Article

Discovery Medicine 2026; 38(204): 132–142
https://doi.org/10.24976/Discov.Med.202638204.11

Efficacy Comparison of Cetuximab Monotherapy or Combination Therapy With Irinotecan in Colorectal Cancer: A Meta-Analysis

Jing Tong[1,*], Yi Ding[1], Dongping Zhang[1]

[1]Department of Pharmacy, Shengzhou People's Hospital (Shengzhou Branch of The First Affiliated Hospital of Zhejiang University School of Medicine), 312400 Shengzhou, Zhejiang, China
*Correspondence: tongjing19831007@163.com (Jing Tong)
Submitted: 22 July 2025 Revised: 20 August 2025 Accepted: 3 September 2025 Published: 20 January 2026

Background: Colorectal cancer (CRC) poses a significant global health burden. Cetuximab, an epidermal growth factor receptor (EGFR)-targeting monoclonal antibody, and irinotecan, a topoisomerase I inhibitor, are established therapeutic agents for CRC. Although cetuximab can be administered as monotherapy or in combination with irinotecan, the differences in efficacy and safety between these treatment strategies remain unclear. Therefore, this meta-analysis aimed to comprehensively compare the efficacy and safety between cetuximab alone and cetuximab plus irinotecan for treating patients with CRC.

Methods: Studies about randomized controlled trials on cetuximab monotherapy or combination therapy with irinotecan for treating CRC were retrieved from Cochrane Library, PubMed, and China National Knowledge Infrastructure (CNKI) since inception until 1 April 2024. The subjects were categorized into combination and monotherapy groups. The quality assessment of literature was analyzed using Cochrane risk-of-bias tool. Review Manager Software was utilized for meta-analysis. Progression-free survival (PFS) and grade 3–4 adverse events (AEs) were applied as primary outcome indicators. Overall survival (OS), objective remission rate (ORR) and disease control rate (DCR) were used as secondary outcome indicators.

Results: Six studies and 875 CRC patients were finally included. Meta-analysis results showed that the combination group had a longer PFS than the monotherapy group (hazard ratio [HR] = 0.69, 95% confidence interval [CI]: 0.42–1.16, $p = 0.16$), while there was no significant difference in OS between the two groups (HR = 0.84, 95% CI: 0.70–1.00, $p = 0.05$). The incidence of grade 3–4 AEs was higher in the combination group than in the monotherapy group (relative risk [RR] = 1.38, 95% CI: 1.17–1.64, $p = 0.0002$). In addition, the DCR of the combination group was significantly higher than that of the monotherapy group (RR = 1.45, 95% CI: 1.16–1.81, $p = 0.001$), while the ORR was not significantly different between the two groups (RR = 1.12, 95% CI: 0.96–1.31, $p = 0.13$).

Conclusion: Our findings indicate that cetuximab plus irinotecan confers higher anti-tumor protection than the monotherapy, with a compromise in an evidently increased risk of severe adverse events. The trade-off between efficacy and toxicity must be carefully considered in clinical decision-making.

Registration number: CRD420251124881.

Keywords: cetuximab; irinotecan; colorectal cancer; meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignant tumors worldwide and is a leading cause of cancer-related mortality in both China and the United States, with the CRC incidence rate showing trend of increase in China [1]. As the conventional treatment for early-stage CRC, surgical resection is generally effective [2], but its efficacy diminishes in intermediate or advanced stages, which is when most CRC patients are initially diagnosed [3]. For patients experiencing unsatisfactory surgical outcomes or who are ineligible for a resection, combined chemoradiotherapy, targeted therapy and immunotherapy can be used to prolong survival and improve quality of life [2,4].

Cetuximab is a monoclonal antibody that can specifically bind to epidermal growth factor receptors (EGFRs) in many cancers. While providing more diverse treatment options, cetuximab—particularly when combined with other drugs—offers high-degree specificity during treatment, making it a promising candidate in personalized therapy for CRC [5]. With a deeper understanding on the molecular heterogeneity of CRC, clinicians can now tailor treatment plans based on specific genetic mutations in tumors [6], and intriguingly, cetuximab can be used for targeted therapies for *B-Raf proto-oncogene, serine/threonine kinase (BRAF)*-mutant CRC [7]. First-line chemotherapy combined with cetuximab improves progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) in *Rat*

sarcoma (RAS)-wildtype (WT) CRC patients [8]. *RAS* mutations are associated with resistance to EGFR inhibitors [9,10].

Irinotecan is a common chemotherapeutic drug for CRC. It is a DNA topoisomerase I inhibitor that prevents the DNA replication of cancer cells by inducing fragmentation of DNA single strands [11]. A single-arm clinical trial showed that cetuximab plus irinotecan was therapeutically more effective in patients with *RAS* and *BRAF* WT metastatic CRC compounded by drug resistance [12]. Despite the reported efficacy of cetuximab combined with irinotecan, it has been found that treated patients with the cancer generally experienced relatively poor remission, with only a small portion of them showing controlled status of disease progression [13]. Currently, the therapeutic effect of cetuximab combined with irinotecan on CRC has not been fully clarified.

In this study, we collected research literature on the treatment of CRC using cetuximab alone or together with irinotecan to analyze whether the combination of the two drugs can improve the therapeutic efficacy and prolong the survival time of the patients, as well as to explore whether this treatment option can meet the therapeutic demand of CRC patients. Accordingly, this meta-analysis aimed to provide a reference for clinical management of CRC using medications.

Methods

Literature Retrieval

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, studies on randomized controlled trials, which were published since the database inception until 1 April 2024, were retrieved from public databases, including Cochrane Library, PubMed, and China National Knowledge Infrastructure (CNKI). Only articles in English were collected. Included literature was screened according to the PRISMA 2020 protocol (PRISMA Checklist, **Supplementary Table 1**). Firstly, following the principle of PICOS, articles were independently selected by two reviewers based on their subject headings and keywords (Search Strategy, **Supplementary Table 2**). When there was a disagreement in decision between the two reviewers on the same article, a third reviewer would be responsible for making the final decision.

