.00 (0.67,1.47)	**FOLFOXIRI/Bev**														
1.07 (0.75,1.52)	1.05 (0.77,1.42)	1.02 (0.76,1.37)	1.85 (1.21,2.81)	1.11 (0.75,1.63)	1.04 (0.75,1.45)	1.15 (0.93,1.42)	0.65 (0.44,0.95)	1.05 (0.86,1.28)	0.90 (0.69,1.18)	0.91 (0.63,1.31)	**FOLFIRI/Bev**													
1.14 (0.84,1.53)	1.11 (0.80,1.55)	1.08 (0.79,1.48)	1.96 (1.25,3.08)	1.17 (0.87,1.58)	1.11 (0.88,1.39)	1.22 (0.88,1.68)	0.69 (0.50,0.95)	1.11 (0.77,1.60)	0.96 (0.70,1.32)	0.96 (0.70,1.32)	1.06 (0.78,1.44)	**CapeOX**												
1.12 (0.84,1.49)	1.10 (0.80,1.50)	1.06 (0.78,1.44)	1.86 (1.15,2.98)	1.15 (0.86,1.55)	1.09 (0.92,1.29)	1.20 (0.89,1.62)	0.68 (0.50,0.92)	1.09 (0.77,1.54)	0.94 (0.70,1.26)	0.95 (0.70,1.29)	1.04 (0.79,1.39)	0.98 (0.85,1.14)	**FOLFOX**											
1.08 (0.79,1.47)	1.06 (0.75,1.49)	1.03 (0.74,1.43)	1.86 (1.17,2.97)	1.12 (0.90,1.39)	1.05 (0.81,1.36)	1.16 (0.83,1.62)	0.65 (0.46,0.92)	1.06 (0.73,1.54)	0.91 (0.65,1.27)	0.92 (0.66,1.27)	1.01 (0.73,1.39)	0.95 (0.78,1.16)	0.97 (0.80,1.17)	**CapeOx/Bev**										
1.02 (0.81,1.29)	1.00 (0.76,1.32)	0.97 (0.75,1.27)	1.77 (1.14,2.74)	1.06 (0.78,1.43)	1.00 (0.78,1.27)	1.10 (0.82,1.47)	0.62 (0.46,0.83)	1.00 (0.72,1.39)	0.86 (0.64,1.16)	0.87 (0.67,1.12)	0.96 (0.74,1.24)	0.90 (0.75,1.09)	0.92 (0.77,1.08)	0.95 (0.77,1.16)	**FOLFOX/Bev /Vismodegib**								

Figure 2. Pooled Estimates for All Possible Treatment Effects for Each Outcome. A: Overall survival. B: Progression-free survival. C: Grade 3 + Adverse Events. XELIRI: CAPIRI, Irinotecan plus capecitabine, FOLFIRI: irinotecan plus fluorouracil plus leucovorin; BEV: bevacizumab; SOX: oxaliplatin; FUOX: high-dose fluorouracil plus oxaliplatin; FUFOX: fluorouracil plus folinic acid plus oxaliplatin; FOLFOX fluorouracil and leucovorin with oxaliplatin. CapeOX: XELOX, capecitabine plus oxaliplatin.

other treatments (Figure2(a)). The key comparison treatments included FOLFOXIRI/Bev vs FOLFOX/Bev with HR, 1.03 (95% CrI, .69-1.52), and FOLFOXIRI/Bev vs FOLFIRI/Bev with HR, 1.07 (95% CrI, .84-1.34). The estimated SUCRA values were 77.2 and 77.1% for FOLFOXIRI/Bev and FOLFOX/Bev treatment strategies, respectively (Figure 3(a)), suggesting that these 2 treatment strategies exhibited the highest probability of being the best treatment for improving OS of patients with mCRC (sTable 3A in the Supplement).

Progression-free Survival

Twenty-two trials comprising 9588 patients with mCRC comparing 25 treatments were included in the PFS analysis (Supplemental sFigure 2B; Supplemental sTable 2). FOLFOXIRI/Bev treatment strategy was the most likely regimen to exhibit a higher PFS compared with other strategies (Figure2(b)). Consistently, the SUCRA analysis also suggested that FOLFOXIRI/Bev treatment strategy demonstrated the highest probability of being associated with best PFS (SUCRA: 93.2%) (Figure 3(b)), followed by FOLFOXIRI (SUCRA: 79.9%), whereas CapeOX/cetuximab treatment strategy was least likely to be the optimal treatment strategy in improving PFS (SUCRA: 17.2%) (Supplemental sTable 3B).

