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Original Article

Triplet chemotherapy combined with anti Epidermal Growth Factor Receptor treatment in RAS wild-type colorectal cancer: a network metanalysis

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Abstract

Background: The optimal first-line treatment for Rat Sarcorma Virus (*RAS*) wild-type metastatic colorectal cancer remains undetermined. Several studies have compared the efficacy of different first-line regimens, including doublet- or triplet-chemotherapy (CT) alone or in combination with targeted therapies (anti-EGFR/anti-VEGF), without conclusive results.

Methods: We conducted a systematic review and meta-analysis of phase II/III randomized clinical trials (RCT) comparing triplet-CT+anti-EGFRs with alternative first-line regimens in *RAS* wild-type patients. Pairwise- and network-meta-analyses were performed to assess overall response rate (ORR). Furthermore, we evaluated PFS and OS with pairwise-metanalyses.

Results: A total of 1283 patients across seven RCT were included. Four treatment arms were analyzed: Arm A (triplet-CT+anti-EGFR), Arm B (doublet-CT+anti-EGFR), Arm C (triplet al.ne), and Arm D (triplet+anti-VEGF). Arms A, B, and D demonstrated higher ORR compared to Arm C, while no significant differences were found among Arms A, B, and D (OR 1.05, 95% CI 0.73-1.49; $P = .804$, for Arm B in comparison to Arm A; OR 0.80, 95% CI 0.52-1.25; $P = .328$, for Arm D in comparison to Arm A). Pairwise-meta-analysis revealed significantly lower ORR for Arm C compared to Arm A (OR 4.23, 95% CI 2.06-8.68, $P = .002$). P-scores ranked Arm B highest for effectiveness (0.808), followed by Arm A (0.746), then Arm D (0.444) and lastly Arm C (0.002). The pooled Hazard ratios (HRs) for OS demonstrated a superiority for arm A (0.82, 95% CI 0.70-0.97, $P = .022$)

Conclusions: Triplet-CT+anti-EGFR demonstrated no clear ORR advantage over other targeted regimens but was superior to triplet-CT alone. Preliminary data indicate a potential OS benefit. Due to increased toxicity, routine use of triplet-CT+anti-EGFR should be carefully evaluated.

Key words: colorectal cancer; first-line treatment; triplet CT; doublet CT; anti-EGFR treatment; RAS wild-type.

Implications for Practice

Current evidence does not provide a definitive recommendation for first line treatment choice for RAS wild-type metastatic colorectal cancer despite several trials have been conducted in order to establish if the intensification of chemotherapy backbone associated to anti-EGFR antibodies could provide a clinical benefit, with no conclusive results. In our metanalysis, no significant ORR benefit was found for the combination of a triplet chemotherapy associated with anti-EGFR treatment compared association with an anti-VEGF therapy or to a doublet chemotherapy combined with anti-EGFR treatment; however, available data suggests an improvement in OS, therefore, although the routinary use of triplet chemotherapy plus anti-EGFR is not supported, our results hint that properly selected subgroup of patients may profit from an intensification of the CT backbone and that further research is needed.

Introduction

Colorectal cancer (CRC) ranks as the third most common cancer worldwide, with over 1.9 million new cases annually, and it is the second leading cause of cancer-related death.[1] Approximately 15%-30% of patients present with *de novo* metastatic disease, and among those undergoing curative treatments, 20%-50% experience recurrence, especially within the first three years.[2]

For patients with proficient mismatch repair (pMMR)/microsatellite-stable (MSS) metastatic colorectal cancer (mCRC), the standard first-line treatment involves a

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combination of polychemotherapy(fluoropyrimidines plus oxaliplatin and/or irinotecan) alongside targeted agents such as bevacizumab or anti-EGFR antibodies (anti-EGFR Ab). Molecular profile and sidedness guide treatment selection, with anti-EGFR therapy recommended for left-sided tumor *RAS* or *BRAF (murine sarcoma viral oncogene homolog B)* wild-type (wt) tumors without HER2/*ERBB2* amplification.[2,3]

Two pivotal studies, CRYSTAL and PRIME, evaluated the addition of anti-EGFR Ab to standard chemotherapy (CT) in the first-line setting,[4–8] showing a significant improvement in RAS wt patients. Other trials compared the combination of standard CT with anti-EGFR Ab to the combination of CT plus bevacizumab. Among them, post-hoc analyses of the FIRE-3 and the PARADIGM trials demonstrated an improvement in OS and overall response rate (ORR) in left-sided *KRAS* wt patients, while the CALGB/SWOG 80405 trial did not demonstrate any improvement in OS in *KRAS* wt patients not selected for sidedness;[9–11] a subsequent analysis confirmed an improved OS for the left-sided cancers.[12]

Another effective strategy in CRC patients consists in intensifying the treatment with a CT triplet (FOLFOXIRI). Studies such as TRIBE, TRIBE2, STEAM, and CHARTA have shown that intensified CT in addition to bevacizumab can be considered for some subgroups of patients.[13–16] The intensified treatment was associated with longer OS, PFS and higher ORR and R0 resection rates when compared to doublets plus bevacizumab, irrespectively from RAS status.[17] Considering the same strategy, several trials investigated the role of intensified CT in association with anti-EGFR Ab in patients with *RAS*wt CRC (some of them enrolling only RAS and BRAF wt patients), with conflicting results. Early trials reported promising data, mostly regarding capability of inducing tumor shrinkage and, therefore, improve conversion surgery rates. Hence, subsequent trials investigated the comparison of a treatment intensification with triplet CT (mFOLFOXIRI regimen) plus anti-EGFR Ab to either standard CT doublet (FOLFOX/FOLFIRI) with anti-EGFR Ab, triplet CT alone or the association of triplet CT and anti-VEGF Ab; however, results from these trials are not univocal.

On this basis, we conducted a systematic review and network meta-analysis to assess whether intensifying treatment with a triplet backbone adds benefit when combined with anti-EGFR therapy in the first-line treatment of RAS/BRAF wt mCRC patients. In fact, while anti-EGFR agents drive efficacy in this setting, the role of a triplet CT remains uncertain, particularly due to its higher toxicity.