Literature Screening

Inclusion Criteria

(1) Subjects: pathologically confirmed CRC; (2) Types: randomized controlled trials on CRC; (3) Interventions: a prospective study on efficacy comparison of cetuximab alone or together with irinotecan for CRC patients; (4) Outcome indicators: the results including any of the following indicators: ORR, disease control rate (DCR), PFS, OS, and incidence of grade 3–4 adverse events (AEs) during drug treatment in CRC patients; (5) For the same clinical trial that has been reported multiple times, only the most updated study with the most comprehensive data will be selected.

Exclusion Criteria

(1) A single-arm trial; (2) Animals and cells as subjects; (3) Published in the form of overviews, guidelines, personal cases, conferences, expert experiences, editorials, technical reports, letters, etc.; (4) Repeated studies; (5) Untrue, incomplete and unobtainable data; (6) Poor quality of the publications; (7) Unofficially approved drug used in the study.

Quality Assessment

The finally included studies were determined by two reviewers after screening conducted based on inclusion and exclusion criteria. When there was disagreement on results, a third senior staff member would make the final decisions. The Cochrane Randomized Trials Risk of Bias Assessment [14] was used for quality assessment by three reviewers. There were mainly six fields for assessment, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). In each field, the risk of bias was graded as “low risk”, “unclear risk”, and “high risk”. A paper was considered to be of good quality if all assessments of risk of bias for all included studies were of “low risk”. If one of the assessments was of “high risk”, the paper was considered to be of low quality. The risk-of-bias graph and the risk-of-bias summary were plotted using Review Manager Software (version 5.3, Cochrane RevMan, London, UK).

Data Extraction

Two reviewers were responsible for extracting the basic information of the included studies after reading the full article. Herein, the basic information included: the first author, publication time, sample size, intervention methods and duration, gender proportion, age range, Eastern Cooperative Oncology Group (ECOG) performance status score, proportion of people with liver metastasis, lung metastasis and lymph metastasis, primary outcome indicators (PFS and grade 3–4 AEs), and secondary outcome indicators (OS, ORR and DCR) in the cetuximab monotherapy group and combination therapy group (cetuximab plus irinotecan).

Statistical Analysis

Review Manager Software (version 5.3, Cochrane RevMan, London, UK) was utilized for conducting meta-analysis, and the outcome data extracted for this study were categorical variables. ORR, DCR and AEs were used as

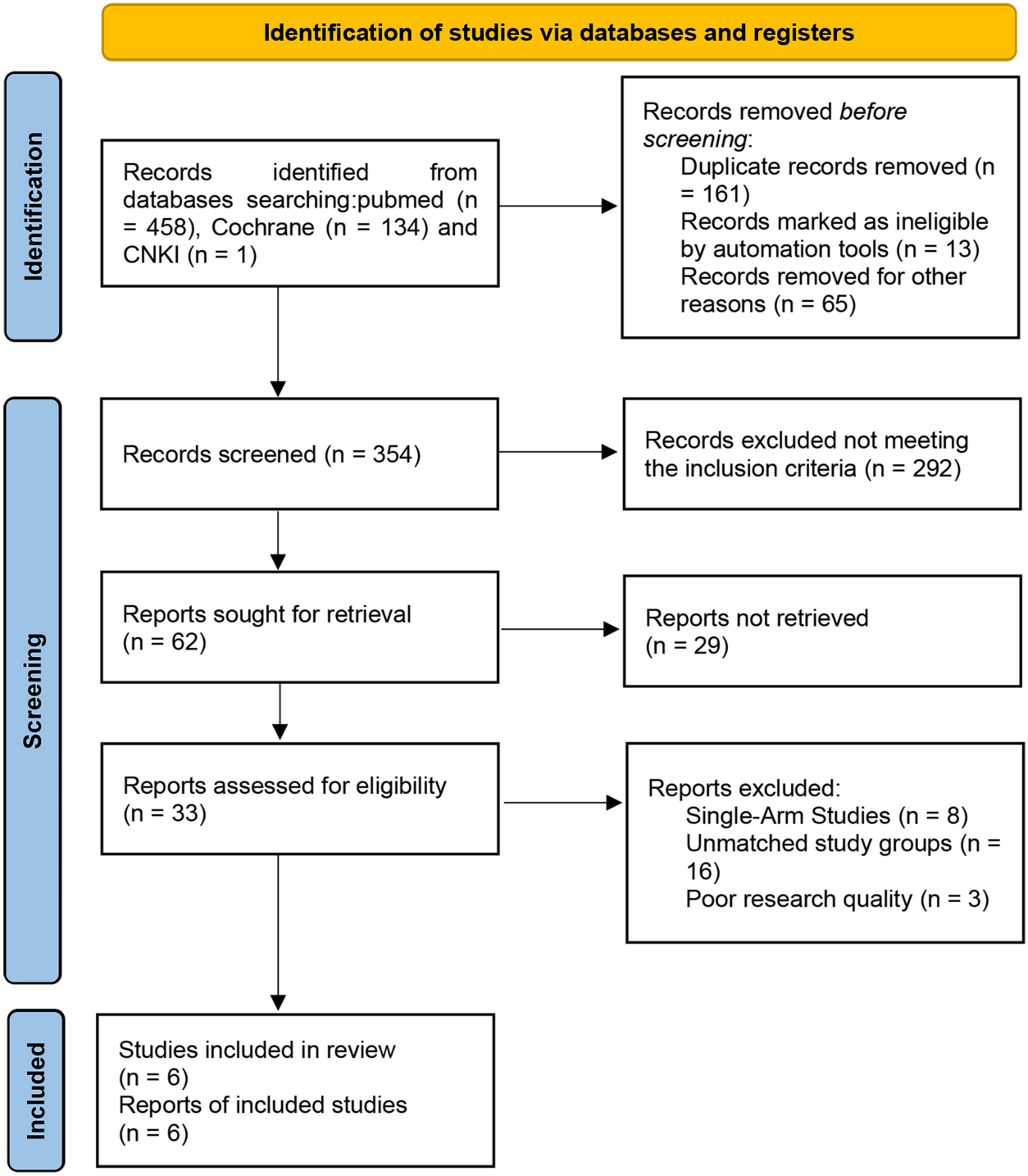

Fig. 1. A flowchart of literature searching and screening.

