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ORIGINAL ARTICLE

Role of Anti-Epidermal Growth Factor Receptor Therapy Compared with Anti-Vascular Endothelial Growth Factor Therapy for Metastatic Colorectal Cancer: an Update Meta-Analysis of Randomized Clinical Trials

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Abstract
Monoclonal antibodies targeting epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) have showed clinical benefit in combination with chemotherapeutic cytotoxic drugs in the first-line therapy of metastatic colorectal cancer (mCRC). Data from randomized studies comparing these monoclonal antibodies as initial therapy is conflicting, and their comparative efficacy remains unknown. This study aimed to evaluate the impact of the combination of anti-epidermal growth factor receptor (anti-EGFR) therapy and anti-vascular endothelial growth factor therapy on mCRC patient outcomes by combining the data from randomized clinical trials. Three trials meeting the eligibility criteria, and four randomized studies were included in the meta-analysis. For MCRC patients with KRAS wild type (KRAS-WT), the ORR was superior in patients treated with anti-EGFR compared with those who treated with anti-VEGF therapy. This effect was even better for all RAS-WT patients. Progression-free survival (PFS) rates were not significantly different for KRAS-WT mCRC and all RAS-WT mCRC between the two groups. The overall survival (OS) was higher for RAS wild-type (RAS-WT) mCRC patients who received anti-EGFR, but the KRAS-WT patients compared to the anti-VEGF therapy. The results of our research indicate that superior ORR and OS between the addition of anti-EGFR therapy VS anti-VEGF therapy in all RAS-WT patients with MCRC. There was no significant difference in OS and PFS between the two groups for KRAS-WT mCRC. These results suggest that anti- EGFR monoclonal antibodies can achieve an equivalent efficacy when compared with anti-VEGF therapy of all RAS-WT mCRC patients.

Keywords Colorectal cancer · Anti-EGFR · Anti-VEGF · Chemotherapy · Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed malignance worldwide [1, 2]. It has been reported that about approximately 50–60% of patients develop inoperable metastasizing [3]. The standard first-line chemotherapy of metastatic colorectal cancer (mCRC) is adding the monoclonal antibodies to the chemotherapy. These targeted agents include the antievascular endothelial growth factor (VEGF) inhibitor bevacizumab or the antieepidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab.

Previous studies have shown that a survival benefit associated with the addition of cetuximab in KRAS wild-type mCRC, when with different chemotherapy regimens consisting on drugs such as infusional 5-fluorouracil (5-FU) and folinic acid plus either irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen) [4, 5]. Retrospective results of the OPUS and CRYSTAL trials have did not achieve clinical benefit when cetuximab was added to chemotherapy for KRAS-mutated mCRC [6–9]. Several studies have analyzed the efficacy of the using of bevacizumab to first-line chemotherapy has led to improvement in survival time in previously untreated patients with mCRC [10–12]. Furthermore, retrospective analyses analyzed the survival benefit that adding bevacizumab to chemotherapy in patients with mCRC with either the mutant or wild-type KRAS gene [12, 13].

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The analysis of the FIRE-3 [14, 15] and PEAK [16] trials showed that the addition of anti-EGFR to chemotherapy is associated with OS. By contrast, the randomized Phase III CALGB 80405 [17] study have not confirmed the same findings in OS in KRAS-WT mCRC between the two therapies.

The combination chemotherapy and targeted therapy proved feasible results and appeared to be more active than the chemotherapy alone [12]. These new options for patients with advanced or metastatic colorectal cancer raised the question to determine the best monoclonal antibody-chemotherapy combination.

Methods and Materials

Search Strategy

Two investigators independently searched electronic databases: Pubmed, Embase, Cochrane library up to May 2017.We searched for all randomized clinical trials of MCRC comparing an anti-EGFR drug with an anti-VEGF agent, both in