Grade 3 + Adverse Events

Eighteen trials comprising 8424 patients with mCRC comparing 16 treatment strategies reported adverse events of Grade 3 or higher (Supplemental sFigure 2C, Supplemental sTable 2). Bevacizumab treatment strategy was significantly associated with a lower risk of Grade 3 + AEs compared with all other treatments (Figure2(c)). On the other hand, FOLFOXIRI/Bev treatment strategy had a well-tolerated Grade 3 + AEs. Consistently, the SUCRA analysis also suggested that bevacizumab and FOLFIRI treatment strategies were the most likely regimens to exhibit the lowest risk of Grade 3 + AEs with SUCRA values of 98.3% and 80.2%, respectively (Figure 3(c)). Next is FOLFOXIRI/Bev treatment strategy with SUCRA values of 75.7%. Besides, FOLFOX/Bev/onartuzumab treatment strategy was associated with a higher risk of Grade 3 +AEs compared with all other treatments (SUCRA values was 7.9%) (Supplemental sTable 3C in the Supplemental Material).

Discussion

Incremental advancements have been made in mCRC therapy ever since the introduction of 5-FU over 40 years ago.[13] Moreover, the treatment of mCRC has been facilitated significantly with the introduction of several new cytotoxic and biologic agents to the 5-FU regimen. Notably, combination regimens that incorporate infusional schedules of 5-FU in various combinations, including XELOX regimen (oxaliplatin and capecitabine), FOLFOX regimen (leucovorin, 5-FU and oxaliplatin), and FOLFIRI regimen (leucovorin, 5-FU and irinotecan), with or without monoclonal antibody, have significantly improved the clinical outcomes and median overall survival of patients with mCRC.

In this systematic review and NMA meta-analysis, we estimated the relative efficacy of the different combinations of treatment strategies for outcomes involving OS and PFS in patients with mCRC. Overall survival remains the fundamental endpoint in clinical trials; this meta-analysis found that triple combination FOLFOXIRI plus bevacizumab provided significant survival benefits over all the other treatments, except FOLFOX plus bevacizumab. Therefore, they are equally likely to be associated with the best OS. Notably, FOLFOXIRI plus bevacizumab was also found to be most effective in promoting PFS. These results are also consistent with the TRIBE study. In TRIBE study, mCRC patients receive FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab. As a result, FOLFOXIRI plus bevacizumab significantly improved OS (29·8 months vs 25·8 months) and PFS (12·3 months vs 9·7 months) in patients with mCRC.[14] In addition, another VISNU-1 trial study, mCRC patients were treated with FOLFOX plus bevacizumab or FOLFOXIRI plus bevacizumab. In conclusion, FOLFOXIRI plus bevacizumab exhibited statistically significant improved PFS (12.4 months vs 9.3 months), and QUATTRO study has also shown that mCRC patients who received FOLFOXIRI plus bevacizumab exhibited statistically significant improved PFS to 13.3 months.[15,16] FOLFOXIRI + bevacizumab has the advantage of both being clinically meaningful and statistically significant. There is a report of the decrease of 19% of the risk of death.[17] Meanwhile, the median OS has a 4.4-month absolute difference. The estimated 5-year OS rate has an increase of 11.6%, which grows to 22.3% with FOLFOXIRI + bevacizumab.

Survival benefits needed to be justified against the toxicity of chemotherapy. In the majority of mCRC patients with advanced colorectal cancer, systemic treatment remains noncurative, and thus the quality of life becomes a priority. In this meta-analysis, rates of Grade 3 + AEs were high for all treatment strategies; however, FOLFOXIRI plus bevacizumab regimen exhibited well-tolerated adverse events. One of the reasons is that the ECOG performance status of 90% patients was 0 among the FOLFOXIRI plus bevacizumab treatment group. The average age of the patients in this group was 61 years. The patient's clinical characteristics of FOLFOXIRI