statistical effect sizes and calculated with relative risk (RR) and 95% confidence interval (95% CI). PFS and OS were applied as statistical effect sizes measured by hazard ratio (HR) and 95% CI. The threshold of *p*-value less than 0.05 was considered statistically significant. The results of the heterogeneity analysis in this study were judged according to the results of the I^2 test. When $I^2 < 50\%$, a fixed-effects model was employed. When $I^2 > 50\%$, there was significant heterogeneity, and thus a random-effects model was employed. In addition, when fewer than five studies were included, the fixed-effects model was still used regardless of the magnitude of heterogeneity [15]. The Stata Software (version 12, Stata Corp., Lakeway Drive, TX, USA) was employed to perform subgroup analyses and sensitivity analysis.

Table 1. Summary of baseline information of patients from the included literature.

Literature	Treatment	Sample size	Male	Age (years)	ECOG performance status (≥1 grade)	Liver metastasis	Lung metastasis	Lymph metastasis	Treatment course
Cunningham *et al*. (2004) [16]	Cetuximab + Irinotecan	218	143 (66%)	26–82	NA	NA	NA	NA	3 months
	Cetuximab	111	63 (57%)	39–84	NA	NA	NA	NA	
Saltz *et al*. (2007) [17]	Cetuximab + Irinotecan	43	26 (60%)	43–86	NA	NA	NA	NA	NA
	Cetuximab	40	26 (65%)	24–80	NA	NA	NA	NA	
Nakamura *et al*. (2017) [13]	Cetuximab + Irinotecan	19	13 (68%)	37–83	4 (21%)	12 (63%)	9 (47%)	7 (37%)	NA
	Cetuximab	10	8 (80%)	58–50	6 (60%)	5 (50%)	7 (70%)	3 (30%)	
Segelov *et al*. (2016) [18]	Cetuximab + Irinotecan	26	20 (77%)	48–85	16 (62%)	16 (62%)	14 (54%)	10 (38%)	6 months
	Cetuximab	25	19 (76%)	49–82	15 (60%)	19 (76%)	17 (68%)	10 (40%)	
Shapiro *et al*. (2018) [19]	Cetuximab + Irinotecan	25	18 (72%)	38–76	18 (72%)	18 (72%)	11 (44%)	10 (40%)	6 months
	Cetuximab	21	13 (62%)	41–75	14 (67%)	15 (71%)	13 (62%)	5 (24%)	
Pinto *et al*. (2024) [20]	Cetuximab + Irinotecan	154	99 (64.3%)	34–79	35 (22.7%)	18 (11.7%)	NA	NA	3 months
	Cetuximab	183	126 (68.9%)	22–82	38 (20.8%)	15 (8.2%)	NA	NA	

Notes: ECOG represents Eastern Cooperative Oncology Group; NA represents unavailable information; the values for age are expressed as ranges, while all other parameters, except sample size and age, are expressed as *n* (%).

Results

Literature Retrieval

A total of 593 relevant publications was identified through systematic screening. Based on the inclusion and exclusion criteria, six studies were finally included. A flow chart depicting the processes of literature screening is presented in Fig. 1.

Basic Features and Quality Assessment of the Included Studies

There were a total of 875 enrolled patients in the six included studies, with 57%–80% of males who aged 22–86 years and had CRC. After categorization, 485 patients were assigned to the combination therapy group, while 390 patients were to the monotherapy group. The basic information of patients is detailed in Table 1 (Ref. [13,16–20]).

The six included studies are randomized controlled trials, in which randomized grouping methods were employed. Of the included studies, two reported allocation concealment [18,19], while four utilized blinding method [13,16,17,20]. Our assessments showed that all six studies have complete outcome data, showing no signs of selective reporting. Therefore, the quality of the included literature in this meta-analysis was generally high. The quality-related results are presented in Fig. 2 (Ref. [13,16–20]).

Outcomes of Meta-Analysis

PFS and OS

There were five studies reporting PFS and OS outcomes. A random-effects model was adopted despite the significant heterogeneity of PFS outcomes (I^2 = 87% and $p < 0.00001$). The meta-analysis data showed that PFS was higher in the combination group than in the monotherapy group, but the difference was not statistically significant (HR = 0.69, 95% CI: 0.42–1.16, p = 0.16). The heterogeneity in OS outcomes was low, as reflected by I^2 = 0% and p = 0.88; therefore, a fixed-effects model was applied. There was no significant difference in OS between the combination and monotherapy groups (HR = 0.84, 95% CI: 0.70–1.00, p = 0.05), as shown in Fig. 3 (Ref. [13,16,18–20]).

Grade 3–4 AEs

The outcomes of grade 3–4 AEs were reported in all six included studies. Compared with the monotherapy group, the combination group suffered from significantly higher incidence rate of grade 3–4 AEs (RR = 1.38, 95% CI: 1.17–1.64, p = 0.0002, Fig. 4 (Ref. [13,16–20])). Besides, no significant heterogeneity was found among these studies (I^2 = 0%, p = 0.93, Fig. 4).

ORR and DCR

The outcomes of ORR were reported in only four studies. Despite heterogeneity detected (I^2 = 85%, p = 0.001), a fixed-effects model was selected. The meta-analysis outcomes showed no significant difference in ORR between the two groups (RR = 1.12, 95% CI: 0.96–1.31, p = 0.13, Fig. 5 (Ref. [13,16,19,20])). Only three studies reported DCR, and a fixed-effects model was chosen despite heterogeneity (I^2 = 79%, p = 0.009). The results of the meta-analysis revealed a significantly higher DCR in the combination group relative to the monotherapy group (RR = 1.45, 95% CI: 1.16–1.81, p = 0.001, Fig. 5).

