Comparative efficacy and safety of first-line treatments for RAS wild-type metastatic colorectal cancer: A systematic review and network meta-analysis

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Abstract. Optimal first-line treatments for RAS wild-type metastatic colorectal cancer (mCRC) remain uncertain, despite the availability of numerous targeted therapies. Direct comparisons between all available regimens are limited, necessitating indirect evidence synthesis. A systematic review and network meta-analysis of randomized controlled trials (RCTs) comparing first-line treatments for RAS wild-type mCRC was conducted in the present study. MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials and Web of Science were searched from inception to September 2025. Primary outcomes included overall survival (OS) and progression-free survival (PFS), while secondary outcomes included objective response rate (ORR) and safety profiles. Random-effects network meta-analyses were performed and treatments were ranked using P-scores. In total, 15 RCTs involving 6,298 patients and seven primary treatment nodes were included. The network demonstrated high levels of consistency for OS (I^2=0%) and moderate heterogeneity for PFS (I^2=44.8%) and ORR (I^2=40.9%). For OS, both cetuximab + chemotherapy [hazard ratio (HR)=0.853; 95% CI: 0.775-0.938; P=0.001] and panitumumab + chemotherapy (HR=0.855; 95% CI: 0.738-0.992; P=0.038) exhibited statistically significant superiority compared with bevacizumab + chemotherapy. Cetuximab + chemotherapy ranked highest for OS (P-score=0.814) and PFS (P-score=0.914). Subgroup analysis demonstrated a pronounced tumor sidedness effect. Anti-EGFR therapy provided a 25.0% reduction in OS risk for left-sided tumors (HR=0.750; 95% CI: 0.672-0.836; I^2=0%), whereas no survival benefit was observed for right-sided tumors (HR=1.097; 95% CI: 0.909-1.325). Anti-EGFR regimens were associated with higher rates of grade ≥3 toxicities, reaching up to 83.3%, compared with bevacizumab-based regimens, which fell between 23.4-68.3%. In the present sensitivity analysis, UDP glucuronosyltransferase family 1 member A1-guided bevacizumab + 5-fluorouracil, leucovorin and irinotecan demonstrated favorable outcomes, with OS and PFS P-scores of 0.932 and 0.992, respectively; however, these findings were derived from a single trial with limited comparability. Overall, anti-EGFR antibodies combined with chemotherapy demonstrated consistent and statistically significant survival benefits as first-line treatment for RAS wild-type mCRC, with cetuximab + chemotherapy ranking as the optimal regimen. Treatment benefit from anti-EGFR therapy was markedly influenced by primary tumor location, with notable benefit observed in left-sided tumors and no benefit in right-sided tumors. These findings support tumor sidedness-guided treatment selection in clinical practice, favoring anti-EGFR-based therapy for left-sided and bevacizumab-based therapy for right-sided RAS wild-type mCRC.

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Introduction

Colorectal cancer (CRC) represents a major global health burden, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-associated mortality worldwide (1). In 2022, ~1.93 million new cases and 904,000 mortalities were attributed to CRC globally, with incidence rates continuing to rise in numerous developing countries and among younger populations in developed nations (2). The 5-year survival rate for patients with metastatic CRC (mCRC) remains low at 14-15%, despite marked therapeutic advances across the past two decades (3). This poor prognosis highlights the need for optimized treatment strategies that improve survival while maintaining quality of life.

The identification of RAS (including KRAS and NRAS) mutational status has emerged as a key biomarker in the management of mCRC, markedly impacting treatment strategies (4). In total, 40-45% of patients with mCRC harbor RAS wild-type tumors, which are sensitive to anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab (5). This molecular stratification has enabled personalized treatment approaches, as patients with RAS wild-type tumors demonstrate improved outcomes when treated with anti-EGFR therapies, compared with patients harboring RAS mutations (6). The therapeutic landscape for RAS wild-type mCRC has evolved notably, with numerous targeted agents available for first-line treatment (7). Available options include anti-EGFR antibodies, such as cetuximab and panitumumab, anti-VEGF agents, such as bevacizumab and biosimilar agents, all of which may be combined with standard chemotherapy backbones including 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) (8). Previous clinical trials have also explored UDP glucuronosyltransferase family 1 member A1 (UGT1A1)-guided dose escalation strategies and the addition of adjuvant agents, such as vitamin C, to enhance therapeutic efficacy (9,10).

Although these advances have expanded treatment options, they have also increased complexity in clinical decision-making. Patient heterogeneity, including differences in performance status, comorbidities and prior adjuvant therapy exposure, further complicates treatment selection (11). In addition, the financial burden associated with biological therapies presents challenges for healthcare systems and patients, emphasizing the need for evidence-based treatment optimization (12).

A major limitation in current evidence is the lack of comprehensive comparative effectiveness data across all available treatment options. Although a number of randomized controlled trials (RCTs) have evaluated individual regimens (7,8,13-16), numerous studies include only two or three treatment arms, limiting direct comparisons across all available therapies (17). Traditional pairwise meta-analyses cannot synthesize evidence in the absence of direct comparisons and therefore fail to provide a comprehensive evaluation of relative efficacy and safety (18). However, network meta-analysis offers an effective approach by enabling simultaneous comparison of numerous treatments using both direct and indirect evidence (19). This methodology preserves the benefits of randomization while allowing estimation of relative treatment effects between interventions that have not been directly compared in head-to-head trials (20). For clinicians managing RAS wild-type mCRC, network meta-analysis can provide a treatment hierarchy based on numerous efficacy endpoints, supporting evidence-based clinical decision-making (21).

Therefore, the present network meta-analysis aimed to comprehensively compare the efficacy and safety of available first-line treatment options for patients with RAS wild-type mCRC. By synthesizing evidence from RCTs, treatment rankings were established based on overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and safety outcomes, with the aim of providing evidence-based guidance for optimal treatment selection in clinical practice.

Materials and methods

Study design. Firstly, the present network meta-analysis was registered in the International Prospective Register of Systematic Review (ID: CRD420251138090) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Inclusion and exclusion criteria. Studies were considered eligible for inclusion if they met the following criteria: i) Population: Adult patients aged ≥18 years with histologically determined RAS wild-type MCRC, including initially metastatic or recurrent disease; ii) intervention: Any first-line systemic anticancer treatment, including chemotherapy, targeted therapy, immunotherapy or combination regimens; iii) comparison: No restrictions on comparator arms; iv) outcomes: Reporting at least one primary outcome, including OS or PFS; and v) study design: RCTs.

Studies were excluded if they met any of the following criteria: i) Non-randomized study designs, including observational studies, case series or case reports; ii) inclusion of RAS-mutant patients without separately extractable data for RAS wild-type subgroups; iii) focus on adjuvant or neoadjuvant treatment settings; iv) inclusion of patients with resectable metastatic disease; v) duplicate publications or overlapping patient populations; vi) conference abstracts when full-text publications of the same study were available; or vii) letters, editorials, reviews or commentaries.

Search strategy. A comprehensive systematic literature search was conducted across MEDLINE (https://www.nlm.nih.gov/medline/medline_home.html)/PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), the Cochrane Central Register of Controlled Trials through the Ovid platform (https://ovidsp.ovid.com/) and Web of Science (https://www.webofscience.com/) from inception to September 1, 2025. The search strategy combined Medical Subject Headings and free-text keywords associated with CRC, RAS wild-type status, metastatic disease and first-line treatment. No language restrictions were applied. In addition, reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible studies. The complete search strategy is provided in Table SI.