Methods

We performed a systematic review of the literature concerning RAS/BRAFwt mCRC patients who received first-line therapy with triplet CT and anti-EGFR drugs. Databases searched included MEDLINE (via PubMed), Embase (via OVID), and Cochrane Central Register of Clinical Trials (CENTRAL, Wiley interface) from January 1, 2010, to May 31, 2025. In addition, we reviewed on-line abstract books from major oncology conferences [American Society for Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Gastrointestinal Cancer Symposium (ASCO GI), and World Congress on Gastrointestinal Cancer (WCGIC)]. The search string used was focused on the following MeSH terms and keywords: 'colon/colorectal cancer/carcinoma' AND ('FOLFOXIRI' OR 'triplet') AND ('cetuximab' OR 'panitumumab' OR 'anti-EGFR'). The recommendations of the Cochrane Collaboration were followed to identify all relevant RCTs. When duplicate publications were identified, only the most recent and complete reports of RCTs were included. Phase II/III RCTs published in the form of full papers, or as abstracts if full papers were not available, were included in the present analysis. This review is registered on the PROSPERO (ID CRD42024568878; https://www.crd.york.ac.uk/prospero/, accessed on July 11, 2025).

All phase II/III randomized clinical trials (RCT) comparing a combination of triplet CT and anti-EGFR Ab with other first-line regimens were included. Non-English publications, editorials, and reviews were excluded. We performed an initial screening based on titles and abstracts. Data were independently extracted and cross-verified by three investigators (D.B., E.O., and P.D.N.). Two investigators (D.B. and P.D.N.) extracted data from included trials and the third investigator (E.O.) checked the extracted data. Any discrepancies were resolved through a final consensus. The clinical outcomes of interest were overall response rate (ORR, defined as the percentage of patients who had a partial or complete response, according to RECIST 1.1 criteria, during the whole treatment), progression-free survival (PFS, defined as the time from randomization to either death or disease progression, whichever occurred first) and overall survival (OS, defined as the interval from randomization to death for any cause). After a first screening by title and abstract, among 37 PubMed records, 12 were selected. Similarly, 83 of the 358 Embase studies retrieved and 66 of the 159 Cochrane studies were included. Out of the 47 ESMO conferences abstracts, 18 were selected; also 13 of the 18 abstracts retrieved from ASCO conferences were deemed suitable. Once duplicates were removed, 74 articles (both full-text and abstracts) remained; of these, 2 were excluded due to the inclusion of immunotherapy in the trial treatments; 7 trials were not randomized; 4 trials had no published results, and 3 manuscripts regarded a trial with unsuitable CT protocol. Based on the aforementioned strategies, the remaining manuscripts pertaining a total of 10 randomized clinical trials were identified and screened (TRIPLETE, Macbeth, FOCULM, FIRE 4.5, AIO CELIM 2, VOLFI, TRICE, DEEPER, PANIRINOX, PRODIGE-14). Among these, 3 were excluded:

- Fire 4.5: this trial investigated only BRAF V600E mutant mCRC, and it was felt that such a limited subset of patients was not representative and therefore would have biased the analysis
- Macbeth: although it is a randomized trial, the randomization concerns only the maintenance arms, and does not affect the first-line strategy, which is the focus of this analysis;
- Prodige14: lack of data regarding the RAS wt cohort

Therefore, a total of 1283 patients from 7 RCT were included in the analysis (Figure 1 and Table 1).

All treatment arms considered in these trials were collected/clustered into four groups encompassing all possible combinations of CT, anti-EGFR and anti-VEGF drugs: Arm A (triplet CT plus anti-EGFR), Arm B (doublet CT plus anti-EGFR), Arm C (triplet CT alone), and Arm D (triplet CT plus anti-VEGF).

All analyses were performed with the frequentist model using the software "R" version 4.2.3 [R Core Team (2023). R: A

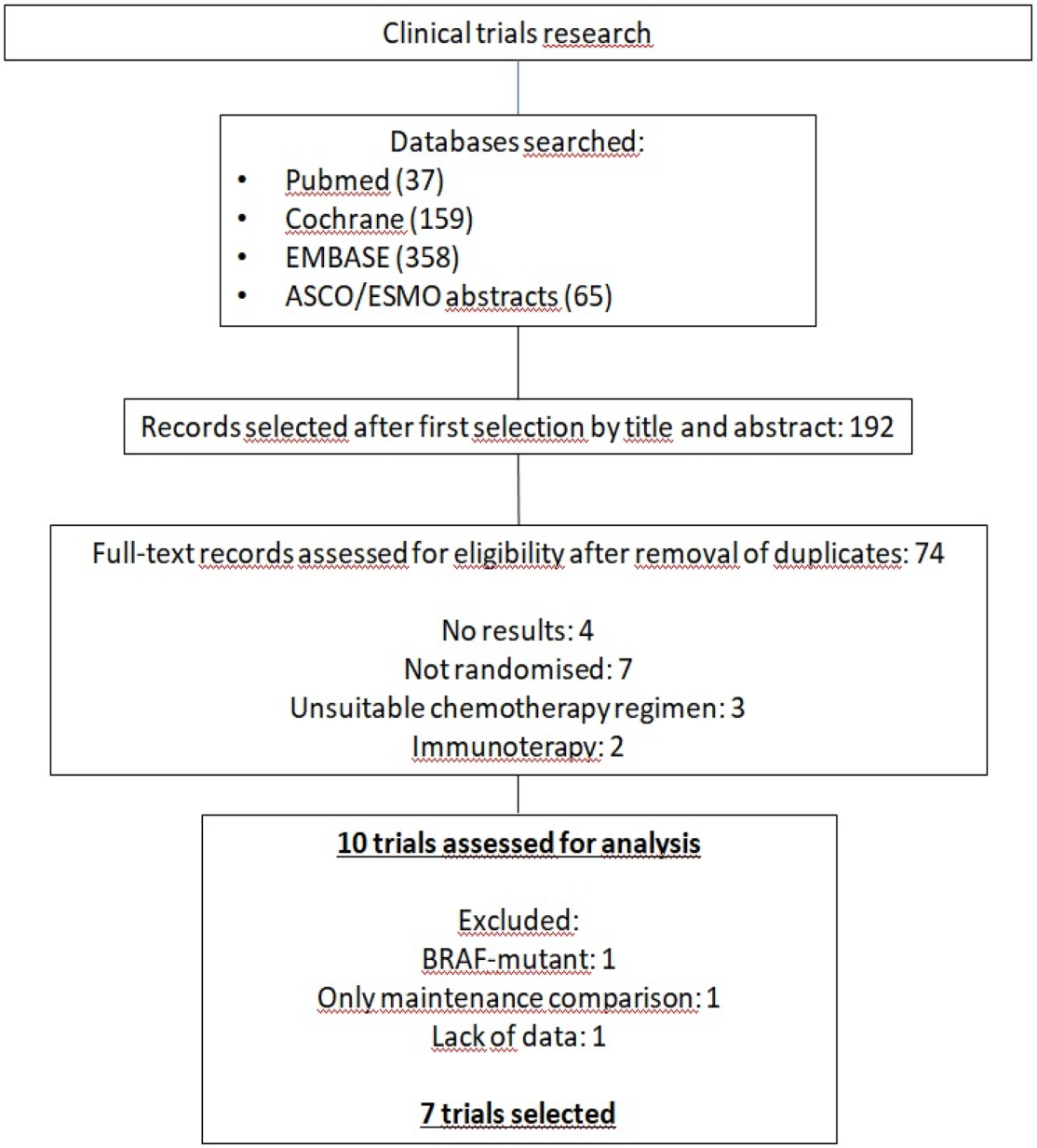

Figure 1. Consort diagram reporting the methodology of systematic review.

Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/].

The proportion of patients achieving an ORR was selected as a primary outcome and the measures of response rate were odds ratios (ORs) with 95% confidence intervals (CIs). We estimated summary ORs using fixed or random-effects pairwise and network meta-analysis (NMA) implemented in the R package "netmeta" [netmeta: Network Meta-Analysis using Frequentist Methods. https://github.com/guido-s/netmeta http://meta-analysis- with-r.org]. A network plot was created to present the structure of the data. Statistical heterogeneity was assessed considering the magnitude of the between-study variance (^{2}).[27] We evaluated inconsistency (ie, non-agreement between direct and indirect intervention effects) using the net-splitting method and we also investigated the cross-network extent of inconsistency using net heat plots. Forest plots of ORs according to selected reference group were performed. Finally, we ranked the treatments for the primary outcome using P-scores, which provide an average degree of certainty for a treatment to be better than the other interventions in the network.[28] Due to the small number of included trials (< 10), we did not examine publication bias with Begg and Egger tests. The data obtained using Begg and Egger tests have poor results and cannot achieve the analysis purpose. Efficacy outcomes (secondary outcomes), ie, progression free survival (PFS) and overall survival (OS) were compared descriptively. Hazard ratios (HRs) for OS and PFS were not available in most studies. Thus, we pooled the medians of these variables through the method proposed by McGrath et al.[29] using the median of medians (MM), and weighted median of medians (WM) (with weights proportional to the number of patients in the study

Table 1. List of studies included in the metanalysis.

Trial	References	Regimen arms	PTS	ORR (%)	PFS (mo)	OS (mo)
TRIPLETE	Rossini et al.[18]	FOLFOXIRI-PANITUMUMAB	218	73	12.7	41.1
NCT03231722	Conca et al.[19]	FOLFOX-PANITUMUMAB	213	76	12.3	33.3
FOCULM	Hu et al.[20]	FOLFOXIRI-CETUXIMAB	67	95.5	15.5	NR
NCT02063529		FOLFOXIRI	34	76.5	14.2	33.2
AIO-CELIM2	Folprecht et al.[21]	FOLFOXIRI-CETUXIMAB	28	86	15	55
NCT01802645		FOLFIRI-CETUXIMAB	26	81	12.7	42
		FOLFOXIRI	18	72	17.5	28
		FOLFOXIRI-BEVACIZUMAB	16	70	15	44
VOLFI	Modest et al.[22]	FOLFOXIRI-PANITUMUMAB	71	87.3	9.7	35.7
NCT01328171		FOLFOXIRI	34	60.6	9.7	29.8
TRICE	Wang et al.[23]	FOLFOXIRI-CETUXIMAB	72	84.7	11.7	ND
NCT03493048		FOLFOX-CETUXIMAB	74	79.7	13.4	ND
DEEPER	Sunakawa et al.[24]	FOLFOXIRI-CETUXIMAB	159	69.1	13	42.9
NCT02515734	Shiozawa et al.[25]	FOLFOXIRI-BEVACIZUMAB	162	71.1	12.3	42.1
PANIRINOX	Mazard et al.[26]	FOLFOXIRI-PANITUMUMAB	65	75.4	8.1	NR
NCT02980510		FOLFOX-PANITUMUMAB	27	77.8	9	20.4

and normalized to sum to 1); we performed pooled HRs with the available data. These methods have been shown to perform better than transformation-based approaches, where the sample mean and its sampling variance are estimated from median data.[30] Approximate 95% CIs for pooled medians and weighted pooled medians were calculated in R using the metamedian package.[31]

The study was a NMA of anonymous aggregate data without any direct or indirect intervention on patients; thus, no ethical approval was required.

Results

In total, 1283 patients from 7 randomized clinical trials (TRIPLETE, VOLFI, TRICE, PANIRINOX, AIO-CELIM2, FOCULM, and DEEPER) were included in the present analysis (Table 1).[13]

The network for the included interventions is presented in Figure S1 (see online supplementary material for a color version of this figure). Since comparisons between arms B, C, and D cannot be performed with a traditional pairwise meta-analysis we used a network meta-analysis which is a highly useful statistical method when direct comparisons between treatments are scarce (as in our study: B vs C, B vs D, and D vs C had only 1 direct comparison), as it integrates direct evidence with indirect evidence to provide comprehensive rankings and more precise estimates for all treatment pairs, even those never directly studied.

In terms of ORR, no differences were observed among groups A, B, and D, while all treatments associated with targeted therapy (both anti-EGFR and anti-VEGF) showed a benefit when compared to triplet CT alone. In particular, no significant differences were found between doublet and triplet CT when associated with anti-EGFR therapy, with an OR of 1.05 (95% CI 0.73-1.49; $P = .8037$) for Arm B in comparison to Arm A. These data are summarized in Figure 2.

Tests of heterogeneity (within designs, $P = .7268$) and inconsistency (between designs, $P = .2696$) for the NMA assumptions were carried out. In all the comparisons of treatments p-value was not statistically significant, showing no inconsistency. Therefore, the consistency network model was supported.

Treatments were ranked according to their relative efficacy using P-scores values, ranging from 0 to 1, with higher values indicating higher rank. Treatment rankings based on P-scores were consistent with OR estimates. The highest-ranking therapies were doublet CT + anti-EGFR (0.808), followed by triplet CT+ anti-EGFR (0.746), then triplet + anti-VEGF (0.444). Triplet CT alone ranked lowest in effectiveness, with a P-score of 0.002.