Reporting Bias

The Begg's test and Egger's test were applied to explore publication bias of the included literature. The results of Begg's test and Egger's test for PFS, OS, AEs, ORR, and DCR were p = 0.624 and p = 0.557, p = 0.624 and p = 0.863, p = 0.188 and p = 0.231, p = 0.602 and p = 0.167, and p = 0.602 and p = 0.685, respectively. These results indicated that there was no significant publication bias for any of the outcomes in the included literature.

Heterogeneity

Patients were categorized into three groups (RAS WT, N/A, KRAS G13D mutation) according to whether they carried RAS mutation or not, and subgroup analyses were performed to assess the source of heterogeneity. For PFS, heterogeneity was significantly lower in the KRAS G13D mutation subgroup (I^2 = 0%, p = 0.893), suggesting that patients carried RAS mutation may be a possible source of heterogeneity (Fig. 6 (Ref. [13,16,18–20])). For ORR, heterogeneity was also reduced in the RAS WT subgroup (**Supplementary Fig. 1A**). For DCR, the three studies were evenly distributed among the three subgroups, so no further descriptions were provided (**Supplementary Fig. 1B**).

Sensitivity Analysis

Sensitivity analyses were performed for each outcome data (Table 2, Ref. [13,16–20]). For grade 3–4 AEs, the combined results of the remaining literature data remained unchanged after excluding all literature individually, indicating robust results. For PFS, after excluding the study of Pinto *et al.* 2024 [20], the combined results of the remaining four studies showed that the combination group displayed better outcomes than the monotherapy group. For OS, after excluding Cunningham *et al.* 2004 [16] or Segelov 2016 *et al.* [18], the remaining four studies showed better combined results in the combination group. However, we noted that the combined results of the remaining four studies had a p-value of 0.05 (**Supplementary Fig. 2**). For ORR, after excluding the study of Pinto *et al.* 2024 [20], the remaining two studies exhibited better combined results in the combination group. For DCR, after excluding the study of Cunningham *et al.* 2004 [16], the combined results of the remaining two studies showed no significant difference between the two groups.

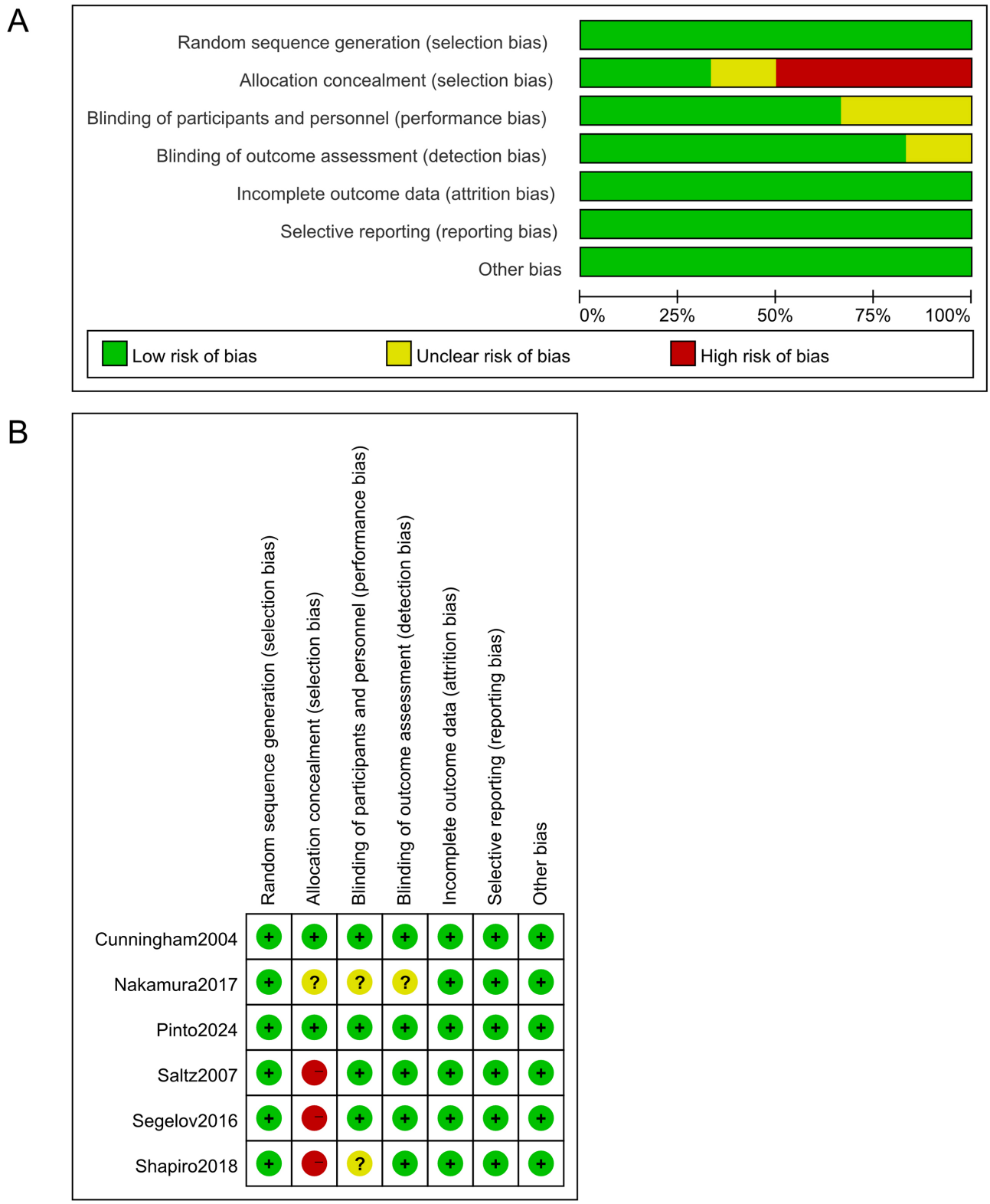

Fig. 2. A summary of bias risk assessments for included studies. (A) Graph on risk of bias. (B) Summary of risk of bias.