Data extraction. Data was extracted from eligible studies by two independent reviewers using a standardized data extraction form. Discrepancies were resolved through discussion or consultation with a third reviewer. The following information was extracted from each study: i) Trial identification, including trial ID, publication year and study region; ii) study characteristics, including trial phase and sample size; iii) patient demographics, including mean age and sex distribution; iv) tumor characteristics, including primary tumor sidedness and metastatic status; v) interventions compared; and vi) reported clinical outcomes. For efficacy outcomes, OS, PFS, ORR and duration of response were extracted, along with corresponding hazard ratios (HRs), odds ratios (ORs) and 95% CIs. Safety data, including incidence of grade ≥3 treatment-emergent adverse events (TEAEs), were also extracted when available.

Risk of bias assessment. Methodological quality of included studies was assessed using the Cochrane Collaboration Risk of Bias tool (22). The two independent reviewers evaluated each study across seven domains: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential sources of bias. Each domain was classified as low risk, high risk or unclear risk of bias. Disagreements were resolved through consensus or consultation with a third reviewer. Risk of bias summary figures and graphs were generated using Review Manager (version 5.4; The Cochrane Collaboration).

Statistical analysis. A random-effects network meta-analysis was conducted within a frequentist framework using the 'netmeta' package in R (version 4.5.2; Posit Software, PBC) (23). This approach applied a graph-theoretical model based on electrical network theory. Network plots were generated to visualize the evidence base, where node size was proportional to total sample size for each intervention and line thickness corresponded to the number of trials for each comparison. The statistical model accounted for associated treatment effects and addressed zero-event studies by applying a continuity correction to trials with zero events in a single arm, while trials with zero events in both arms were excluded. Results were presented as ORs or HRs with corresponding 95% CIs, depending on the outcome.

Treatment rankings were determined using P-scores, representing the frequentist equivalent of the surface under the cumulative ranking curve, to estimate treatment superiority. Consistency between direct and indirect evidence within closed loops was assessed using the node-splitting method. Potential small-study effects were evaluated through visual inspection of funnel plots and formally tested using Egger's test. Heterogeneity was assessed using the Cochran Q statistic, decomposed into within-design and between-design components and quantified using the I^2 statistic. I^2 values of 25-49, 50-74 and ≥75% were interpreted as low, moderate and high heterogeneity, respectively. All statistical tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of included studies. Study selection processes for the present analysis are outlined in the PRISMA flow diagram (Fig. 1). The initial database search identified 3,799 records. After removal of 614 duplicates, 1,484 records were screened, resulting in retrieval of 102 full-text articles for eligibility assessment. Following detailed evaluation, 15 RCTs met the inclusion criteria and were included in the present network meta-analysis (7-10,13-16,24-30). Study characteristics are summarized in Table I. Collectively, the 15 trials included 6,298 patients. Among the included studies, 10 were phase III trials and 5 were phase II trials.

Patient characteristics were generally balanced across studies. The mean age was 55-77 years, with a predominance of male patients ranging from 61-76% across studies. Primary tumor location was predominantly left-sided, accounting for 61-100% of patients, consistent with the known favorable prognosis of left-sided tumors in RAS wild-type disease (17,18). The liver was the most common site of metastasis, reported in 12-92% of patients, followed by lung metastases in 21-33% and lymph node involvement in 20-25% of patients (Table I).

Risk of bias in studies. Overall methodological quality of the included studies was satisfactory (Fig. 2). All trials demonstrated low risk of bias for random sequence generation and allocation concealment, indicating appropriate randomization procedures. The majority of studies also exhibited low risk of attrition bias and selective reporting bias, indicating that outcome data were generally complete and that no major selective outcome reporting was identified according to the aforementioned prespecified risk-of-bias criteria.

The main methodological limitation was lack of blinding of participants and personnel, with 93% of studies classified as high risk for performance bias. This was largely due to open-label study designs required when comparing treatments with different administration schedules or toxicity profiles.

A notable proportion of studies (~67%) exhibited unclear or high risk of other bias, primarily associated with pharmaceutical industry funding or involvement of industry-affiliated authors. Although industry sponsorship does not necessarily compromise study validity, the potential for conflicts of interest justified classification as unclear risk in the present domain.

Network meta-analysis results. Evidence network for the primary analysis included 12 RCTs, seven treatment nodes and eight distinct pairwise comparisons (Fig. S1). UGT1A1-guided bevacizumab + FOLFIRI (trial ID: NCT02256800), vitamin C + bevacizumab + FOLFOX (10) and A140 + FOLFOX (trial ID: NCT04835142) were excluded because they were single-trial nodes with small sample sizes. The primary analysis comprised the following seven treatment nodes: Bevacizumab + chemotherapy (Bev + Chemo), cetuximab + chemotherapy (Cet + Chemo), panitumumab + chemotherapy (Pan + Chemo), FOLFOX, FOLFIRI, 5-fluorouracil/leucovorin (5-FU/LV) and cetuximab maintenance. The network was fully connected, with Bev + Chemo serving as the most frequently used comparator. In the network plot, node size reflects cumulative sample size and edge thickness is proportional to the number of contributing studies per comparison.

OS. Primary network meta-analysis for OS incorporated 12 RCTs. The network demonstrated excellent statistical consistency, with no significant between-design inconsistency ($Q_{between}=0.53$; df=2; P=0.768), negligible overall heterogeneity ($Q_{total}=2.67$; df=6; P=0.849; $\tau^2=0$; $I^2=0\%$) and no statistically significant disagreement between direct and indirect evidence in node-splitting analysis for any evaluable comparison (all $P>0.05$; Table SII). Forest plots presenting OS HRs relative to Bev + Chemo under the random-effects model are shown in Fig. 3A. A total of two treatment regimens demonstrated statistically significant superiority compared with Bev + Chemo: Cet + Chemo (HR=0.853; 95% CI: 0.775-0.938; P=0.001) and Pan + Chemo (HR=0.855; 95% CI: 0.738-0.992; P=0.038). The remaining treatments, including cetuximab maintenance, FOLFIRI, FOLFOX and 5-FU/LV, did not differ significantly from Bev + Chemo. Complete pairwise