Using the common-effect model, Figure 3 highlights how many of the data used were retrieved directly from trials publications, and which ones on the contrary had to be inferred. Direct data were mostly available for the triplet plus anti-EGFR group (Arm A).

We performed a pairwise standard meta-analysis alongside a network meta-analysis as a critical sensitivity analysis to validate the NMA's findings. The pairwise standard meta-analysis included all pairs of interventions that have been directly compared in at least two or three studies (A vs B, A vs C, and A vs D) (Table 2).

This meta-analysis did not demonstrate a significant difference between treatments associated to a targeted agent in terms of ORR (OR 0.97 (95% CI 0.68-1.38) for Arm A vs B, OR 1.21 (95% CI 0.47-3.12) for Arm A vs D), although it showed an OR of 4.23 (95% CI 2.06-8.68; $P = .0016$) in the comparison between Arm A (triplet CT plus anti-EGFR group) vs Arm C (triplet CT group), thus demonstrating a significant inferiority in terms of ORR for Arm C (Figure 4A).

Regarding survival outcomes—PFS and OS—the NMA was not performed due to the paucity of HR data retrieved from the publications. The pairwise metanalysis showed a non-significant pooled HR for PFS when comparing Arm A vs Arm B (2 trials included) and A and C (2 trials included); respectively, the HR were 1.08 (95% CI 0.78-1.51) and 0.91 (95% CI 0.63-1.30). The pooled HR for PFS was 0.96 (95% CI 0.84-1.09; $P = .544$) (Figure 4B and C).

Weighted median PFS for triplet CT plus anti-EGFR therapy (Arm A) was 12.7 months (95% CI 9.7-15), while it was 12.3 months (95% CI 9-13.4) for doublet CT plus anti-EGFR (Arm B). For groups C and D, weighted median PFS was not considered significant due to the availability of only 3 and 2 trials, respectively.

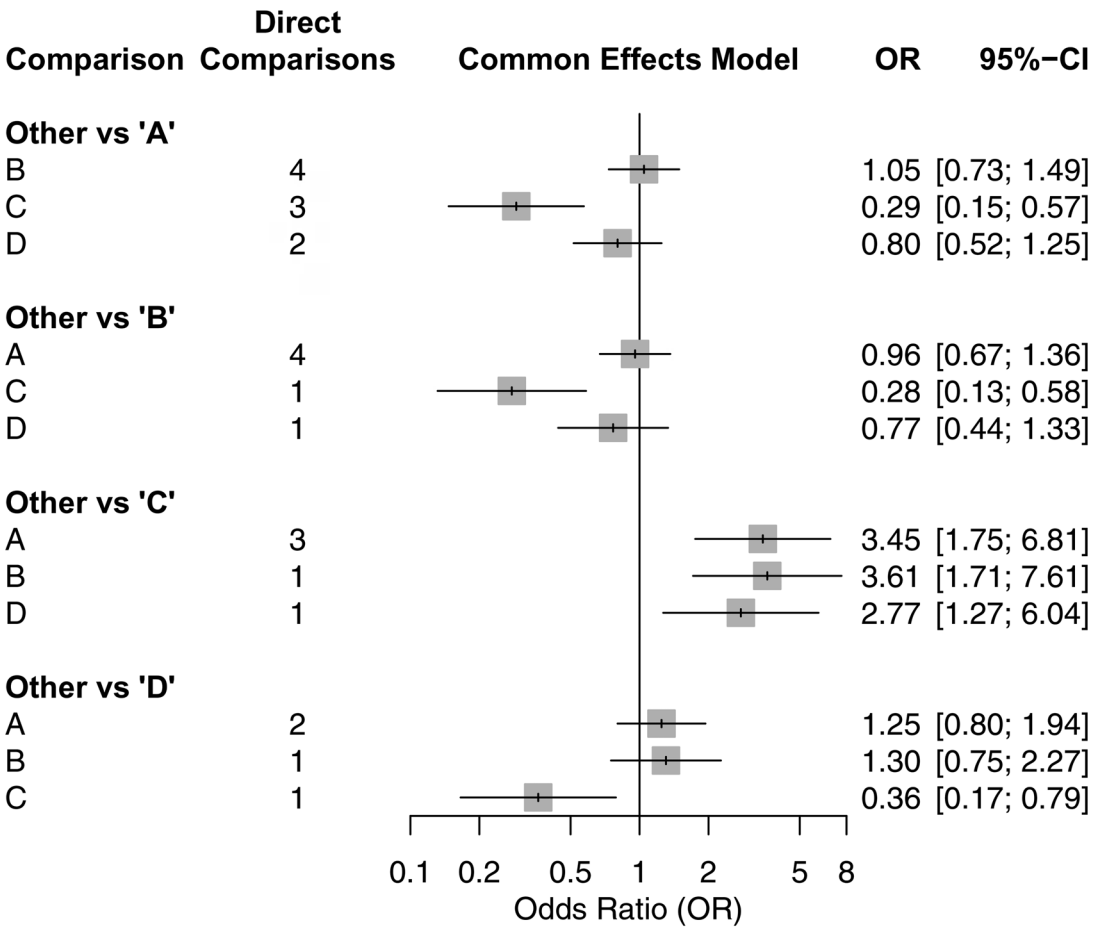

Figure 2. Forest plots of odds ratio (OR) showing the network meta-analysis for overall response rate (ORR) according to selected reference group (Arms A, B, C, and D).

As shown in Figure 5A, weighted median OS was numerically higher in the groups A and D, with respectively 42.9 (95% CI 35.7-55) and 42.1 (95% CI 42.1-44) months.

Hazard ratios data pertaining OS were available only for three studies; with this limitation, the pooled HR was statistically significant in favor of the triplet + anti-EGFR arm (0.82; CI 0.70; 0.97, $P = .022$) (Figure 5B).

Discussion

The landscape of first-line treatments for fit patients with a mCRC and a proficient MMR status is mainly constituted by a fluoropyrimidine-based doublet or triplet CT, associated to the most appropriate targeted agent according to RAS/BRAF status and tumor sidedness. While the efficacy of a triplet treatment associated with bevacizumab in patients with a right-sided cancer or a RAS/BRAF mutation is well established,[13] the potential role for a triplet CT associated to an anti-EGFR antibody for RAS wt patients is yet to be defined.

In 2022, Folprecht et al. reviewed the available data on the role of triplet CT associated to anti-EGFR.32 Nowadays, several studies had been conducted regarding this combination, but few of them were randomized in a direct comparison. First results about the potential efficacy of this combination seemed promising and led to the development of more randomized studies to confirm the potential benefits of this strategy.