Discussion

Cetuximab is frequently used in combination with chemotherapeutic drugs such as oxaliplatin and irinotecan to treat CRC, and it has a good therapeutic effect on unresectable or metastatic cancer [21]. Cetuximab has been confirmed to potentiate the cytotoxic effect of irinotecan on cancer cells via inhibiting EGFR and the downstream RAS-

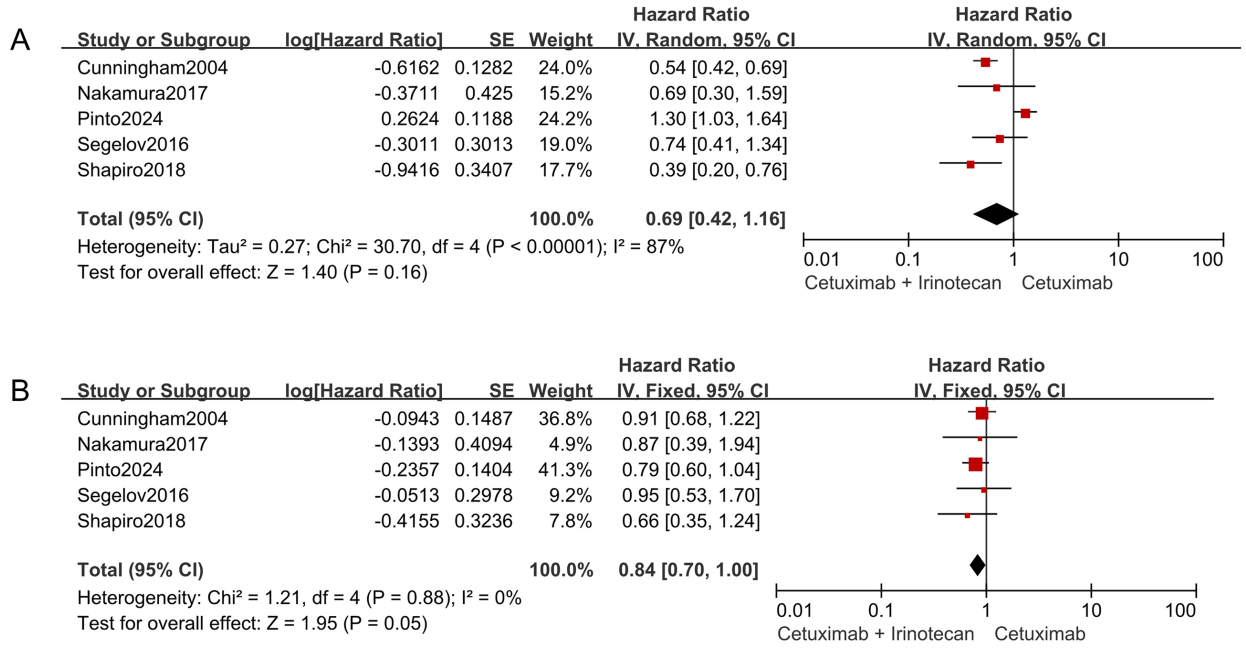

Fig. 3. Pooled analysis of PFS (A) and OS (B). Abbreviations: OS, Overall survival; PFS, Progression-free survival.

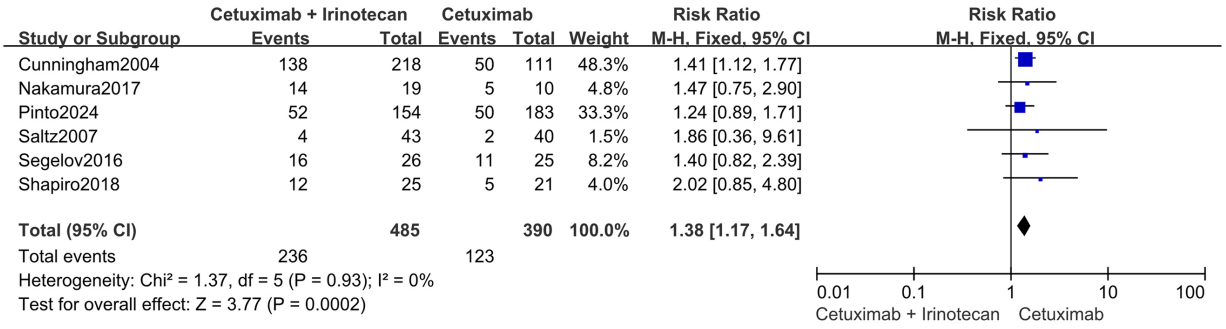

Fig. 4. Pooled analysis of grade 3–4 AEs. Abbreviations: AEs, Adverse events.