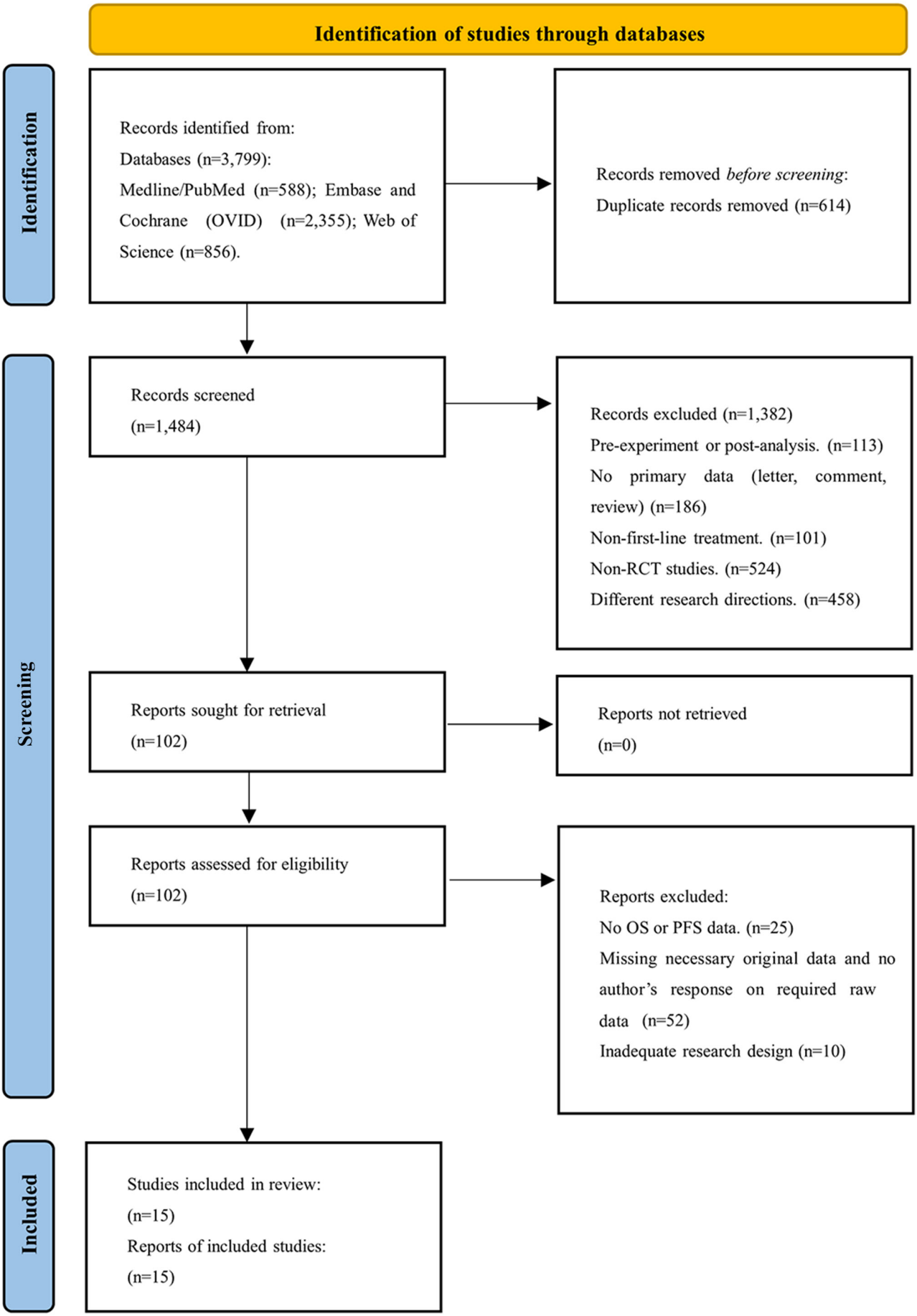

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of search results and selections. OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials.

Table I. Characteristics of the included randomized controlled trials.

First author, year	Trial ID (region)	Phase	Sample size	Average age, years	Sex	Interventions compared	PTS	Metastatic status	OS, months	PFS, months	ORR, months	DOR, months	Safety profile (grade ≥3 TEAEs)	(Refs.)
Aranda *et al*, 2018	NCT01161316 (Spain)	II	193 (129/64)	60	M: 64%, F: 36%	Cet vs. FOLFOX + Cet	Left: 73%, Right: 22%	Single site 68.0%, Multiple: 32.0%	23/27 (HR=1.24; 95% CI: 0.85-1.79)	9/10 (HR=1.19; 95% CI: 0.80-1.79)	48.0/ 39.0% (OR=1.44; 95% CI: 0.78-2.66)	NA	70.0/ 68.0%	(26)
Tsai *et al*, 2020	NCT02256800 (China)	III	213 (107/106)	61	M: 67%, F: 33%	FOLFIRI + Bev (UGT1A1-guided dose escalation) vs. Bev + standard FOLFIRI	Left: 81%, Right: 19%	NA	30.0/22.0 (HR=0.693; 95% CI: 0.503-0.955)	14.0/10.0 (HR=0.539; 95% CI: 0.398-0.730)	71.9/41.5% (OR=4.067; 95% CI: 2.240-7.384)	NA	23.4/ 23.6%	(9)
Venook *et al*, 2017	NCT00265850 (USA)	III	1137 (578/559)	59	M: 61%, F: 39%	Cet + FOLFOX/ FOLFIRI vs. Bev + FOLFOX/ FOLFIRI	Left: 61%, Right: 25%	Liver: 74.0%; Lung: 33.0%	30.0/29.0 (HR=0.88; 95% CI: 0.77-1.01)	10.5/10.6 (HR=0.95; 95% CI: 0.84-1.08)	59.6/55.2% (NA)	NA	Overall incidence: 53.0%	(8)
Watanabe *et al*, 2023	NCT02394795 (Japan)	III	823 (411/412)	66	M: 66%, F: 34%	Pan + FOLFOX vs. Bev + mFOLFOX	Left: 75.3%, Right: 23.3%	Liver: 81.4%	37.9/34.3 (HR=0.82; 95.8% CI: 0.68-0.99)	13.1/11.9 (HR=1.00; 95% CI: 0.83-1.20)	80.2/68.6% (NA)	13.1/ 11.2 (HR=0.86; 95% CI: 0.70-1.10)	NA	(13)
Qin *et al*, 2018	NCT01228734 (China)	III	393 (193/200)	56	M: 70%, F: 30%	Cet + FOLFOX vs. FOLFOX	Left: 79.2 vs. 81.3%/ Right: 15.2 vs. 15.4%	Liver: 79.2/ 84.6%	20.7/17.8 (HR=0.76; 95% CI: 0.61-0.96)	9.2/7.4 (HR=0.69; 95% CI: 0.54-0.89)	61.1/39.5% (OR=2.41; 95% CI: 1.61-3.61)	NA	43.2/ 26.0%	(14)

Table I. Continued.

First author, year	Trial ID (region)	Phase	Sample size	Average age, years	Sex	Interventions compared	PTS	Metastatic status	OS, months	PFS, months	ORR, months	DOR, months	Safety profile (grade ≥3 TEAEs)	(Refs.)
Modest *et al*, 2021	NCT01991873 (Germany)	II	248 (125/123)	66	M: 65%, F: 35%	Pan + FU/FA vs. FU/FA	Left: 79.2 vs. 81.3%/ Right: 15.2 vs. 15.4%	Liver: 79.2/ 84.6%; Perito-neum: 10.4/ 17.9%	28.7/ 25.7 (HR=0.84; 95% CI: 0.60-1.18)	8.8/5.7 (HR=0.72; 80% CI: 0.60-0.85)	40.8/26.0% (OR=1.96; 95% CI: 1.14-3.36)	NA	43.2/ 26.0%	(28)
Liu *et al*, 2025	NCT04835142 (China)	III	688 (341/347)	59	M: 65%, F: 35%	A140 + FOLFOX vs. Cet + FOLFOX	Left: 87.7 vs. 87.0%/ Right: 12.3 vs. 13.0%	Liver: 76.2/ 75.8%	28.1/NR (HR=1.10; 95% CI: 0.84-1.42)	10.9/10.8 (HR=1.03; 95% CI: 0.83-1.28)	71.0/77.5% (ORR Ratio= 0.93; 90% CI: 0.87-0.99)	10.2/9.5 (HR=0.91; 95% CI: 0.70-1.18)	66.6/ 68.3%	(29)
Shi *et al*, 2025	NCT03206151 (China)	III	505 (257/248)	57	M: 69%, F: 31%	Cet β + FOLFIRI vs. FOLFIRI	Left: 85.6 vs. 85.9%/ Right 13.2 vs. 12.5%	Liver: 69.6/ 76.2%	28.3/23.1 (HR=0.729; 95% CI: 0.551-0.965)	13.1/9.6 (HR=0.639; 95% CI: 0.468-0.872)	69.1/42.3% (OR=3.090; 95% CI: 2.280-4.189)	NA	83.3/ 66.9%	(30)
Bond *et al*, 2023	NCT02162563 (The Netherlands)	III	230 (114/116)	62	M: 62%, F: 38%	FOLFOX/ FOLFIRI + Bev vs. FOLFOX/ FOLFIRI + Pan	Left: 100%	Liver: 12.0%	39.9/38.3 (HR=0.95; 95% CI: 0.68-1.32)	10.8/10.4 (HR=1.11; 95% CI: 0.84-1.48)	53.0/80.0% (OR=NA)	NA	54.0/ 69.0%	(16)
Douillard *et al*, 2014	NA (global)	III	656 (325/331)	62	M: 65%, F: 35%	Pan + FOLFOX vs. FOLFOX	NA	Liver: 19.0/ 17.0%; Other: 12.0/14.0%	23.9/19.7 (HR=0.88; 95% CI: 0.73-1.06)	10.0/8.6 (HR=0.80; 95% CI: 0.67-0.95)	57.0/48.0% (OR=1.47; 95% CI: 1.07-2.04)	NA	NA	(15)