This analysis indicates that, in RAS wt mCRC, efficacy is primarily determined by anti-EGFR treatment, with limited additional benefit from intensifying the CT backbone. While anti-EGFR combined with triplet CT showed a benefit over triplet al.ne, it did not demonstrate a consistent superiority compared to doublet CT plus anti-EGFR or triplet plus bevacizumab in terms of ORR. Although a potential OS benefit emerged in some trials, such as the TRIPLETE, DEEPER and the AIO-CELIM2 trial, these data are far from mature and inconsistent across studies.

To our knowledge, this is the first comparison to evaluate systematically the efficacy of triplet therapy associated with anti-EGFR treatment when compared to the other available treatment options in the untreated RAS/BRAF wt mCRC population. The strength of this study lies in its systematic approach, which allowed for a reliable evaluation of the available evidence.

The TRIPLETE and the PANIRINOX trial investigated a direct comparison between FOLFOX and FOLFOXIRI associated to an anti-EGFR; both trials failed to demonstrate any benefit in terms of ORR, ETS, DoR, and PFS; however, in the TRIPLETE study there were a significantly longer OS (HR: 0.79; $P = .049$) and post-PFS (HR: 0.73; $P = .012$) in the triplet arm. Interestingly, the toxicity profile of triplet CT remains the major concern; in the TRIPLETE study the experimental arm showed a significant increase in several G3-G4 adverse events (neutropenia: 32% in the experimental group vs 20% in the

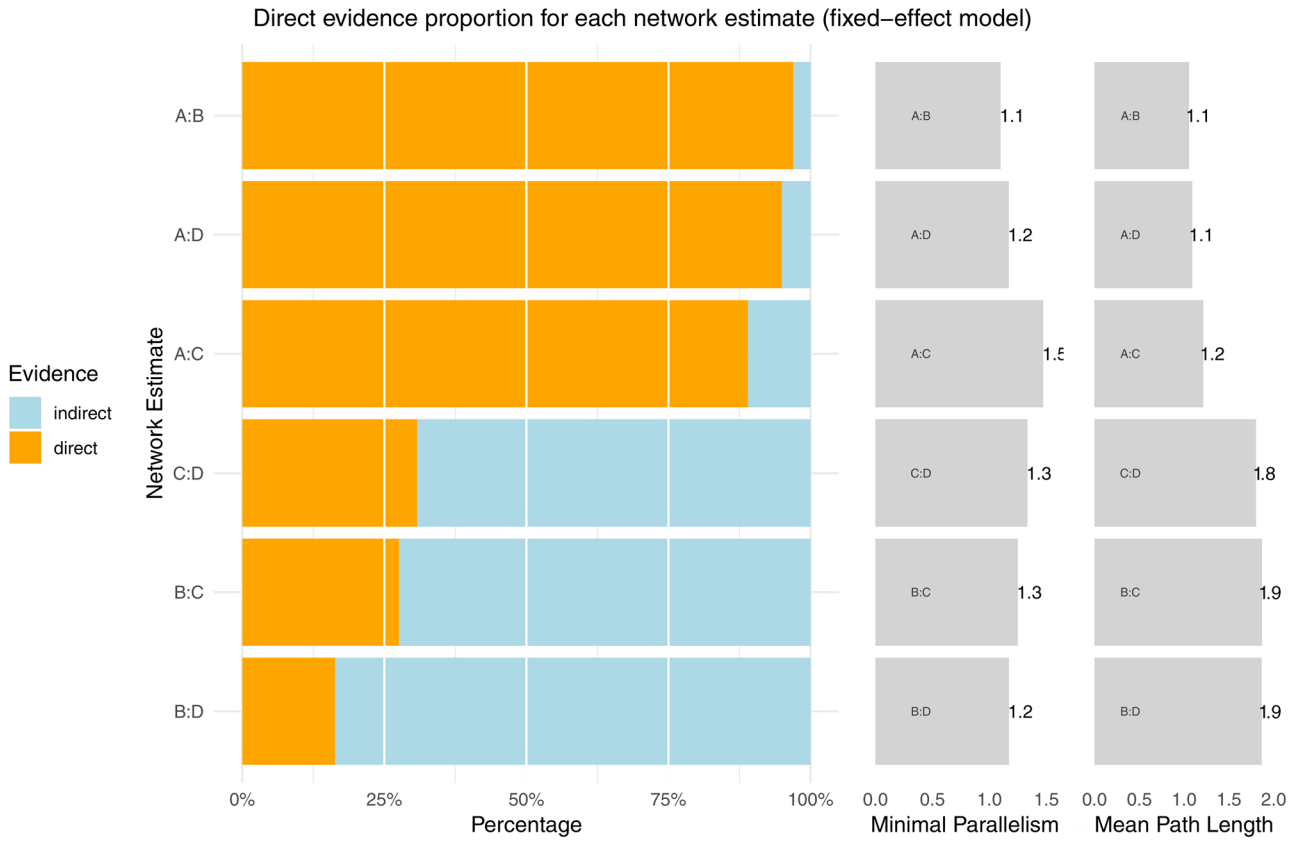

Figure 3. Proportion of direct evidence for each network estimate (common effect model). The plot also provides two additional metrics: the minimal parallelism and mean path length of each estimated comparison. A mean path length >2 means that a comparison estimate should be interpreted with caution (no evidence for this network model).

control group; diarrhea: 23% vs 7%; nausea: 5% vs 2%; hypokalemia: 7% vs 4%; fatigue: 7% vs 2%) without a clear benefit ORR and PFS benefit; in the PANIRINOX trial, a significant increase in G3/G4 diarrhea was reported (39% vs 9%).[18,19,26] The vast majority (88%) of patients in both arms of the TRIPLETE trial had a left-sided cancer.

Table 2. Treatment arms comparisons for each trial included in the pairwise meta-analysis.