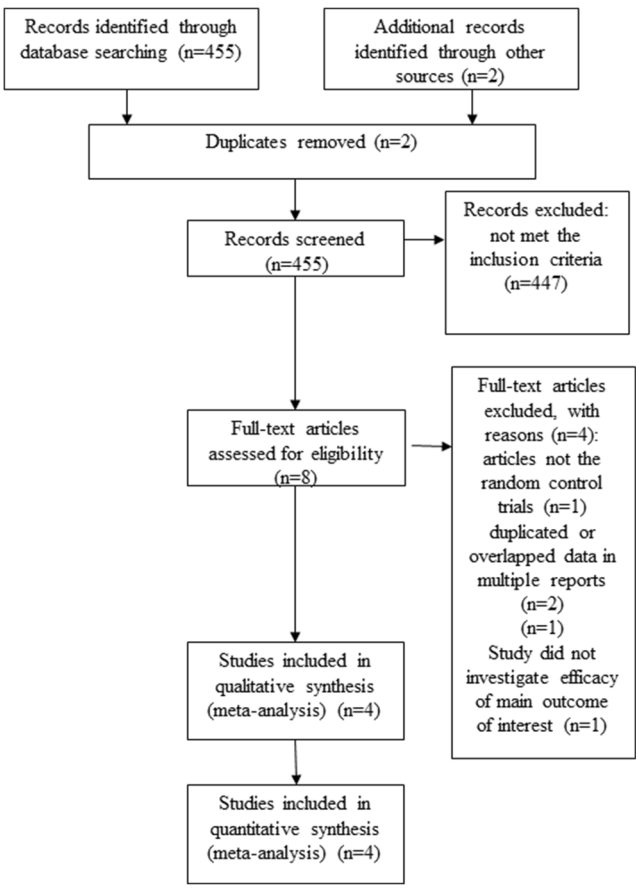

Fig. 1 PRISMA flow chart of selection process to identify studies eligible for pooling

Table 1 The primary characteristics of the eligible studies in more detail

Author	Year	Study	Study	Study design	Treatment groups	No of patients	Regimen
Heinemann et al.	2014	FIRE-3	Germany	Randomized Phase III study	Group A	297	A: FOLFIRI cetuximab
					Group B	295	B: FOLFIRI bevacizumab
Stintzing et al.	2016	FIRE-3	Germany	Randomized Phase III study	Group A	297	A: FOLFIRI cetuximab
					Group B	295	B: FOLFIRI bevacizumab
Schwartzberg et al.	2014	PEAK	Spain	Randomized Phase II study	Group A	142	A: mFOLFOX6 panitumumab
					Group B	143	B: mFOLFOX6 bevacizumab
Venook et al.	2017	CALGB/SWOG 80405	USA	Randomized Phase III study	Group A	578	A: FOLFIRI/mFOLFOX6 cetuximab
					Group B	559	B: FOLFIRI/mFOLFOX6 bevacizumab

combination with the conventional combination chemotherapy in the first-line setting. The process was established to find all articles with the keywords: "metastatic colorectal cancer" AND "chemotherapy" AND "anti-EGFR" AND "anti-VEGF", and relevant Medical Subject Heading (MeSH) terms were utilized. The reference lists of all articles that dealt with the topic of interest were also hand-searched to check for additional relevant publications.

Eligibility Criteria

Studies were included in the meta-analysis should meet the following criteria: (1) the studies are designed as random control trials (RCTs);(2) trials that adding anti-EGFR therapy and anti-VEGF therapy to chemotherapy as first-line chemotherapy for mCRC;(3) the outcomes of interest were efficacy (survival, tumor response), and HRs with corresponding 95% CIs were provided; (4) the full texts were only included. If we found duplicated or overlapped data in multiple trials, we just include the one with the latest data. And papers not in English were excluded.

Quality Assessment

The quality of the retrieved studies was assessed by two investigators independently.

Assessing the risk of bias items (ROBI) was based on the recommendations given by The Cochrane Handbook for Systematic Reviews of Interventions.

Data Extraction

Data extraction was performed by two authors from each study independently. Disagreement was revolved by consensus. From each of the eligible studies, the main categories based on the following: first author family name, publication year, Study name, study design, sample size, ORR, PFS, and OS for both KRAS-WT and all RAS-WT patients. We extracted the corresponding hazard ratios (HRs) and risk ratios (RRs) to describe the strength of the association for survival (overall (OS) and progression-free survival (PFS)) and dichotomous (overall response rate (ORR)) data, respectively, with corresponding 95% confidence intervals (CIs).