Table I. Continued.

First author, year	Trial ID (region)	Phase	Sample size	Average age, years	Sex	Interventions compared	PTS	Metastatic status	OS, months	PFS, months	ORR, months	DOR, months	Safety profile (grade ≥3 TEAEs)	(Refs.)
Heinemann *et al*, 2021	NCT00433927 (Germany and Austria)	III	352 (169/183)	64	M: 76%, F: 24%	FOLFIRI + Cet vs. FOLFIRI + Bev	Left: 82%, Right: 18%	NA	33.0/26.0 (HR=0.75; 95% CI: 0.59-0.94)	10.0/11.0 (HR=0.99; 95% CI: 0.81-1.24)	77.0/65.0% (OR=1.84; 95% CI: 1.15-2.93)	NA	64.0/ 51.0%	(7)
Wang *et al*, 2022	NA (China)	III	442 (221/221)	55	M: 61%, F: 39%	Vitamin C + FOLFOX + Bev vs. FOLFOX + Bev	Left: 72.9 vs. 71.5%/ Right: 27.1 vs. 28.5%	NA	20.7/19.7 (HR=1.04; 95% CI: 0.81-1.33)	8.6/8.3 (HR=0.86; 95% CI: 0.70-1.05)	44.3/42.1% (OR=NA)	NA	33.5/ 30.3%	(10)
Modest *et al*, 2019	NCT01328171 (Germany)	II	96 (63/33)	59	M: 67%, F: 33%	FOLFOX + Pan vs. FOLFOX	Left: 84.1 vs. 75.8%/ Right: 15.9 vs. 24.2%	Liver: 92.1/ 78.8%; Lung: 28.6/ 21.2%; Lymph nodes: 20.6/24.2%	35.7/29.8 (HR=0.67; 95% CI: 0.41-1.11)	9.7/9.7 (HR=1.07; 95% CI: 0.69-1.67)	87.3/60.6% (OR=4.469; 95% CI: 1.61-12.38)	NA	81.3/ 66.7%	(27)
Boige *et al*, 2023	NCT02404935 (France)	II	139 (67/72)	66	M: 68%, F: 32%	FOLFIRI + Cet vs. FOLFIRI	Left: 76.1 vs. 80.3%/ Right: 23.9 vs. 18.3%	NA	24.8/19.7 (HR=0.79; 95% CI: 0.50-1.25)	5.3/2.0 (HR=0.36; 95% CI: 0.24-0.53)	17.5/4.8% (OR=NA)	NA	NA	(25)
Lonardi *et al*, 2019	NCT02904031 (Italy)	II	183 (91/92)	77	M: 63%, F: 37%	FOLFOX + Pan vs. 5-FU/LV + Pan	Left: 77 vs. 79%/ Right: 23 vs. 21%	Single site: 42.9/41.3%, Multiple: 51.7/58.7%	23.5/22.0 (HR=1.00; 95% CI: 0.73-1.38)	9.6/9.0 (HR=1.08; 95% CI: 0.80-1.46)	69.0/52.0% (OR=0.48; 95% CI: 0.26-0.89)	NA	60.0/ 37.0%	(24)

OS, overall survival; PFS, progression-free survival; ORR, objective response rate. FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin; M, male; F, female; HR, hazard ratio; NA, not applicable; OR, odds ratio; PTS, primary tumor side; UGT1A1, UDP glucuronosyltransferase family 1 member A1; TEAEs, treatment-emergent adverse events; DOR, duration of response; Cet, cetuximab; Cet(maint.), Cet maintenance; Chemo, chemotherapy; Bev, bevacizumab.