Study	Odds ratio (OR)	95% CI	Comparison
TRIPLETE	0.84	[0.54-1.31]	AvsB
PANIRINOX	0.88	[0.30-2.55]	AvsB
VOLFI	4.47	[1.61-12.38]	AvsC
TRICE	1.41	[0.60-3.32]	AvsB
AIO-CELIM2	1.43	[0.34-6.03]	AvsB
AIO-CELIM2	2.57	[0.62-10.72]	AvsD
AIO-CELIM2	2.31	[0.53-10.12]	AvsC
FOCULM	6.56	[1.61-26.70]	AvsC
DEEPER	0.89	[0.55-1.44]	AvsD

In the VOLFI trial the combination of panitumumab and mFOLFOXIRI improved ORR (87.3% vs 60.6%; OR 4.469; $P = .004$) and secondary resection rate (33.3% v 12.1%; $P = .02$ in cohort 1; 75% vs 36.4% in cohort 2; $P = .05$) in comparison to triplet CT alone; however, PFS was similar in the treatment arms, and OS showed a non-significant trend in favor of the experimental arm.[22] Similarly to the TRIPLETE trial, in the VOLFI trial most patients (respectively 84.1% and 75.8% in Arm A and B) presented with a left-sided cancer. Some exploratory analyses suggest that triplet plus anti-EGFR could play a key role in specific subgroups. For example, in patients with left-sided tumors and RAS/BRAF wild-type disease the DEEPER trial showed similar results in the all-comers population, with an improvement of ORR, and but no difference in PFS and OS; however, in the subgroup with *RAS/BRAF*wt and left-sided tumors, median DoR was 63.6% vs 47.8% ($P = .0003$), ORR was 83.6% vs 72.9% ($P = .14$) and both PFS (HR 0.68) and OS (HR 0.54) were significantly improved in the cetuximab arm, while the bevacizumab arm performed better in the right-sided cancer.[24,25] However, the observed benefit may reflect the effect of anti-EGFR vs anti-angiogenic therapy in left-sided disease rather than the specific advantage of triplet chemotherapy combined with anti-EGFR in a selected population. All these trials confirmed an increased toxicity for the experimental arm: in the VOLFI trial, grade 3 or 4 adverse events were reported in 81.3% vs 66.7% of patients, especially diarrhea (25% vs 12%) nausea (9.4% vs 0%), vomiting (9.4% vs 3.0%), mucositis/stomatitis (9.4% vs 0%), dermatitis (14.1% vs 0%), and fatigue (7.8% vs 0%), while G3/4 peripheral neuropathy was prevalent in the control arm (3.1% vs 12.1%); in the DEEPER trial, difference between arms of treatment were less sharp, mainly pertaining an increase in diarrhea in the anti-EGFR arm (12% vs 8%), stomatitis (9.7% vs 2.3%)

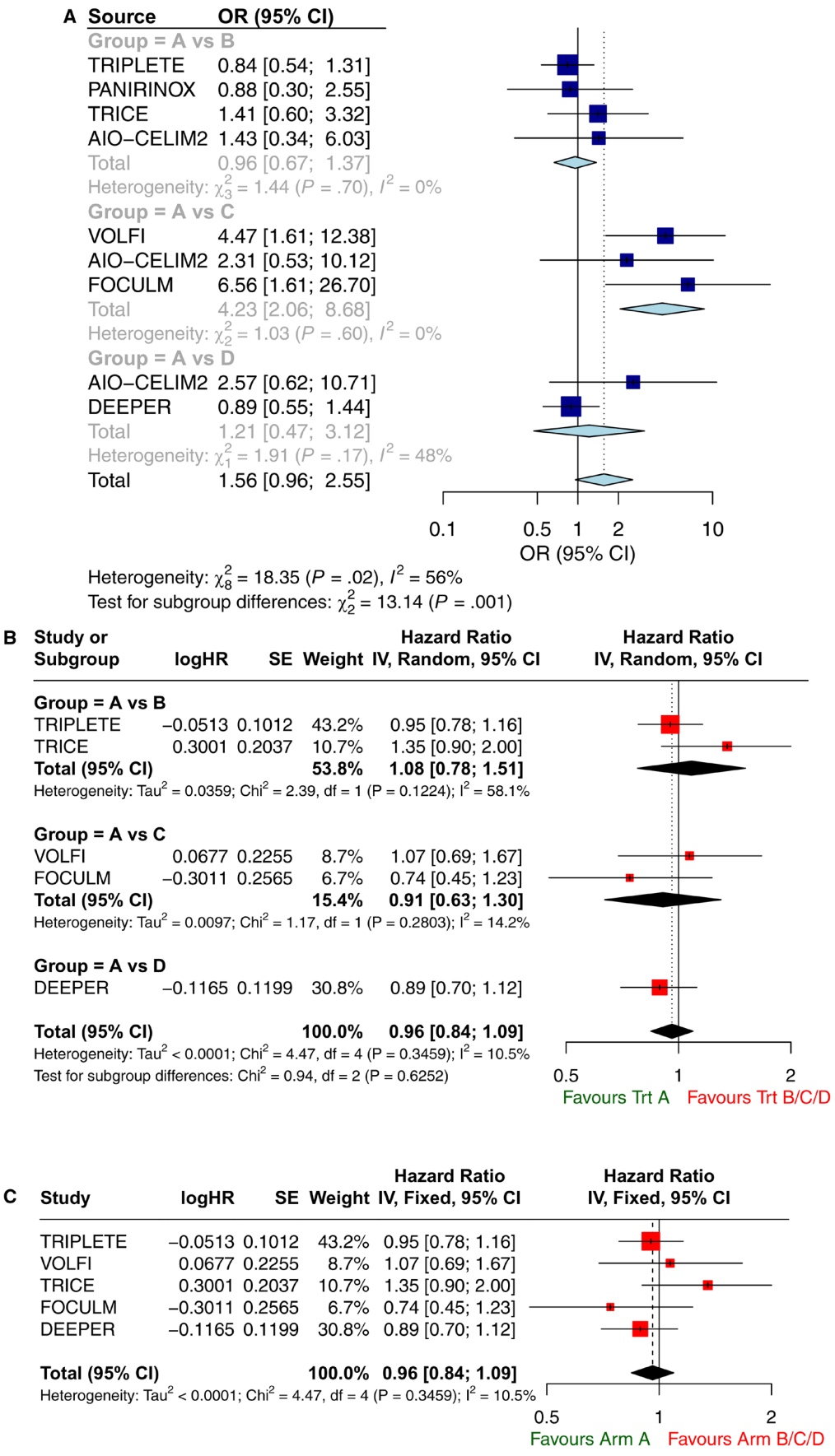

Figure 4. (A) ORR comparison between treatment arms in the different trials. (B) PFS comparison between treatment Arms A vs B and A vs C in the different trials. (C) Pooled HR for PFS comparison between treatment arms in the different trials.