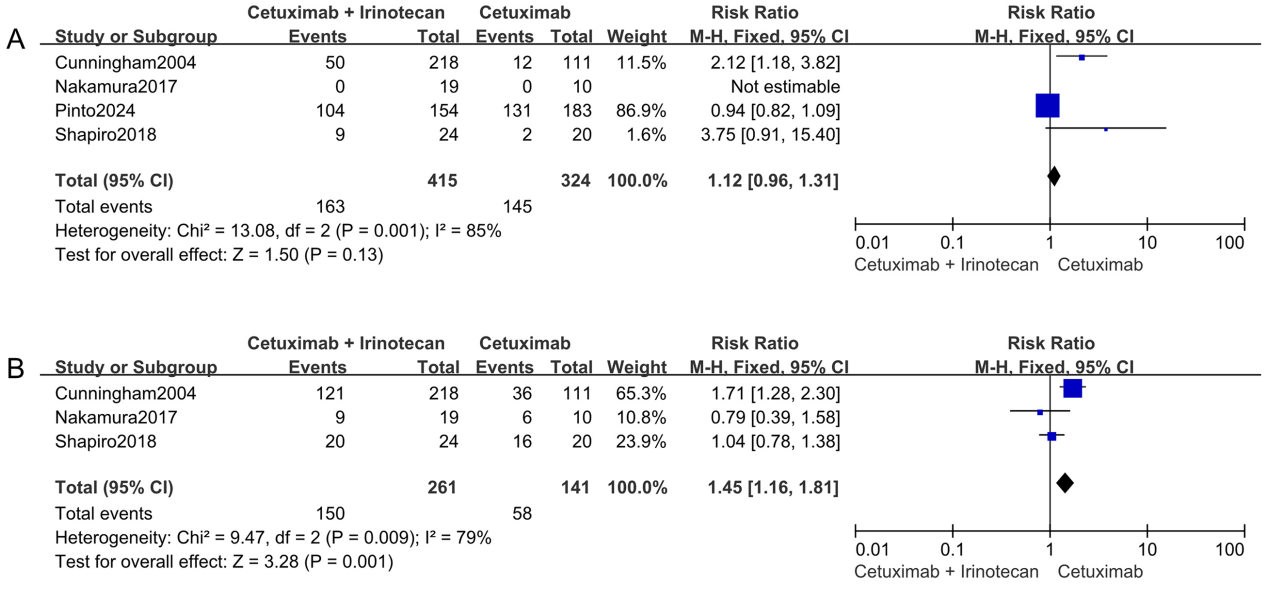

Fig. 5. Pooled analysis of ORR (A) and DCR (B). Abbreviations: DCR, Disease control rate; ORR, Objective remission rate.

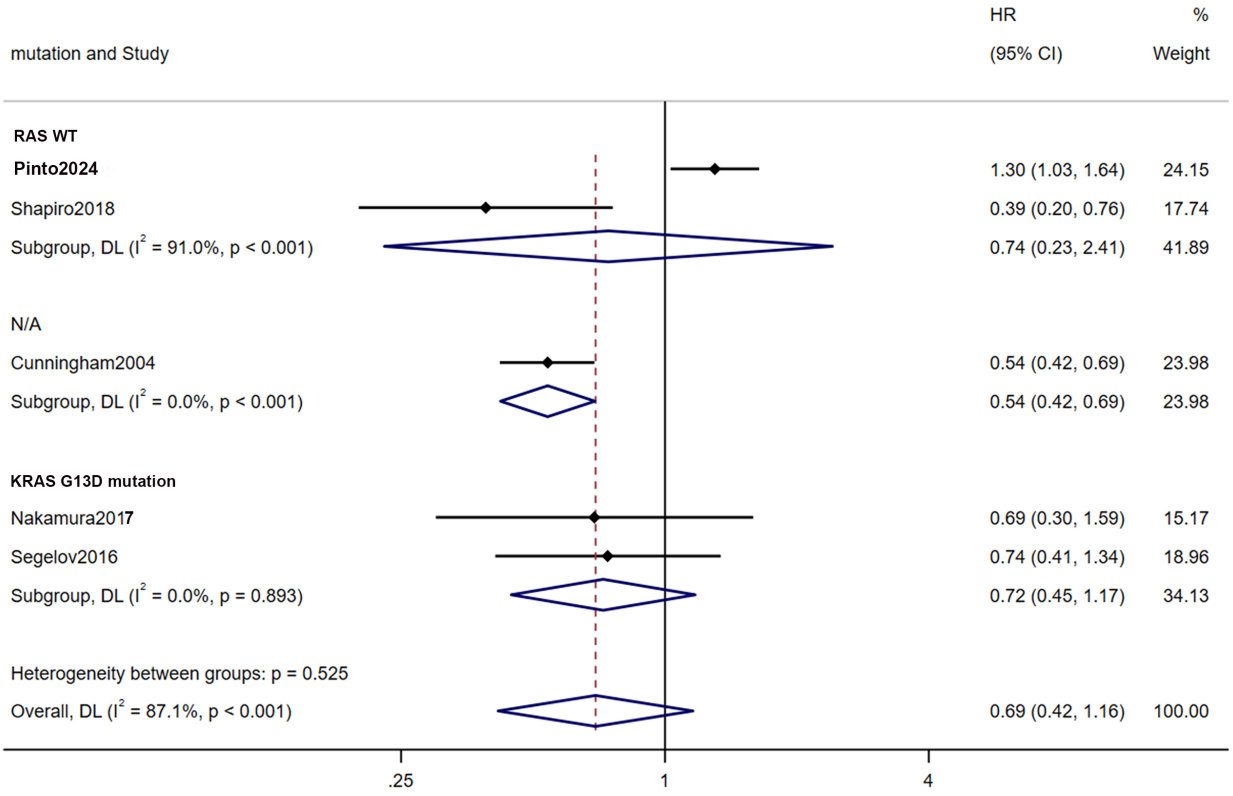

Fig. 6. Heterogeneity analyses of PFS. Abbreviation: DL, Dersimonian and Laird; PFS, Progression-free survival.

RAF-MEK-ERK signaling pathway, exerting a stronger anti-cancer effect [22]. Irinotecan can be used in the third-line treatment for patients who suffered from RAS and BRAF WT metastatic CRC and had cetuximab resistance [12]. Regrettably, our meta-analysis revealed that there was no significant difference in PFS, OS, or ORR between the monotherapy group and the combination group, with the latter also featuring significantly higher AE incidence.

However, through sensitivity analysis, we found that excluding the study of Pinto *et al.* [20], the pooled results of the remaining data supported longer PFS in the combination group. This is probably due to the emphasis of Pinto *et al.*'s study [20] on patients with disease under control, with an objective to use cetuximab monotherapy as a de-escalation treatment to maintain efficacy. Therefore, when evaluating efficacy in patients with malignant tumor progression, our results demonstrated that the combination treatment can prolong PFS in patients. Additionally, our results supported previous findings that cetuximab was not suitable for CRC patients with RAS mutations [23].

The results of the sensitivity analysis seem to indicate the limited reliability of our findings regarding OS. However, when we carefully examined the remaining data after excluding the studies of Cunningham *et al.* [16] or Segelov *et al.* [18], we found that the *p*-values were all 0.05. A *p*-value of 0.05 is commonly used as the threshold for statistical significance; however, its interpretation remains a topic of ongoing debate within the statistical community [24]. In this study, after comprehensive consideration of all opinions, we reached the conclusion that there was no significant difference in OS between the two groups, which was definite even when including the data from Cunningham *et al.* [16] or Segelov *et al.* [18]. Herein, the combined therapy regimens primarily targeted patients with intermediate-stage or advanced-stage CRC. Treatment for advanced patients primarily aims to control tumor progression, alleviate tumor-induced pain, and improve the patient's quality of life. In a study comparing the efficacy of EGFR tyrosine kinase inhibitors combined with dual-drug chemotherapy versus bevacizumab combined with dual-drug chemotherapy in RAS WT metastatic CRC patients, there is no statistically significant difference in OS for patients with right-sided tumors [25], consistent with our results.