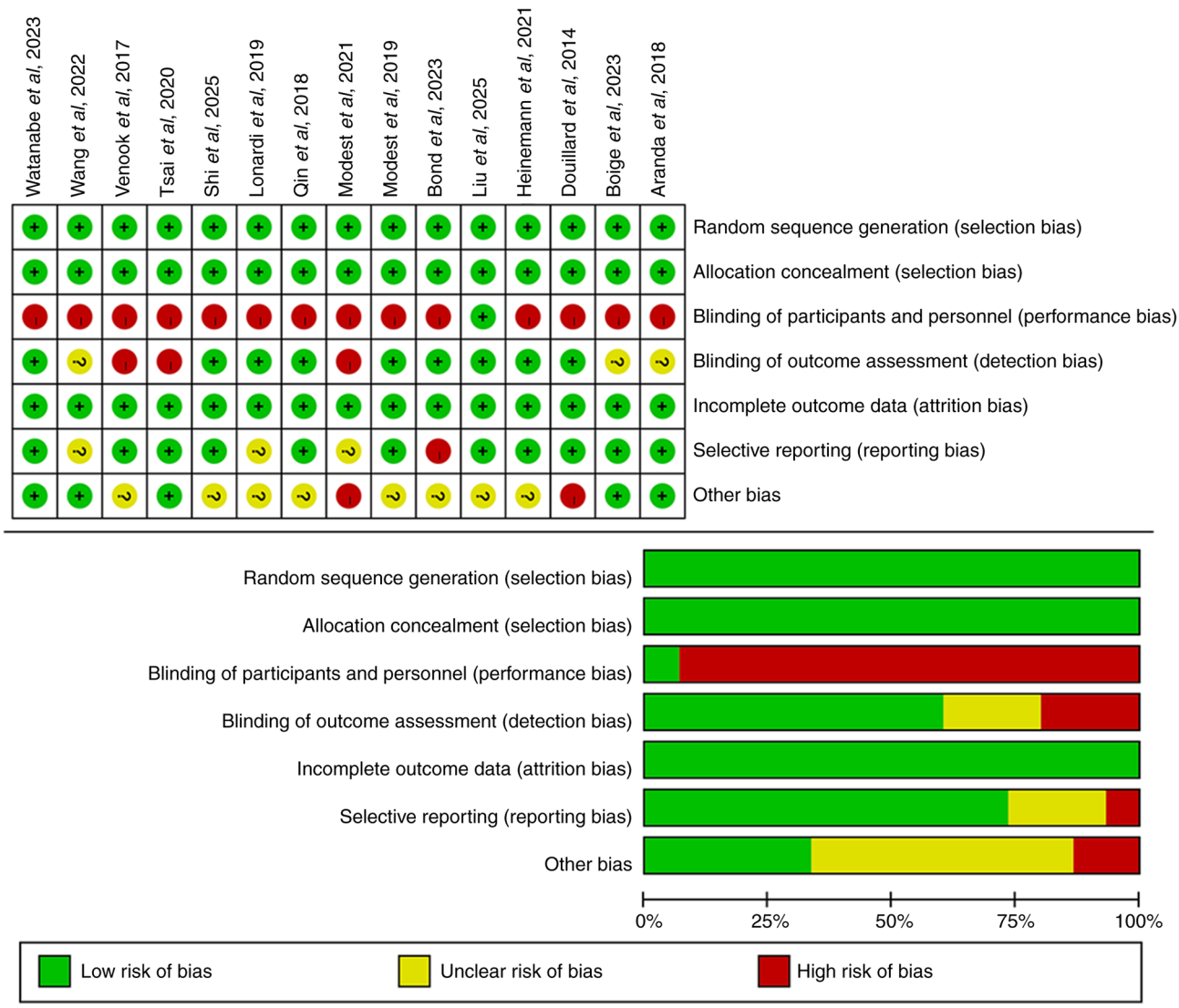

Figure 2. Risk of bias assessment (A) in individual studies and (B) across the included studies.

comparisons between all treatment nodes are provided in the league table (Tables SIII and SIV). Treatment ranking based on P-scores identified Cet + Chemo as the regimen most likely to provide the highest OS (P-score=0.814), followed by Pan + Chemo (P-score=0.798) and 5-FU/LV (P-score=0.735). Bev + Chemo ranked fourth (P-score=0.420), followed by cetuximab maintenance (P-score=0.350), FOLFIRI (P-score=0.225) and FOLFOX (P-score=0.158; Fig. 4A).

PFS. PFS analysis included the same 12 RCTs and 7 treatment nodes, with moderate between-study heterogeneity (I^2=44.8%; Q_{total}=10.87; df=6; P=0.092). Between-design inconsistency was not statistically significant ($Q_{between}$=1.308; P=0.520) and node-splitting determined no statistically significant direct-indirect disagreement for any evaluable comparison (all P>0.05; Tables SII and SV). Forest plots for PFS are presented in Fig. 3B. Under the random-effects model, Cet + Chemo showed a non-significant trend toward PFS benefit over Bev + Chemo (HR=0.880; 95% CI: 0.766-1.011; P=0.072). Notably, FOLFIRI alone was significantly inferior to Bev + Chemo for PFS (HR=1.631; 95% CI: 1.294-2.056; P<0.001), reflecting the marked PFS benefit conferred by bevacizumab addition to chemotherapy. No other treatment differed significantly from Bev + Chemo in PFS. P-score ranking placed Cet + Chemo as the top-ranked treatment for PFS (P-score=0.914), followed by Bev + Chemo (P-score=0.654), 5-FU/LV (P-score=0.598) and cetuximab maintenance (P-score=0.561; Fig. 4B).

ORR. ORR analysis incorporated 8 RCTs and 7 treatment nodes, with moderate heterogeneity (I^2=40.9%) and borderline between-design inconsistency ($Q_{between}$=2.784; P=0.095). Forest plots for ORR are presented in Fig. 3C, with estimates expressed as ORRs relative to Bev + Chemo (OR >1 indicates higher ORR compared with Bev + Chemo). A total of three regimens demonstrated significantly higher ORR than Bev + Chemo under the random-effects model: Cet + Chemo (OR=1.612; 95% CI: 1.087-2.390; P=0.017), cetuximab maintenance (OR=2.321; 95% CI: 1.011-5.327; P=0.047) and 5-FU/LV (OR=2.989; 95% CI: 1.012-8.828; P=0.047). Pan + Chemo, FOLFIRI and FOLFOX did not differ significantly from Bev + Chemo. P-score ranking identified 5-FU/LV (P-score=0.915) and cetuximab maintenance (P-score=0.830)

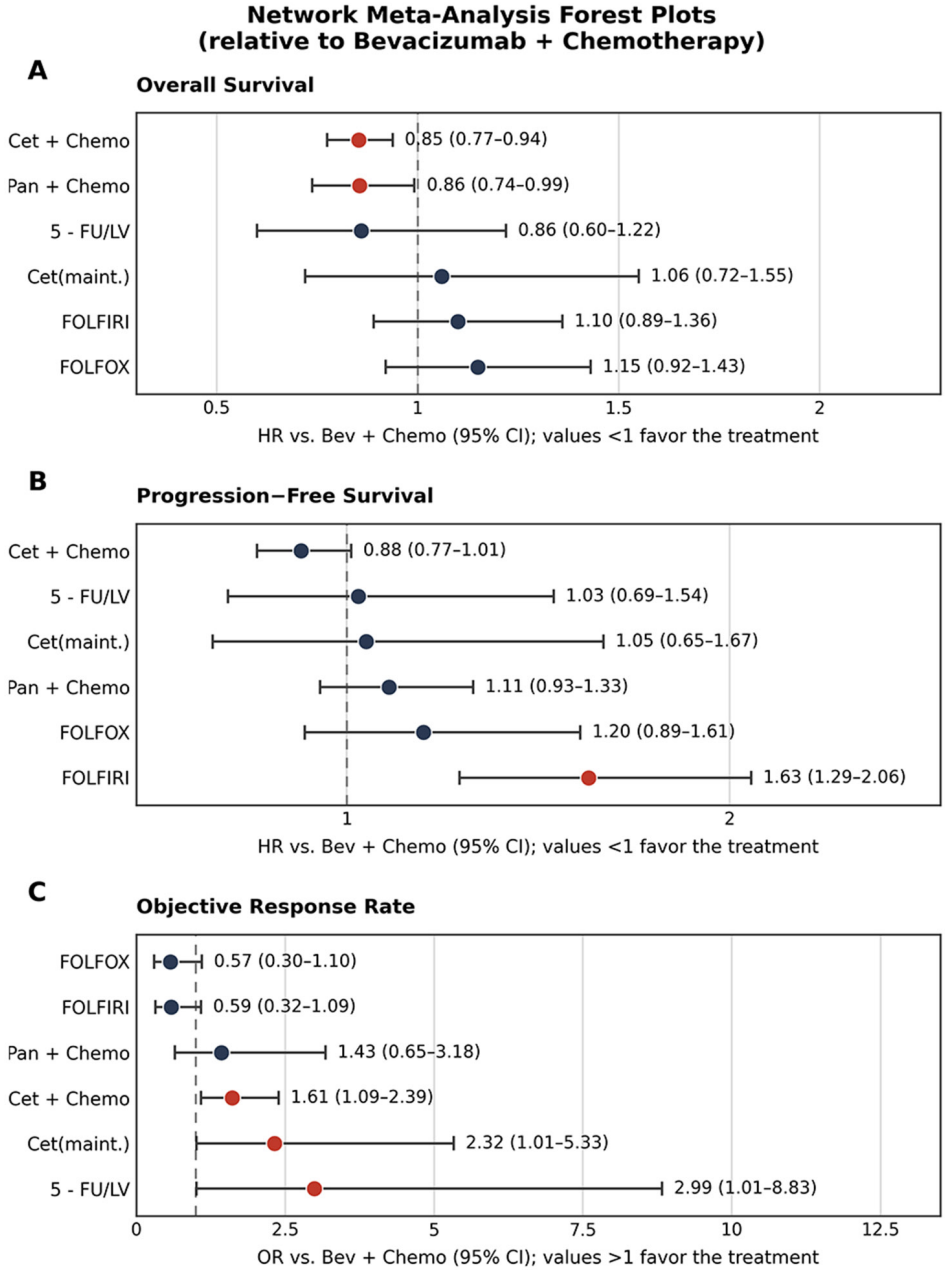

Figure 3. Network meta-analysis forest plots comparing therapies for (A) overall survival, (B) progression-free survival and (C) objective response rate. HR, hazard ratio; 5-FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; Cet, cetuximab; Cet(maint.), Cet maintenance; Chemo, chemotherapy; Bev, bevacizumab.

as top-ranked, followed by Cet + Chemo (P-score=0.650) and Pan + Chemo (P-score=0.562; Fig. 4C).