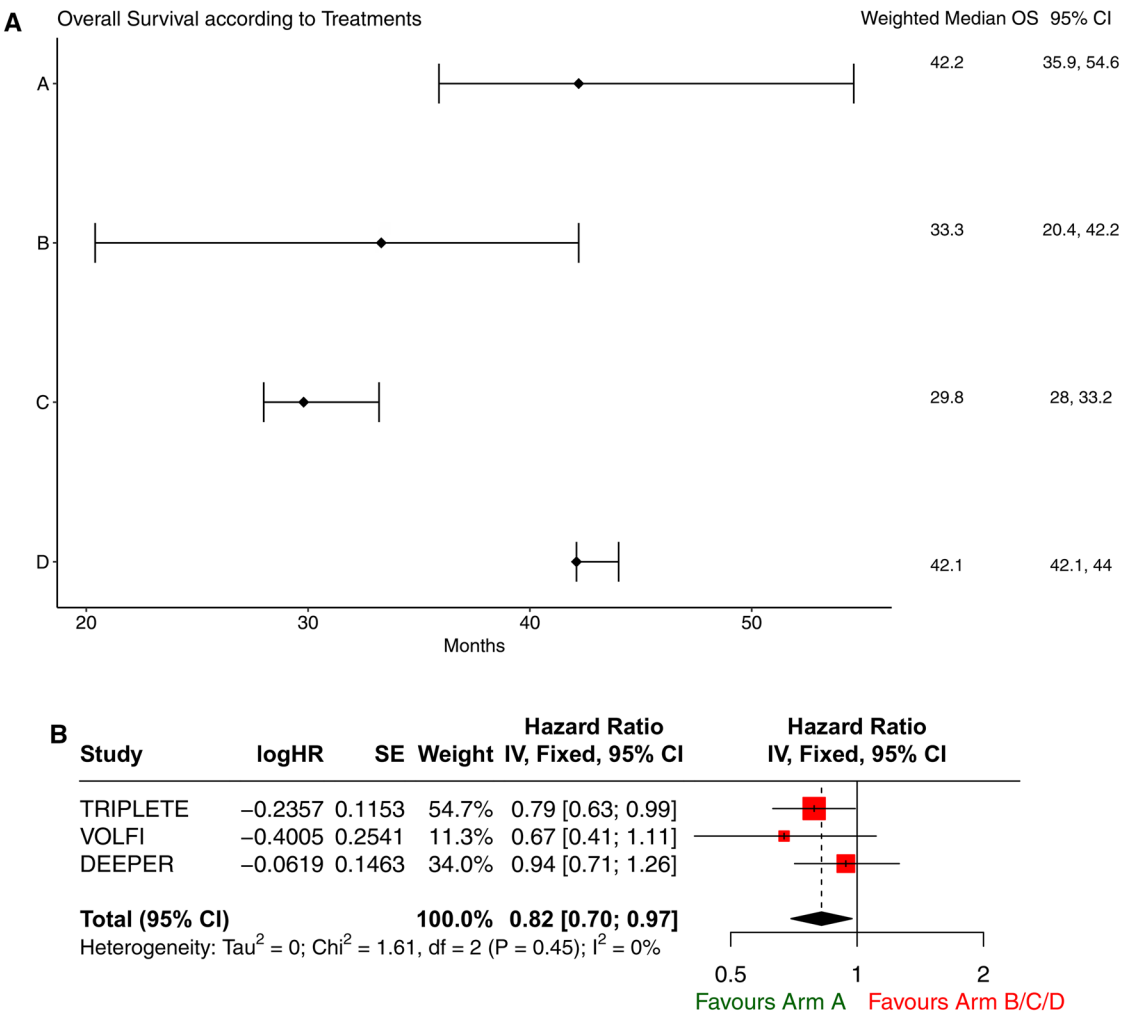

Figure 5. (A) Weighted median OS per treatment group. A=FOLFOXIRI+cetuximab/panitumumab; B=FOLFOX+ cetuximab/panitumumab; C=FOLFOXIRI; D=FOLFOXIRI+bevacizumab. (B) Pooled HR for OS comparison.

and acneiform rash (13.0% vs 0%), while the bevacizumab arm had, as expected, an increase in the G3/4 hypertension events reported (17.1% vs 33.5%).

Likewise, triplet chemotherapy plus anti-EGFR agents may retain its role in the conversion settings with liver-limited metastases. Trials such as the FOCULM investigated a modified FOLFOXIRI protocol, with or without cetuximab, as conversion therapy: the addition of cetuximab improved ORR (95.5% vs. 76.5%) and the rate of patients who achieved a "no evidence of distant disease" (NED) status (70.1% vs 41.2%). 55.2% of patients in the cetuximab group and 29.4% in the control group underwent surgical resection (P = .014), while 20 patients had thermal ablation. In this trial, almost all patients presented with a left-sided cancer (98.5% and 91.2% in arm A and B, respectively); there were no significant differences in toxicity between arms.[20] The TRICE trial compared, instead, different CT schemes (doublet or triplet) associated to cetuximab: in this trial, ORR (84.7% vs 79.7%) Early Tumor Shrinkage (ETS) (80.6% vs 77.0%), R0/R1 resection rate (54.2% vs 52.7%) and median PFS (11.8 m vs 13.4 m) were comparable between arms of treatment Left-sided patients were 85.1% and 88.9% respectively; notably, even the 13% of patients with a right-sided cancer who received treatment also achieved a ORR of 89.5%, with a PFS of 12.47 months, but had a lower conversion rate (36.8%). Neutropenia and diarrhea were most common in the triplet arm (G1-G4 neutropenia: 86.8% vs 71.6%, P = .03; grade ≥ 3 neutropenia: 44.1% vs 27.0%, P = .03; G1-G4 diarrhea, 73.5% vs 23%, P < .001; G3/G4 diarrhea, 5.9% vs 0%, P = .03).[23] Lastly, in the RAS wt Arms of the AIO-CELIM2 trial, patients were randomized to a comparison between doublet and triplet CT associated to anti-EGFR. In this study, the doublet + cetuximab/triplet + cetuximab showed respectively an ORR of 81% and 86%, the mPFS was 12 m vs 15 m, and the mOS was 42 m vs 55 m. Nevertheless, the sample size of the AIO-CELIM2 trial was limited (54 patients), and as such these results should be considered with caution.[21]

In mCRC, OS and PFS are often related to radical resection of sites of metastatic disease, especially when these are confined to the liver.[33,34] Hence, ORR is often selected as primary endpoint for trials which explore first-line treatment for mCRC, as a treatment which improves response rates could, potentially, also lead to increased chances for conversion surgery with safe rates of R0 resections, thus indirectly improving prognosis for this subgroup of patients. It is, indeed, known that R0/R1 resections lead to a conspicuous improvement in OS. However, results of our analysis seem to suggest that the role of properly selected targeted agents, in this subgroup of patients, is more relevant than an intensification of the CT

backbone. Although there is some evidence that different endpoints, as DoR and ETS may be related to an improved prognosis in mCRC,35 these endpoints have not been fully validated yet and have been investigated only by few selected studies,[36] thus not allowing a complete analysis of the results.