Statistical Analysis

The endpoints of interest in the pooled analysis were OS、PFS and ORR according to the RAS status, and the endpoint outcome were using hazard ratio (HR) and its 95% confidence intervals (CI). If HRs and corresponding 95% CIs were reported, lnHRs and the corresponding lnLLs and lnULs were used as data points in pooling analysis. Heterogeneity was examined by calculating I^2. Heterogeneity with an I^2 of 25–50%, 50–75%, or >75% were indicated low, moderate, or high heterogeneity, respectively [18]. When there was low heterogeneity among studies, data were analyzed using a fixed-effects model. Otherwise, the random effects model was used. *P*-value of 0.05 was considered statistically significant. The statistical analyses were per- formed using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). The results of our meta-analysis were shown in forest plots. The Begg test and the Egger test were conducted to evaluate publication bias.

Results

Overview of Literature Search and Study Characteristics

A total of 455 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 8 publications were evaluated in more detail, but some did not provide enough detail of outcomes of two approaches. Therefore, a final total of four RCTs [14–17] determine the impact of anti-EGFR and anti-VEGF therapies in the first-line therapy for mCRC. The search process is described in Fig. 1. All included studies in this study were based on moderate to high quality evidence. Table 1 describes the primary characteristics of the eligible studies in more detail.

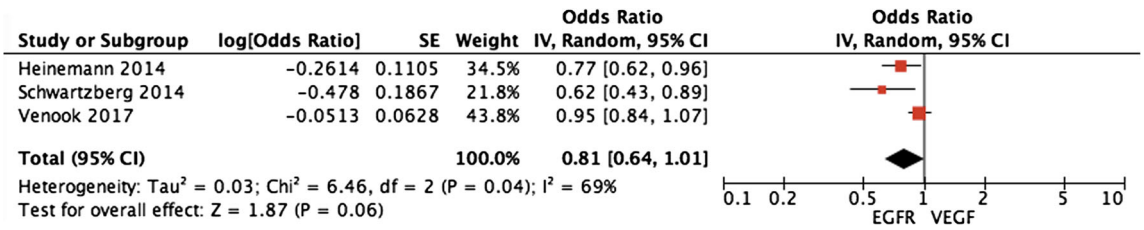

Fig. 2 Pooled analysis of OS compared anti-EGFR and anti-VEGF therapies in the first-line setting for KRAS-WT mCRC

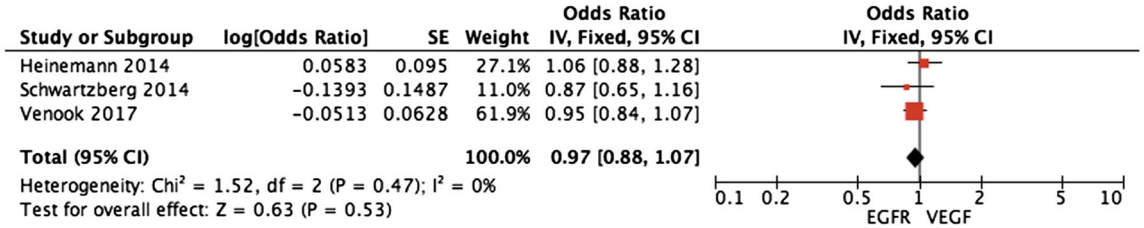

Fig. 3 Pooled analysis of PFS compared anti-EGFR and anti-VEGF therapies in the first-line setting for KRAS-WT mCRC

Clinical and Methodological Heterogeneity

Pooled Analysis of OS Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for KRAS-WT mCRC

Pooling OS data were available in three RCTs [14, 16, 17]. The aggregated results found that there was no no benefit in OS from anti-EGFR chemotherapy. (OR = 0.81,95%CI = 0.64–1.01, $P = 0.06$) compared with anti-VEGF therapies group (Fig. 2).

Pooled Analysis of PFS Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for KRAS-WT mCRC

Three articles provided data on PFS. The pooled data showed that anti-EGFR targeted agent plus chemotherapy significantly did not improved PFS (OR = 0.97,95%CI = 0.88–1.07, $P = 0.53$) more than anti-VEGF treatment (Fig. 3).

Pooled Analysis of ORR Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for KRAS-WT mCRC

ORR data did not achieve significant advantage in the anti-EGFR regimens (RR = 1.19,95%CI = 1.00–1.43, $P = 0.05$) [14, 16, 17]. In other words, the addition of anti-EGFR did increase the rate of ORR, but significantly (Fig.4).