Subgroup analysis: Primary tumor location. A pre-specified subgroup analysis was conducted stratifying treatment effects by primary tumor sidedness (left-sided vs. right-sided). Subgroup-specific HRs were extractable from 5 trials for OS and 6 trials for PFS. Forest plots are provided in Fig. 5. For OS, anti-EGFR-containing regimens demonstrated consistent benefit in left-sided tumors across all 5 contributing studies. The pooled HR for anti-EGFR vs. control in left-sided tumors was 0.750 (95% CI: 0.672-0.836; I^2=0%), representing a 25.0% mortality risk reduction. In right-sided tumors, the corresponding pooled HR was 1.097 (95% CI: 0.909-1.325; I^2=0%), indicating no OS benefit from anti-EGFR therapy and a non-significant trend favoring bevacizumab-based or chemotherapy-only approaches. For PFS, a broadly consistent directional pattern was observed. In left-sided tumors, the pooled PFS HR for anti-EGFR vs. control was 0.840 (95% CI: 0.687-1.027; I^2=68.6%), reflecting a non-significant trend toward benefit. In right-sided tumors, the pooled PFS HR was 1.143 (95% CI: 0.851-1.536; I^2=54.9%), suggesting no PFS advantage and a non-significant numerical disadvantage, for anti-EGFR agents. Notably, the PARADIGM trial reported a statistically significant PFS detriment for panitumumab plus mFOLFOX6 vs. bevacizumab + mFOLFOX6 in right-sided tumors (HR=1.43; 95% CI: 1.03-1.97) (13).

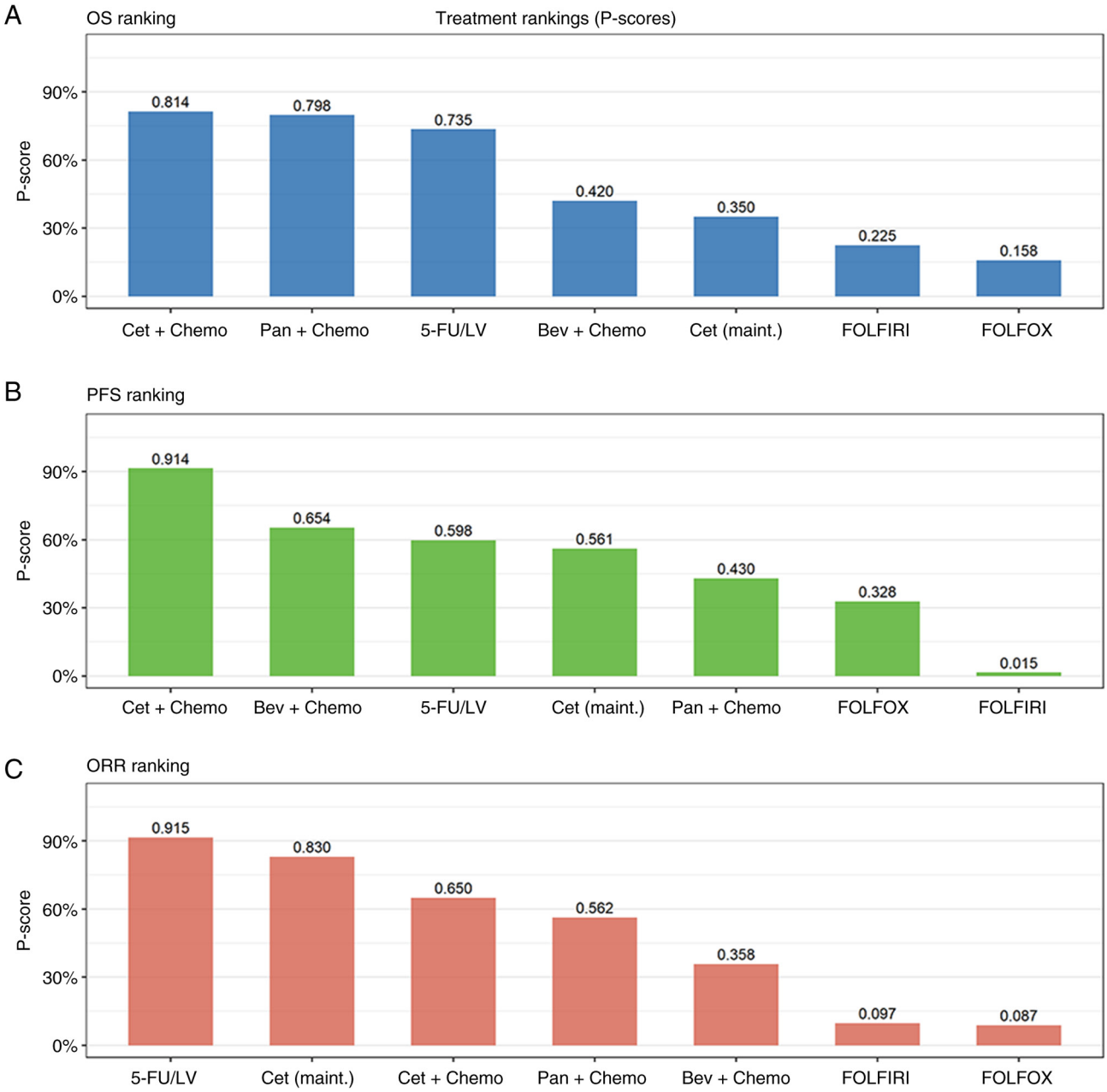

Figure 4. Treatment ranking by P-scores for (A) OS, (B) PFS and (C) ORR. OS, overall survival; PFS, progression-free survival; ORR, objective response rate; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin; Cet, cetuximab; Cet(maint.), Cet maintenance; Chemo, chemotherapy; Bev, bevacizumab.

Safety analysis. Incidence of grade ≥3 TEAEs across included treatments is summarized in Table I. Rates ranged from 23.4-83.3% across treatment arms. Anti-EGFR-based combinations were associated with the highest toxicity burden: Cetuximab biosimilar plus FOLFIRI reported 83.3% grade ≥3 TEAEs (trial no. NCT03206151) and panitumumab plus FOLFOX 81.3% (trial no. NCT01328171). Bevacizumab-containing regimens demonstrated comparatively more favorable toxicity profiles (grade ≥3 TEAE rate: 23.4-68.3% across trials). FOLFIRI alone was associated with grade ≥3 TEAEs in 66.9% of patients. Due to heterogeneous adverse event reporting across trials, a formal network meta-analysis of safety outcomes was not performed. Descriptively, anti-EGFR agents were consistently associated with skin toxicity, hypomagnesemia and infusion reactions, while bevacizumab-based regimens were more commonly associated with hypertension and thromboembolic events. Detailed adverse event data are provided in Table SVI.