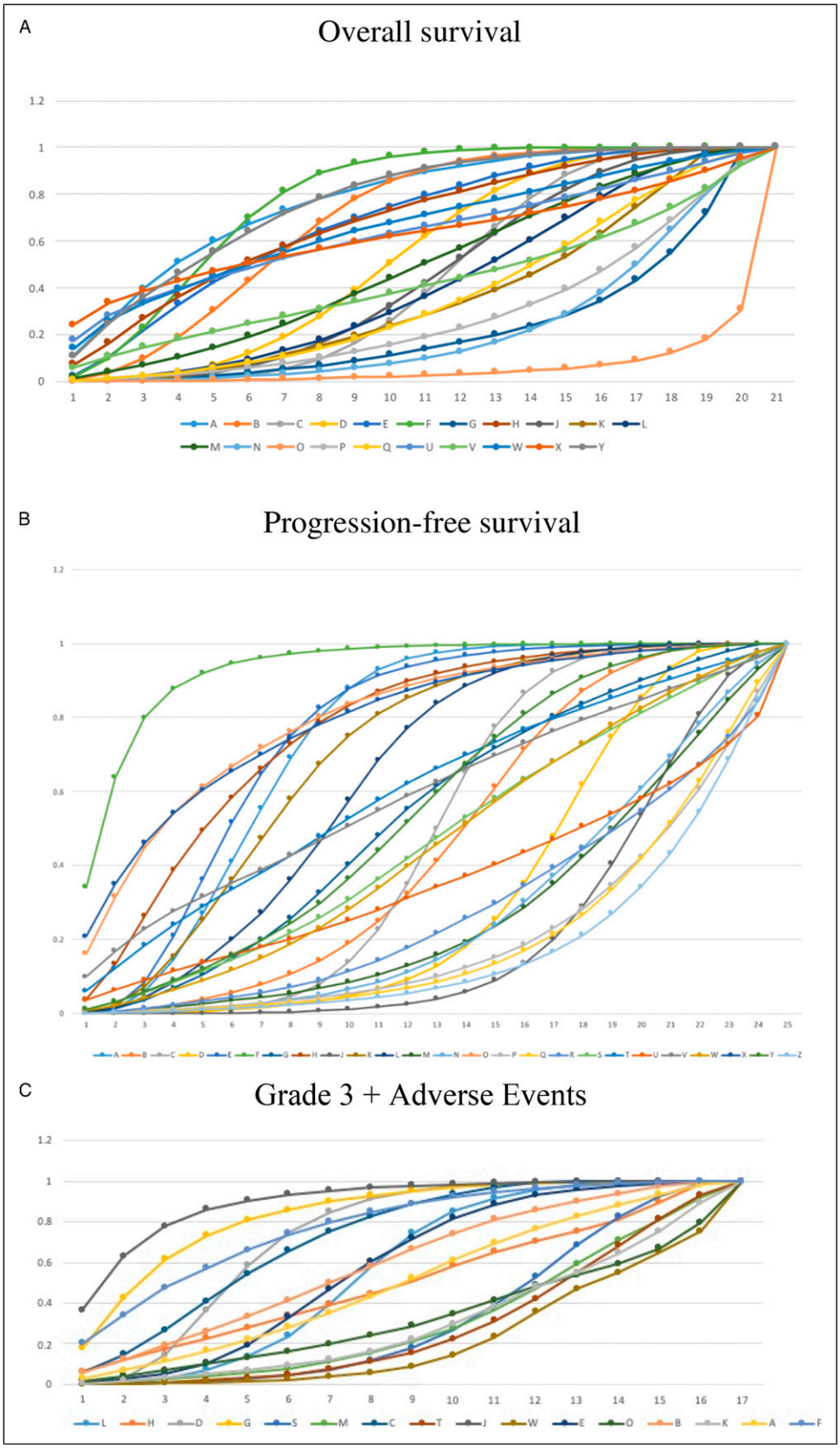
A
Overall survival
B
Progression-free survival
C
Grade 3 + Adverse Events

Figure 3. The SUCRA plot of each treatment. A: Overall survival. B: Progression-free survival. C: Grade 3 + Adverse Events. A: FOLFOX/Bev; B: CapeOx/Bev; C: FOLFOX; D: CapeOX; E: FOLFIRI/Bev; F: FOLFOXIRI/Bev; G: FOLFIRI; H: XELIRI/Bev; J: Bev; K: FOLFIRI/Cetuximab; L: FOLFOX/Cetuximab; M: CapeOx/Bev/Cetuximab; N: FOLFOX/panitumumab; O: FOLFOXIRI; P: FUOX; Q: FUFOX; R: XELIRI; S: FOLFOX/Bev/Vismodegib; T: FOLFIRI/bev/Vismodegib; U: FOLFOX/Axitinib; V: FOLFOX/Axitinib/Bev; W: FOLFOX/Bev/Onartuzumab: X: FOLFOX/bevacizumab/parsatuzumab; Y:CapeOX/SOX; Z: CapeOX/Cetuximab.

plus bevacizumab treatment group is much better than other treatment groups. Besides, it has been confirmed from the recent mCRC studies that there is no increase of the toxicity of FOLFOXIRI-Bev. It is shown from the TRIBE trial that the FOLFIRI-Bev was not seriously impacted by the treatment-relevant severe adverse events (20.4% vs 19.7%).[18] According to the results of TRIBE, STEAM, and OLIVIA trials, no difference was shown in terms of the incidence of fatal adverse events between FOLFIRI-Bev and FOLFOXIRI-Bev groups. Additionally, it is suggested by the recent reviews and trials, including the analysis about RCTs, that the FOLFOXIRI-Bev's toxicity is manageable and tolerable.[19,20] According to our opinion, early identification and active management of adverse events are of great importance for decreasing the side effects.