It is important to note that the addition of irinotecan to the cetuximab treatment regimen significantly increased the incidence of adverse reactions in patients, indicating a higher burden of treatment-related complications. This underscores the need for clinicians to carefully consider safety when prescribing combined therapies. In a study of encorafenib plus cetuximab (EC) with or without chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6]) for BRAF V600E-mutated CRC, EC+mFOLFOX6 resulted in adverse events at grade 3 or above in over half of the patients [26], further highlighting toxicity risk associated with combined therapy.

Table 2. Sensitivity analysis of outcomes.

	Study	Estimate	95% confidence interval	
Grade 3–4 AEs	Pinto *et al.* (2024) [20]	1.502	1.142	1.974
	Cunningham *et al.* (2004) [16]	1.710	1.381	2.117
	Nakamura *et al.* (2017) [13]	1.755	1.407	2.188
	Saltz *et al.* (2007) [17]	1.695	1.372	2.093
	Segelov *et al.* (2016) [18]	1.847	1.436	2.376
	Shapiro *et al.* (2018) [19]	1.653	1.320	2.070
	Combined	1.697	1.376	2.093
PFS	Pinto *et al.* (2024) [20]	0.552	0.448	0.681
	Cunningham *et al.* (2004) [16]	0.752	0.419	1.350
	Nakamura *et al.* (2017) [13]	0.693	0.387	1.240
	Segelov *et al.* (2016) [18]	0.680	0.368	1.258
	Shapiro *et al.* (2018) [19]	0.787	0.451	1.371
	Combined	0.694	0.416	1.158
OS	Pinto *et al.* (2024) [20]	0.874	0.694	1.102
	Cunningham *et al.* (2004) [16]	0.800	0.640	0.999
	Nakamura *et al.* (2017) [13]	0.837	0.698	1.003
	Segelov *et al.* (2016) [18]	0.828	0.688	0.997
	Shapiro *et al.* (2018) [19]	0.856	0.712	1.029
	Combined	0.838	0.702	1.001
ORR	Pinto *et al.* (2024) [20]	2.306	1.340	3.966
	Cunningham *et al.* (2004) [16]	0.953	0.827	1.098
	Shapiro *et al.* (2018) [19]	0.983	0.856	1.129
	Combined	0.996	0.868	1.143
DCR	Cunningham *et al.* (2004) [16]	1.000	0.768	1.302
	Nakamura *et al.* (2017) [13]	1.325	1.080	1.625
	Shapiro *et al.* (2018) [19]	1.524	1.163	1.997
	Combined	1.272	1.045	1.548

Abbreviations: AEs, Adverse events; DCR, Disease control rate; ORR, Objective remission rate; OS, Overall survival; PFS, Progression-free survival.

In the present paper, the combined results of ORR and DCR are not discussed in detail. The sensitivity analysis indicated that our results are not definitive and may be influenced by data from large-scale clinical studies. In summary, the combination of cetuximab and irinotecan demonstrates significant efficacy in improving PFS in patients, particularly in RAS WT patients. However, clinical use of drug combinations requires the formulation of personalized treatment plans for each patient, taking into full consideration the negative impact of adverse reactions on patients' quality of life.

There are some limitations in the present meta-analysis. First, the number of included studies is small, possibly because cetuximab with or without irinotecan is not a popular research protocol in recent years, or the application of the stringent inclusion and exclusion criteria had filtered out many studies during the literature retrieval process. Second, treatment efficacy may be influenced by factors such as climate, socioeconomic conditions, and dietary habits, which can vary significantly across populations. Since all included studies were published in English and conducted in Europe and the United States, the findings may not be fully generalizable to CRC patients in China or other regions in the world. Finally, the included studies fail to meet the requirements for subgroup analysis based on whether CRC patients had metastases. Therefore, it is unable to distinguish the specific effects of cetuximab plus irinotecan on metastatic and non-metastatic cancers.

Conclusion

In conclusion, cetuximab in combination with irinotecan is more effective in the treatment of CRC when compared to cetuximab monotherapy. However, this combined therapy increases the incidence of grade 3–4 AEs, elevating complication-related risks in the patients. Therefore, cetuximab plus irinotecan should be used with caution, taking into account EGFR expression, RAS mutation status, and the patients' physical condition.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

JT and YD designed the research study. YD and DZ collected and analyzed the data. JT and DZ have been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors give final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are addressed.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638204.11.

References

[1] Xia C, Dong X, Li H, Cao M, Sun D, He S, *et al*. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chinese Medical Journal. 2022; 135: 584–590. https://doi.org/10.1097/CM9.0000000000002108.

[2] Dariya B, Aliya S, Merchant N, Alam A, Nagaraju GP. Colorectal Cancer Biology, Diagnosis, and Therapeutic Approaches. Critical Reviews in Oncogenesis. 2020; 25: 71–94. https://doi.org/10.1615/CritRevOncog.2020035067.

[3] Done JZ, Fang SH. Young-onset colorectal cancer: A review. World Journal of Gastrointestinal Oncology. 2021; 13: 856–866. https://doi.org/10.4251/wjgo.v13.i8.856.

[4] Sakata S, Larson DW. Targeted Therapy for Colorectal Cancer. Surgical Oncology Clinics of North America. 2022; 31: 255–264. https://doi.org/10.1016/j.soc.2021.11.006.

[5] Wu J, Wang Z, Jin C, Ren H, Hu Y, Yang B, *et al*. Effect of cetuximab combined with chemotherapy in treating metastatic colorectal cancer and its prognostic analysis. Journal of B.U.ON. 2021; 26: 101–108.