Sensitivity analysis and heterogeneity assessment. A sensitivity analysis incorporating all 15 RCTs and 9 treatment nodes, including UGT1A1-guided bevacizumab + FOLFIRI, vitamin C plus bevacizumab + FOLFOX and A140 + FOLFOX, was conducted. The expanded evidence network is presented in Fig. S2, with full numerical results in Tables SI and II.

The primary analysis conclusions were demonstrated to be robust: Cet + Chemo and Pan + Chemo maintained statistically significant OS benefits in comparison with Bev + Chemo.

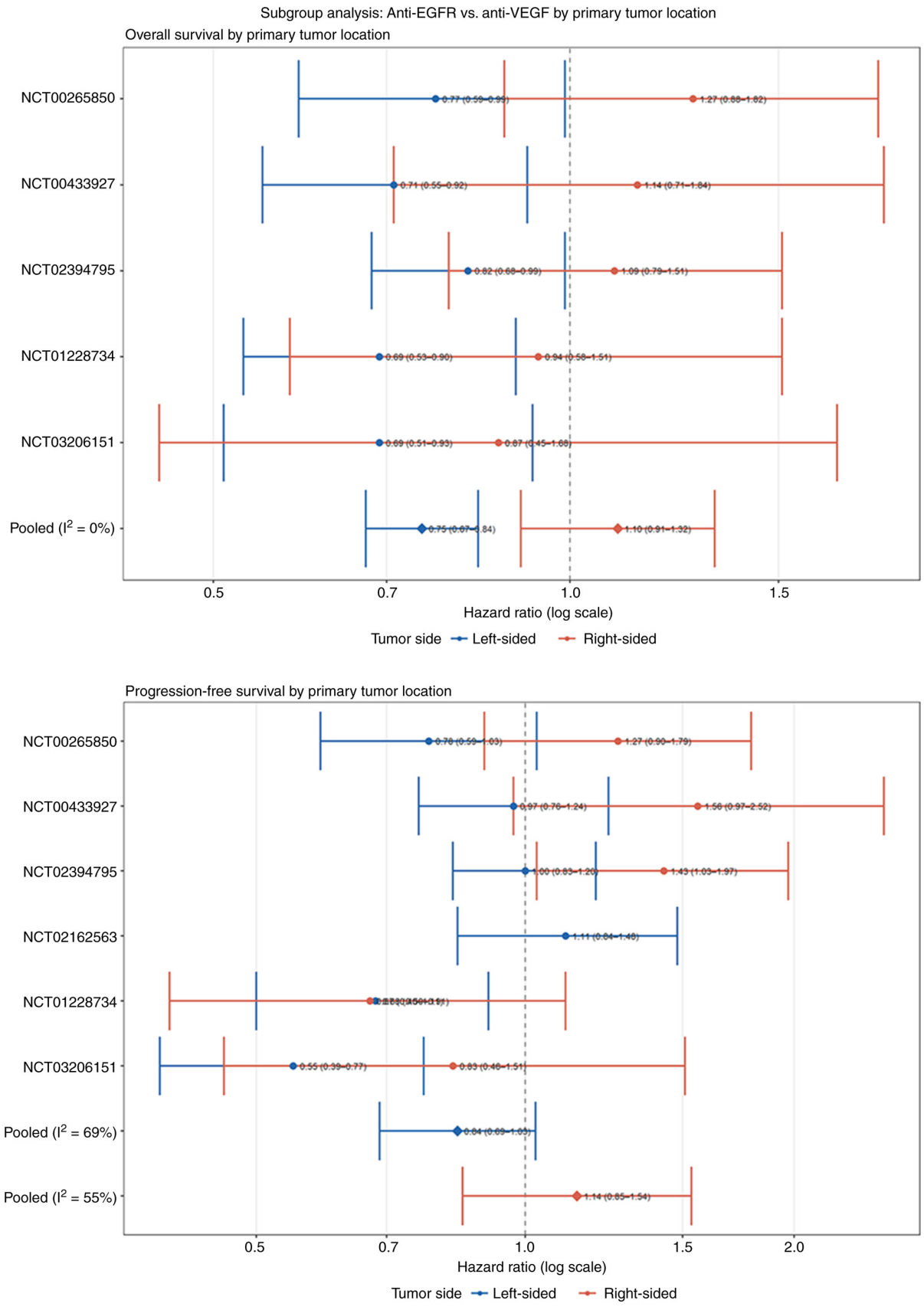

Figure 5. Subgroup analyses according to tumor location.

In the nine-node sensitivity network, the UGT1A1-guided bevacizumab + FOLFIRI node ranked highest for both OS (P-score=0.932) and PFS (P-score=0.992), consistent with the favorable efficacy estimates reported in the single PURE FIST trial (OS HR=0.693; 95% CI: 0.503-0.955; PFS HR=0.539; 95% CI: 0.398-0.730) (9). However, as these estimates derive

from a single study employing a non-genotyped control arm, their comparability with other nodes is limited and they are reported as supplementary findings. A140 + FOLFOX and vitamin C + bevacizumab + FOLFOX showed no statistically significant benefit compared with any comparator.

For PFS (I^2=44.8%; τ^2=0.010) and ORR (I^2=40.9%; τ^2=0.041), where moderate between-study heterogeneity was observed, meta-regression analyses were conducted incorporating publication year, geographic region (Eastern vs. Western), chemotherapy backbone (FOLFOX vs. FOLFIRI) and trial phase (II vs. III) as study-level covariates.

For PFS, none of the examined moderators reached statistical significance: Publication year (P=0.420), region (P=0.523), trial phase (P=0.686) and chemotherapy backbone (P=0.151). Chemotherapy backbone explained the largest, though non-significant, proportion of PFS heterogeneity (R2 analog=9.9%), with FOLFOX-based regimens showing a non-significant trend toward higher HR in comparison with FOLFIRI-based regimens (coefficient=0.128; P=0.151).

For ORR, geographic region was the strongest, though non-significant, moderator (R2 analog=24.5%; P=0.150), with Eastern-region trials showing higher pooled ORR for anti-EGFR regimens compared with Western-region trials (coefficient=0.600). Publication year (P=0.347), trial phase (P=0.359) and chemotherapy backbone (P=0.610) did not explain ORR heterogeneity. Bubble and dot plots illustrating the association between study-level covariates and treatment effects for PFS and ORR are provided in Fig. S3.

Publication bias. Comparison-adjusted funnel plots for OS, PFS and ORR are presented in Fig. S4. The funnel plots for all three outcomes demonstrated broadly symmetric distributions around the null, with no consistent pattern suggestive of small-study effects or publication bias. Formal statistical asymmetry tests were not performed owing to the limited number of studies per individual comparison (k<10 for the majority of direct comparisons).

Discussion

Within the present comprehensive network meta-analysis, evidence from 15 RCTs encompassing 6,298 patients was synthesized to provide the most extensive comparative assessment of first-line treatments for RAS wild-type mCRC to date. In the primary analysis of 12 RCTs and seven treatment nodes, anti-EGFR antibodies combined with chemotherapy demonstrated statistically significant OS benefits compared with bevacizumab + chemotherapy, with cetuximab + chemotherapy reducing mortality risk by 14.7% (HR=0.853; 95% CI: 0.775-0.938) and panitumumab + chemotherapy by 14.5% (HR=0.855; 95% CI: 0.738-0.992). Treatment ranking consistently favored cetuximab plus chemotherapy, which achieved the highest P-scores for both OS (0.814) and PFS (0.914). Critically, the pre-specified subgroup analysis revealed that these survival benefits were strongly modified by primary tumor sidedness: Anti-EGFR therapy conferred a 25.0% OS risk reduction in left-sided tumors (HR=0.750; I^2=0%) but provided no benefit in right-sided tumors (HR=1.097). Furthermore, anti-EGFR regimens were associated with markedly higher rates of grade ≥3 adverse events (up to 83.3%) compared with bevacizumab-based approaches (23.4-68.3%), highlighting an important efficacy-toxicity trade-off that must be weighed in clinical decision-making.