In regard to conversion therapy, the most complete trial is possibly the CAIRO5 study, which evaluated different strategies according to RAS status.[37] Interestingly, for patients harboring a left-sided cancer with a WT RAS and BRAF status, PFS (10.8 months vs 10.4 months, $P = .46$) did not differ between the two available arms of treatment (doublet associated to either bevacizumab or panitumumab). The PRODIGE 14 trial, which we excluded from our analysis due to lack of data regarding the RAS-WT cohort, tested doublet vs triplet chemotherapy associated with a targeted agent (depending from the RAS status) as conversion therapy; however, this trial failed to demonstrate a significant improvement in the resection rate (56.9% vs 48.4%, $P = .17$) and in OS (43.4 months vs 40 months). Improvement in OS was confirmed for those who underwent surgery (54.2 m vs 28.8 m).[38] These studies seem to confirm that, more than intensification of chemotherapy, the most relevant feature of first-line chemotherapy should be association with a targeted agent.

In summary, our results confirm that the efficacy of first-line treatment in patients with RAS wild-type mCRC is primarily driven by anti-EGFR treatment, whereas intensification of the CT backbone with a triplet regimen provides only limited additional benefit. Triplet CT combined with anti-EGFR does not demonstrate a consistent advantage over doublet chemotherapy plus anti-EGFR or triplet CT plus anti-VEGF in terms of. Some data indicate that the combination of triplet CT with anti-EGFR may retain a role in selected subgroups, particularly young and fit patients with left-sided tumors and potentially resectable disease, where maximizing tumor shrinkage could increase the chance of secondary resection. However, the higher incidence of grade 3–4 toxicities observed in triplet + anti-EGFR arms underscores the need for careful patient selection, since in unselected populations the risks may outweigh the benefits.

This study has some limitations, mainly related to heterogeneity and small sample size. Moreover, our analysis relied on published data and was limited by the availability of certain information. Although the results of the TRIPLETE trial are suggestive of a potential OS benefit, available data from the studies we analyzed do not allow us to draw a definite conclusion regarding a potential benefit in OS or PFS due to the limited maturity of survival data.

Notably, although none of the included trials selected patients according to sidedness, the vast majority of the patients enrolled had a left-sided cancer; this is understandable, as it is known that right-sided CRC tend to harbor an intrinsic resistance to anti-EGFR treatments, especially when offered as an upfront choice.[39] In all trials the number of patients with left-sided cancer was balanced between arms, thus limiting the potential bias in our analysis; however, probably due to the limited number of right-sided cancers included in the studies, results according to sidedness were not always available, thus limiting our capability for a comparison. A parallel consideration can be done for BRAF status; results of the phase III FIRE 4.5 trial, which enrolled BRAF V600E-mutant patients, showed lower ORR (51% vs 67%), PFS (6.7 m vs 10.7 m) and OS (12.9 vs 17.1 m) for treatment with FOLFOXIRI-cetuximab when compared to FOLFOXIRI-Bevacizumab, thus confirming the lack of efficacy of anti-EGFR treatment when compared to anti-VEGF in this subgroup of patients, even when associated to an intensified CT backbone.[40] However, the number of BRAF mutant patients in the studies we analyzed was scarce, and unlikely to be relevant for the final analysis. An indirect confirmation of this assumption is that, even accounting for the right-sided and BRAF patients, no significant difference in ORR was found when comparing doublet/triplet CT with anti EGFR treatment and triplet CT associated with anti-VEGF.

Moreover, most available studies were phase II trials, thus toxicity or quality-of-life outcomes were not always systematically reported. Nonetheless, to our knowledge, our NMA provides the most exhaustive overview currently available in literature.

Although current evidence do not allow any recommendation for an intensified chemotherapy regimen associated with anti-EGFR antibodies, the studies we analyzed did not select patients according to molecular status nor sidedness; notably, HER2 status was not an exclusion criteria in any of the studies of our metanalysis, nor BRAF status, although it is widely known that these patients present with a primary anti-EGFR resistance. Looking forward, further randomized studies with more precise biomarker-based stratification (RAS, BRAF, HER2, and primary tumor location) will be needed to identify subgroups of patients who might truly benefit from treatment intensification. An ongoing phase 2 trial (NCT04169347) is currently exploring the combination FOLFOXIRI-Panitumumab in left-sided RAS wt cancers; results of these trials are pending and may help to define a more selected population of patients who may benefit of an intensified regimen.

Benefits of an intensification of treatment with a triplet chemotherapy associated to target treatment according to molecular profile is under investigation for young and fit patients. In our study, no significant ORR benefit was found for the combination of a triplet chemotherapy associated with anti-EGFR treatment compared association with an anti-VEGF therapy or to a doublet chemotherapy combined with anti-EGFR treatment; although available data suggests an improvement in OS, the dearth of data available do not allow definitive conclusions. All regimens incorporating targeted treatment demonstrated superior performance compared to a treatment which consisted of triplet chemotherapy alone. Therefore, current evidence does not support the routine use of triplet chemotherapy plus anti-EGFR in unselected patients. Further research is needed to determine potential subgroups of patients who may profit from an intensification of the CT backbone and confirm potential benefits.

Author contributions

Paola Di Nardo (Conceptualization, Data curation, Supervision, Writing—original draft, Writing—review & editing), Marco de Scordilli (Conceptualization, Data curation, Supervision, Writing—original draft, Writing—review & editing), Fabiola Giudici (Methodology, Writing—original draft, Writing—review & editing), Debora Basile (Conceptualization, Data curation, Writing—original draft, Writing—review & editing), Brenno Pastò (Data curation, Writing—original draft, Writing—review & editing), Simone Rota (Data curation, Writing—original draft, Writing—review & editing), Sara Torresan (Conceptualization, Writing—original draft, Writing—review & editing), Martina Bortolot (Data curation, Writing—original draft, Writing—review & editing), Luisa Foltran (Data curation,

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Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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