Pooled Analysis of OS Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for RAS-WT mCRC

OS data for RAS-WT mCRC was available for three RCTs [15–17]. Results showed that there were better OS in the anti-EGFR than that in the anti-VEGF therapies group. (OR = 0.79,95%CI = 0.68–0.92, $P = 0.002$) (Fig. 5).

Pooled Analysis of PFS Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for RAS-WT mCRC

For the RAS-WT mCRC, no significant differences compared anti-EGFR and anti-VEGF therapies were observed in PFS (HR = 0.94, 95% CI = 0.73–1.20, $P = 0.60$) (Fig. 6).

Pooled Analysis of ORR Compared Anti-EGFR and Anti-VEGF Therapies in the First-Line Setting for RAS-WT mCRC

Three studies [15–17] provided data on ORR in patients with mCRC treated with chemotherapy, and the data are shown in Fig. 7. A significant ORR benefit of anti-EGFR was found in patients without any RAS mutations (OR = 1.55, 95% CI = 1.22–1.98, $P = 0.0004$).

Discussion

The systemic chemotherapy is the major treatment for mCRC. In the past decade, studies have demonstrated that the interactions of anti-epidermal growth factor receptor (anti-EGFR) or anti-vascular endothelial growth factor (anti-VEGF) with chemotherapeutic agents can prolong the survival outcomes compared with conventional chemotherapy [7, 8, 10]. Therefore, the addition of EGFR/VEGF in combination with FOLFOX or FOLFIRI have active treatment options for patients with mCRC. Recent studies have reported conflicting results for the types of antibody (anti-EGFR or anti-VEGF) that regarding better clinical efficacy for mCRC patients [19, 20].In recent years, molecularly targeted therapies, including anti-EGFR and anti-VEGF therapies, have been applied in the treatment of mCRC. Trials have studied the addition of anti-EGFR or anti-VEGF agents to combination chemotherapy improved the survival outcomes in mCRC [21].

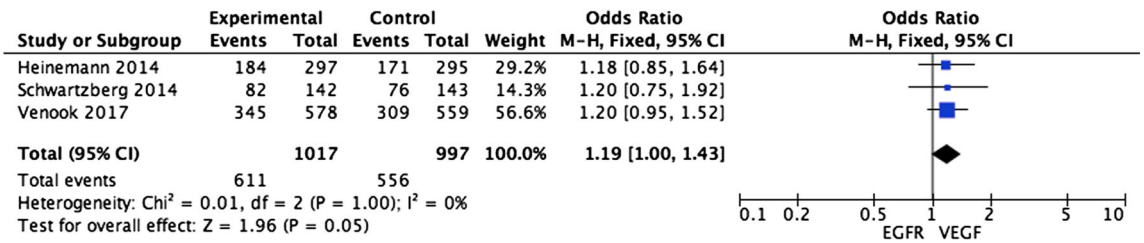

Fig. 4 Pooled analysis of ORR compared anti-EGFR and anti-VEGF therapies in the first-line setting for KRAS-WT mCRC

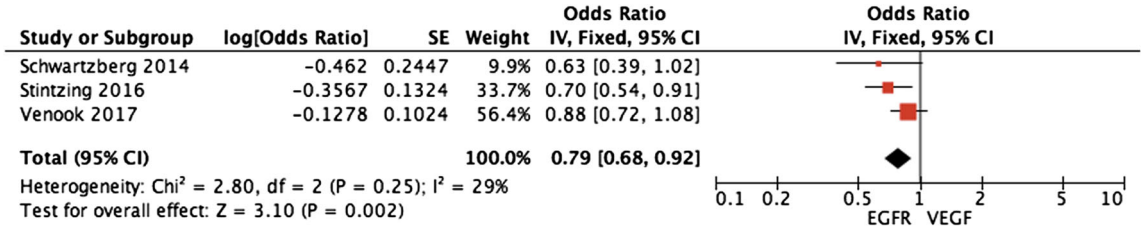

Fig. 5 Pooled analysis of OS compared anti-EGFR and anti-VEGF therapies in the first-line setting for RAS-WT mCRC

A previous meta-analysis [22] assessing data from all three RCTs (FIRE-3, PEAK, and CALGB 80405) compared anti-EGFR and anti-VEGF treatments in the first-line setting for KRAS-WT mCRC. While, the analysis was including meeting abstracts rather than extracted from the update published studies. This meta- analysis included the latest FIRE-3 and CALGB/SWOG 80405 studies data, which has been presented in recent years.