The mechanistic basis for the observed differential efficacy between treatment regimens reflects the distinct biological pathways targeted by anti-EGFR and anti-VEGF therapies in RAS wild-type tumors (31). RAS wild-type status preserves intact EGFR signaling, enabling effective pathway blockade by cetuximab and panitumumab, which competitively inhibit ligand binding and prevent receptor dimerization, ultimately suppressing downstream RAF-MEK/ERK and PI3K/Akt/mTOR cascades key in tumor cell proliferation and survival (32). The superior performance of UGT1A1-guided dosing, observed in a single exploratory phase II trial (PURE FIST) rather than demonstrated by numerous phase III trials, leverages pharmacogenomic optimization of irinotecan metabolism, as patients with favorable UGT1A1 genotypes ($^*1/^*1$ or $^*1/^*28$) can tolerate higher irinotecan doses due to enhanced glucuronidation of the active metabolite, SN-38, thereby achieving greater cytotoxic exposure without proportional toxicity increases (33). The mechanism of bevacizumab involves sequestration of circulating VEGF-A, disrupting tumor angiogenesis and normalizing aberrant vasculature, which enhances chemotherapy delivery while reducing interstitial pressure (34).

The present findings were broadly consistent with previous comparative effectiveness research while providing updated and more comprehensive estimates. The FIRE-3 trial reported an OS HR of 0.70 favoring cetuximab plus FOLFIRI compared with bevacizumab + FOLFIRI in patients with the RAS wild-type (7); the pooled network estimate for cetuximab + chemotherapy vs. bevacizumab + chemotherapy (HR=0.853; 95% CI: 0.775-0.938) showed a directionally concordant but attenuated effect, likely reflecting the integration of more recent trials, such as CALGB/SWOG 80405 and PARADIGM with heterogeneous chemotherapy backbones and evolving subsequent therapy landscapes (8,13). The PARADIGM trial demonstrated a significant OS benefit for panitumumab plus mFOLFOX6 compared with bevacizumab + mFOLFOX6 (HR=0.82), which aligns closely with the pooled panitumumab estimate (HR=0.855; 95% CI: 0.738-0.992) and further reinforces the OS advantage of anti-EGFR therapy (7,35). However, unlike the OS findings, the PFS analysis showed only a non-significant trend favoring cetuximab plus chemotherapy (HR=0.880; P=0.072), consistent with the well-documented dissociation between PFS and OS benefits observed in prior individual trials and meta-analyses, potentially attributable to differential post-progression treatment effects (36,37). Regarding response outcomes, the analysis demonstrated higher ORR with anti-EGFR combinations (OR=1.612; 95% CI: 1.087-2.390; P=0.017), consistent with a prior meta-analysis reporting pooled ORRs of 65-75% for anti-EGFR regimens, supporting their preferential use when rapid tumor shrinkage is clinically imperative (35).

The subgroup analysis stratified by primary tumor sidedness may provide quantitative confirmation of a phenomenon that has been increasingly recognized in the literature. The pooled OS HR of 0.750 (95% CI: 0.672-0.836) favoring anti-EGFR therapy in left-sided tumors, contrasted with the absence of benefit in right-sided tumors (HR=1.097; 95%

CI: 0.909-1.325), is consistent with the landmark retrospective analyses of CRYSTAL and FIRE-3 by Tejpar *et al* (37) which first demonstrated the prognostic and predictive relevance of tumor sidedness in anti-EGFR-treated patients. Arnold *et al* (17) synthesized individual patient data from six randomized trials and reported a similar directional interaction, with anti-EGFR therapy conferring marked OS and PFS benefits exclusively in left-sided tumors (17). The PARADIGM trial further strengthened this evidence by prospectively stratifying patients by tumor sidedness and demonstrating a statistically significant PFS detriment for panitumumab in right-sided tumors (HR=1.43; 95% CI: 1.03-1.97), a finding corroborated in the pooled PFS analysis (18). Holch *et al* (18) conducted a meta-analysis of first-line trials and concluded that primary tumor location was a strong predictive factor for anti-EGFR efficacy, with a magnitude of interaction effect comparable to that observed in the present analysis (18). Notably, the present study extends these prior observations by integrating data from more recently published trials, including PARADIGM, PANDA and CAIRO5 (13,16,24), and by providing pooled estimates within a network meta-analysis framework that allows simultaneous comparison across all available treatment nodes. The negligible heterogeneity in the left-sided OS analysis (I^2=0%) reinforces the robustness and generalizability of the sidedness-treatment interaction, supporting the incorporation of tumor location as a mandatory stratification factor in future RAS wild-type mCRC trial designs and clinical treatment algorithms.

The clinical importance of these findings lies in providing an integrated, evidence-based framework to guide treatment selection based on primary tumor sidedness. The present network meta-analysis demonstrated that anti-EGFR therapy conferred a robust and statistically significant 25.0% OS reduction in left-sided tumors (HR=0.750; I^2=0%), supporting preferential use of cetuximab or panitumumab + chemotherapy in this population. Conversely, the absence of anti-EGFR benefit in right-sided tumors (OS HR=1.097) and the non-significant trend toward PFS detriment (HR=1.143) argue against anti-EGFR therapy in the present subset, favoring bevacizumab-based combinations. The differential toxicity profiles, with anti-EGFR regimens exhibiting higher rates of grade ≥3 adverse events, further reinforce this benefit-risk assessment. Sensitivity analysis showing favorable results for UGT1A1-guided bevacizumab + FOLFIRI (OS P-score=0.932; PFS P-score=0.992) suggests that pharmacogenomic optimization may offer additional personalization, though further demonstration in independent trials is required (38,39).

Notably, the present study exhibits a number of limitations. Firstly, despite including 15 trials, the network remains sparse for certain comparisons, potentially limiting precision. Secondly, the open-label design of 93% of trials introduces potential performance bias, although objective endpoints mitigate this concern. In addition, heterogeneity in response-based endpoints suggests treatment effect modifiers that could not be explored without individual patient data. The single trial evaluating UGT1A1-guided therapy requires external validation and subsequent therapies influencing OS could not be accounted for. In addition, generalizability may be limited because several clinically relevant molecular subgroups, such as BRAF V600E-mutant, MSI-H/dMMR, HER2-amplified and rare gene fusion-positive tumors, were underrepresented or could not be separately analyzed. Finally, quality-of-life outcomes could not be synthesized due to heterogeneous reporting.

In conclusion, anti-EGFR antibodies combined with chemotherapy provide statistically significant OS benefits compared with bevacizumab + chemotherapy as first-line treatment for RAS wild-type mCRC, with cetuximab + chemotherapy consistently ranking as the optimal regimen. The treatment benefit is strongly dependent on primary tumor location, with a robust 25.0% mortality risk reduction in left-sided tumors and no benefit in right-sided tumors. These findings support a tumor sidedness-guided treatment algorithm, favoring anti-EGFR therapy for left-sided disease and bevacizumab-based regimens for right-sided disease, while considering differential toxicity profiles in clinical decision-making.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SK and CS performed data collection, conducted statistical analysis and wrote the manuscript. CS and SY confirm the authenticity of all the raw data. SY designed the present study and revised the manuscript. All authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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