[6] Ros J, Rodríguez-Castells M, Saoudi N, Baraibar I, Salva F, Tabernero J, *et al*. Treatment of *BRAF*-V600E mutant metastatic colorectal cancer: new insights and biomarkers. Expert Review of Anticancer Therapy. 2023; 23: 797–806. https://doi.org/10.1080/14737140.2023.2236794.

[7] Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, *et al*. Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E-Mutated Colorectal Cancer. The New England Journal of Medicine. 2019; 381: 1632–1643. https://doi.org/10.1056/NEJMoa1908075.

[8] Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, *et al*. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. Journal of Clinical Oncology. 2015; 33: 692–700. https://doi.org/10.1200/JCO.2014.59.4812.

[9] Zhou J, Ji Q, Li Q. Resistance to anti-EGFR therapies in metastatic colorectal cancer: underlying mechanisms and reversal strategies. Journal of Experimental & Clinical Cancer Research: CR. 2021; 40: 328. https://doi.org/10.1186/s13046-021-02130-2.

[10] Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, *et al*. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2023; 34: 10–32. https://doi.org/10.1016/j.annonc.2022.10.003.

[11] Fakhr E, Zare F, Azadmanesh K, Teimoori-Toolabi L. LEF1 silencing sensitizes colorectal cancer cells to oxaliplatin, 5-FU, and irinotecan. Biomedicine & Pharmacotherapy. 2021; 143: 112091. https://doi.org/10.1016/j.biopha.2021.112091.

[12] Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, *et al*. Rechallenge for Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan: A Phase 2 Single-Arm Clinical Trial. JAMA Oncology. 2019; 5: 343–350. https://doi.org/10.1001/jamaoncol.2018.5080.

[13] Nakamura M, Aoyama T, Ishibashi K, Tsuji A, Takinishi Y, Shindo Y, *et al*. Randomized phase II study of cetuximab versus irinotecan and cetuximab in patients with chemo-refractory KRAS codon G13D metastatic colorectal cancer (G13D-study). Cancer Chemotherapy and Pharmacology. 2017; 79: 29–36. https://doi.org/10.1007/s00280-016-3203-7.

[14] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical Research Ed.). 2011; 343: d5928. https://doi.org/10.1136/bmj.d5928.

[15] Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. International Journal of Evidence-Based Healthcare. 2015; 13: 196–207. https://doi.org/10.1097/XEB.0000000000000065.

[16] Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al*. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. The New England Journal of Medicine. 2004; 351: 337–345. https://doi.org/10.1056/NEJMoa033025.

[17] Saltz LB, Lenz HJ, Kindler HL, Hochster HS, Wadler S, Hoff PM, *et al*. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. Journal of Clinical Oncology. 2007; 25: 4557–4561. https://doi.org/10.1200/JCO.2007.12.0949.

[18] Segelov E, Thavaneswaran S, Waring PM, Desai J, Robledo KP, Gebski VJ, *et al*. Response to Cetuximab With or Without Irinotecan in Patients With Refractory Metastatic Colorectal Cancer Harboring the KRAS G13D Mutation: Australasian

Gastro-Intestinal Trials Group ICECREAM Study. Journal of Clinical Oncology. 2016; 34: 2258–2264. https://doi.org/10.1200/JCO.2015.65.6843.

[19] Shapiro JD, Thavaneswaran S, Underhill CR, Robledo KP, Karapetis CS, Day FL, *et al*. Cetuximab Alone or With Irinotecan for Resistant KRAS-, NRAS-, BRAF- and PIK3CA-wild-type Metastatic Colorectal Cancer: The AGITG Randomized Phase II ICECREAM Study. Clinical Colorectal Cancer. 2018; 17: 313–319. https://doi.org/10.1016/j.clcc.2018.06.002.

[20] Pinto C, Orlandi A, Normanno N, Maiello E, Calegari MA, Antonuzzo L, *et al*. Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Versus Cetuximab as Maintenance Therapy in First-Line Therapy for *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer: Phase III ERMES Study. Journal of Clinical Oncology. 2024; 42: 1278–1287. https://doi.org/10.1200/JCO.23.01021.

[21] Hu H, Wang K, Huang M, Kang L, Wang W, Wang H, *et al*. Modified FOLFOXIRI With or Without Cetuximab as Conversion Therapy in Patients with RAS/BRAF Wild-Type Unresectable Liver Metastases Colorectal Cancer: The FOCULM Multicenter Phase II Trial. The Oncologist. 2021; 26: e90–e98. https://doi.org/10.1634/theoncologist.2020-0563.

[22] Ge XJ, Jiang JY, Wang M, Li MY, Zheng LM, Feng ZX, *et al*. Cetuximab enhances the efficiency of irinotecan through simultaneously inhibiting the MAPK signaling and ABCG2 in colorectal cancer cells. Pathology, Research and Practice. 2020; 216: 152798. https://doi.org/10.1016/j.prp.2019.152798.

[23] Benson AB, Venook AP, Adam M, Chang G, Chen YJ, Ciombor KK, *et al*. Colon Cancer, Version 3.2024, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2024; 22: e240029. https://doi.org/10.6004/jnccn.2024.0029.

[24] Sedgwick PM, Hammer A, Kesmodel US, Pedersen LH. Current controversies: Null hypothesis significance testing. Acta Obstetricia et Gynecologica Scandinavica. 2022; 101: 624–627. https://doi.org/10.1111/aogs.14366.

[25] Yoshino T, Hooda N, Younan D, Muro K, Shitara K, Heinemann V, *et al*. A meta-analysis of efficacy and safety data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in adult patients with RAS wild-type metastatic colorectal cancer by sidedness. European Journal of Cancer. 2024; 202: 113975. https://doi.org/10.1016/j.ejca.2024.113975.

[26] Elez E, Yoshino T, Shen L, Lonardi S, Van Cutsem E, Eng C, *et al*. Encorafenib, Cetuximab, and mFOLFOX6 in *BRAF*-Mutated Colorectal Cancer. The New England Journal of Medicine. 2025; 392: 2425–2437. https://doi.org/10.1056/NEJMoa2501912.