To our knowledge, the random, phase 3, FIRE-3 (Multicenter Randomized Phase III Study Evaluating Cetuximab adding to FOLFIRI Versus Bevacizumab adding to FOLFIRI in First Line Treatment of Metastatic Colorectal Cancer) was the first head-to-head setting to compare cetuximab (an anti-EGFR agent) to bevacizumab (an anti-VEGF agent) in advanced or metastatic KRAS wild-type (wt) colorectal cancer for the first-line treatment [14].

In the KRAS exon 2 wild-type intention-to-treat patients, median overall survival was better in patients receiving FOLFIRI plus cetuximab versus those receiving FOLFIRI plus bevacizumab. The benefit in overall survival was further enhanced in extended RAS wild-type subgroup (KRAS/NRAS, exons 2–4). The FIRE-3 study reported an OS benefit of 8.1 months for RAS wild-type subgroup, without anti-EGFR therapy improvement of ORR or PFS [15].

The PEAK (Efficacy in mCRC Subjects with Wild-Type KRAS Tumors in Combination Either Panitumumab or Bevacizumab and mFOLOFOX6 as First-Line Treatment) trial [16] enrolled 285 patients who treated with panitumumab (a fully humanized anti-EGFR antibody) to bevacizumab in combination with FOLFOX. There was no statistically PFS difference detected between the 2 monoclonal antibodies. However, there was no significant impact on OS favoring panitumumab over bevacizumab (34.2 vs 24.3 months; $P = .009$). However, our study did not detect any significant differences between the 2 monoclonal antibodies in the Cancer and Leukemia Group (CALGB)/SWOG 80405 study. This result may be because 73.4% of the patients treated with first-line FOLFOX, which might not be the best chemotherapy drug in addition with anti-EGFR therapy [23]. A previous meta-analysis showed significant superior efficacy of anti-EGFR therapy when compare with an irinotecan-based regimen compared to an oxaliplatin-based chemotherapy [24]. Therefore, there was a selection bias in the chemotherapy backbones in this trial. The conflicting results among RCTs, and therefore, the optimal combination of targeted therapy and chemotherapy for the first-line mCRC treatment remains inconclusive.

In our meta-analysis, compared with anti-VEGF therapy, anti-EGFR therapy significantly increased overall survival in patients with all RAS-WT metastatic colorectal cancer, but no KRAS-WT. While, there is no benefit observed for progression-free survival.

Previous retrospective trials of the CRYSTAL and OPUS trials are consistent with our finding, in these studies, the combination of cetuximab to first-line chemotherapy (FOLFIRI and FOLFOX, respectively) induced early tumor shrinkage and the depth of response [25, 26]. Early tumor shrinkage was assessed at 8 weeks in CRYSTAL and OPUS (vs 6 weeks in the study).

Notably, all these were related to post-progression survival and overall survival in both treatment groups. It indicated that higher early tumor shrinkage and higher depth of response, which shows better objective response and predicts the potential depth of response, were associated with improved OS. Thus, a clear biological basis for the FOLFIRI plus cetuximab-conferred overall survival advantage observed in FIRE-3 is apparent after assessment of more refined alternative metrics that better capture the temporal and quantitative effects of therapy on tumour burden.

In our study, the choice of targeted agents had no difference on PFS for KRAS-WT mCRC and all RAS-WT mCRC

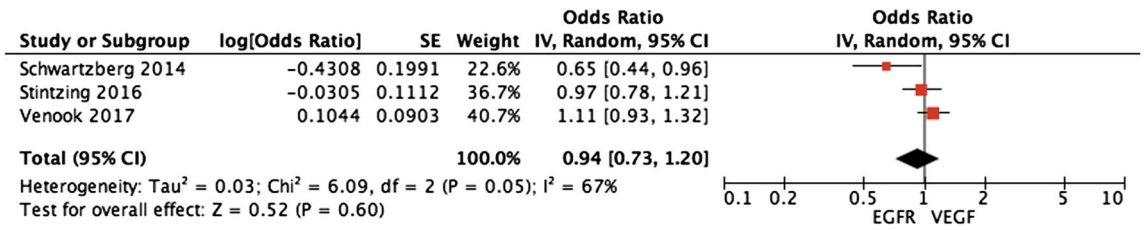

Fig. 6 Pooled analysis of PFS compared anti-EGFR and anti-VEGF therapies in the first-line setting for RAS-WT mCRC