The treatment aim is identified as another factor impacting the decision of the first-line therapy. For the patients who have the potential of having resection, the active upfront treatment permits to not miss the chance for the conversion to resectability. FOLFOXIRI + bevacizumab is usually viewed as a valuable choice when there is an achievable treatment objective of the secondary resection of metastases, particularly in the live-limited spread case. However, an exploratory sensitivity analysis is done by Cremolini18, which does not demonstrate any interaction effect between the achievement of R0 resections and the treatment arm. Therefore, this conforms that the advantages of FOLFOXIRI + bevacizumab are not constrained to those patients who have experienced the radical resection of the lesions. This also indirectly shows that the survival advantages accompanied with the FOLFOXIRI + bevacizumab is not only because of the conversion of higher patients having R0 resection.

There were 75% of the enrolled patients having multiple metastases. Meanwhile, there were about 50% of them having disease in the liver. A comparison was made between FOLFOX plus bevacizumab and FOLFOXIRI plus bevacizumab in the OLIVIA trial[21] among patients having metastatic colorectal cancer who also have liver-constraint metastasis. It has been discovered that the secondary resection of metastases and progression-free survival was improved by the FOLFOXIRI plus bevacizumab. However, the study of Loupakis[18] did not demonstrate any interaction between the treatment effect and the clinical features of the patients.

Given that various drug regimens have been tested by RCTs, there was almost no chance to obtain the results from the identical comparisons. However, the accessible evidence was still exploited to answer the clinically related broad questions: which treatment regimen is the optimum first-line therapy is relevant as many patients do not ultimately receive second-line therapy. This NMA is acknowledged to have several limitations. First, our analysis is not depending on RAS and BRAF status, or left/right status. The most important reason is that in our selected 30 RCTs, only 1 RCT research compared treatment results by left/right side of colon cancer and 9 RCT researches mention RAS and BRAF status. Therefore, we cannot fully evaluate all treatment in mCRC, depending on RAS and BRAF status, or left/right status. Moreover, even though it has been shown that the molecular biomarkers and tumor location, taking BRAF and RAS as examples, can impact the treatment efficacy or/and clinical outcomes in the colorectal tumors, it has been found in the TRIBE that the treatment outcome of FOLFOXIRI-BEV is not impacted by the BRAF and RAS status in comparison with the FOLFIRI-BEV. There was no significant difference shown by the treatment groups between FOLFIRI plus bevacizumab and FOLFIRI plus cetuximab in terms of the progression-free survival, the primary endpoint, and the response rate in terms of the randomized trial in the nonmutated RAS subgroup.[22] Moreover, compared to left-sided tumors,[23] right-sided tumors are usually connected with a markedly poorer prognosis. However, it has been shown from the STEAM study that compared to the left-sided tumors,[24] a higher PFS was impacted to the patients by FOLFOXIRI-BEV with right-sided tumors. Therefore, more studies need to be made in the future regarding the tumor location in mCRC and the role of molecular biomarkers. Third, there are no studies incorporating checkpoint inhibitor immunotherapy in our study. This is because according to systemic therapy for advanced or metastatic disease of NCCN Guidelines Version 4.2020 Colon Cancer, checkpoint inhibitor immunotherapy is not included. Besides, some included studies lacked sufficient comparisons, which may have a certain impact on the result. In addition, the collected results from the included studies were uneven and the sample size of few studies on some drugs was relatively small.

Conclusion

Our study supported the use of FOLFOXIRI-bevacizumab as the best first-line regimen and potentially effective and safe strategy for the management of patients with mCRC. Furthermore, our up-to-date analysis provides new insights into existing controversies on systemic therapy for patients with mCRC.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

Our study did not require an ethical board approval because the meta-analysis study is exempt from ethics approval as the study authors will be collecting and synthesizing data from previous clinical trials in which informed consent has already been obtained by the trial investigators.

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Supplemental Material

Supplemental material for this article is available online.

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