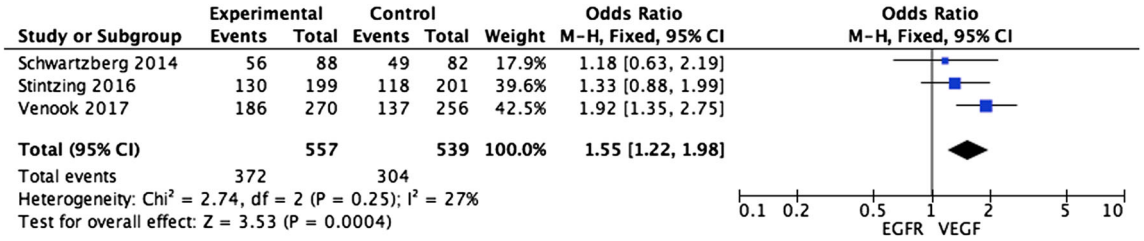

Fig. 7 Pooled analysis of ORR compared anti-EGFR and anti-VEGF therapies in the first-line setting for RAS-WT mCRC

patients. The up-regulation of VEGF associated with the resistance to cetuximab has been proven in experimental models and has become the the use of the second-line anti-VEGF therapy after the first-line anti-EGFR therapy failure [27, 28]. In addition, the data from the previous study reported that the PFS benefit of anti-EGFR therapy relative to anti-VEGF therapy was only available in patients with measurable tumor who are most likely to benefit from objective tumor response to biochemotherapy [29]. Therefore, this result favored that only some subpopulations could draw a PFS benefit by the anti-EGFR therapy.

Moreover, we found that the anti-EGFR therapy was associated with a higher objective response rate compared to anti-VEGF therapy for KRAS-WT mCRC. This effect was even stronger for patients with more extensive RAS analysis who were found to be all RAS-WT after exclusion of rare RAS mutations (KRAS exons 3 and 4 and NRAS exons 2, 3, and 4). Ye et al. [30] also found that cetuximab addition to chemotherapy increase the resectability of liver metastases, response rates, and survival compared with chemotherapy alone in patients with initially unresectable KRAS wild-type colorectal liver metastasis. In contrast, combined the bevacizumab ~~to~~ and oxaliplatin-based chemotherapy did not achieve resectability benefit in the NO16966 trial [31]. This explanation is proven by the CELIM study, in which cetuximab-based triplet increased resectability from 32 to 60% in patients with KRAS wild-type [32].

There are also several limitations of our study. In our meta-analysis did not provide sufficient data between the two antibodies therapies in combination with FOLFOX or FOLFIRI regimen. The imbalance in choice of FOLFOX6 vs FOLFIRI regimens limits the ability to statistically compare the cytotoxic chemotherapy regimens and any possible interaction with the antibodies, so future research are needed to elucidate this association.

Conclusion

Better chemotherapeutic regimens, patient selection, and changing multidisciplinary management likely contributed to these outcomes as did the exclusion of patients with KRAS mutations. The results of our research support the use of first-line anti- EGFR therapy as an alternative option to anti-VEGF therapy in all RAS-WT patients with advanced CRC on the basis of superior ORR and OS benefit. This eligibility change increased the proportion of study patients who are potentially benefit from cetuximab might be the one who improved the prognosis for the entire group by eliminating patients with negatively prognostic RAS mutations (KRAS exons 3 and 4 and NRAS exons 2, 3, and 4).

This result supports the idea that mCRC is a heterogeneous disease and additional novel researches are needed for appropriate targeted triplet in different mCRC subpopulations that benefit from anti-EGFR therapy in the first-line setting. Patient choice is also extremely important. Future research should focus on detailed molecular profiling of CRC tissue with full RAS and even analysis along with biomarkers predictive of response to anti-VEGF therapy. Therefore, further results of randomized phase 3 trials and well- designed studies are needed to define the optimal targeted treatment strategy.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study formal consent is not required.

Informed Consent Not applicable.

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