Original Paper

Efficacy of Bevacizumab in the First-Line Treatment of Patients with *RAS* Mutations Metastatic Colorectal Cancer: a Systematic Review and Network Meta-Analysis

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Key Words

Metastatic colorectal cancer • First line treatment • *RAS* mutations • Network meta-analysis

Abstract

Background/Aims: Whether patients with *RAS* mutation metastatic colorectal cancer (mCRC) obtain benefits from bevacizumab added to first-line chemotherapy remains unclear.

Methods: PubMed, Cochrane Systematic Reviews, the Cochrane Collaboration Central Register of Controlled Clinical Trials, ClinicalTrials.gov, and the American Society of Clinical Oncology and European Society for Medical Oncology databases were searched to identify abstracts for randomized controlled trials (RCTs) evaluating the efficacy of bevacizumab for the first-line treatment of patients with *RAS* mutations mCRC from inception to the end of April 2016. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were estimated. **Results:** Ten eligible papers reporting six RCTs were included. In the network meta-analysis of patients with *RAS* mutations, bevacizumab + chemotherapy prolonged PFS compared with chemotherapy alone (HR 0.75, 95% CI 0.51-1.10), but the difference was not statistically significant. Bevacizumab + chemotherapy did not prolong OS compared with chemotherapy alone (HR 1.10, 95% CI 0.73-1.66). **Conclusion:** There was insufficient evidence to definitively state that patients with *RAS* mutations mCRC could benefit from bevacizumab combined with chemotherapy as first-line treatment.

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Introduction

It has been reported that patients with *RAS* mutations metastatic colorectal cancer (mCRC) have poor prognosis than patients without *RAS* mutations [1]. Additionally, it has

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been shown that *RAS* mutations are negative predictive factors for first-line treatment with an anti-epidermal growth factor receptor (EGFR) combined with chemotherapy [2-4].

Anti-angiogenic treatment is another strategy for the treatment of mCRC. Bevacizumab is a humanized monoclonal antibody (moAb) that can bind to vascular endothelial growth factor (VEGF), and it is currently the most frequently used anti-VEGF moAb [5, 6]. Nowadays, bevacizumab is used in most of the patients with mCRC without previously testing for *RAS* status [7-9]. In a previous study, the median overall survival (OS) of patients with mCRC treated with chemotherapy alone was 13.6-20.7 months [2-4, 9-12]. But the median OS of patients with mCRC treated with bevacizumab combined with chemotherapy, without previous assessment of *RAS* mutations, was 19.9-20.6 months [7-9, 13].

Results of published studies suggest that the addition of bevacizumab to chemotherapy as first-line treatment improved treatment efficacy and OS of patients with mCRC [7-9]. Reportedly, the median OS of patients with *RAS* wild-type mCRC was longer than that of patients with *RAS* mutations [2-4, 7, 8]. However, it remains uncertain whether patients with *RAS* mutations can obtain clinical benefits from the addition of bevacizumab to chemotherapy. This network meta-analysis aimed to assess the efficacy of bevacizumab for the first-line treatment of patients with *RAS* mutations mCRC.

Materials and Methods

Search strategy

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14]. We searched for abstracts of randomized controlled trials (RCTs) evaluating the efficacy of bevacizumab for the first-line treatment of patients with *RAS* mutations mCRC in PubMed, Cochrane Systematic Reviews, the Cochrane Collaboration Central Register of Controlled Clinical Trials, ClinicalTrials.gov, and the American Society of Clinical Oncology and European Society for Medical Oncology databases from inception to the end of April 2016. The bibliographies of included trials and related reviews were revised to identify potential articles, which were searched for manually. In this network meta-analysis, trials that compared two or more first-line treatment strategies of patients with *RAS* mutations mCRC were included.

PubMed. ((“Genes, ras”[MeSH Terms] OR “ras Proteins”[MeSH Terms] OR “KRAS protein,Human”[Supplementary Concept] OR “NRAS protein, Human”[Supplementary Concept] OR “BRAF protein, Human”[Supplementary Concept] OR “Genetic Testing”[MeSH Terms] OR “Mutation*”[MeSH Terms] OR RAS[title/abstract] OR KRAS[title/abstract] OR NRAS[title/abstract] OR BRAF[title/abstract]) AND (“Colorectal Neoplasms”[MeSH Terms] OR “Adenomatous Polyposis Coli”[MeSH Terms] OR “Gardner Syndrome”[MeSH Terms] OR “Colonic Neoplasms”[MeSH Terms] OR “Sigmoid Neoplasms”[MeSH Terms] OR “Colorectal Neoplasms, Hereditary Nonpolyposis”[MeSH Terms] OR “Rectal Neoplasms”[MeSH Terms] OR “Anus Neoplasms”[MeSH Terms] OR “Liver Neoplasms/secondary”[MeSH Terms]) AND (Humans[MeSH Terms] OR Adult[MeSH Terms] OR Aged[MeSH Terms] OR “Middle Aged”[MeSH Terms] OR “Young Adult”[MeSH Terms] OR Male[MeSH Terms] OR Female[MeSH Terms])) AND ((“Organoplatinum Compounds”[MeSH Terms] OR Fluorouracil[Title/Abstract] OR Capecitabine[Title/Abstract] OR Tegafur[Title/Abstract] OR Leucovorin[Title/Abstract] OR Levoleucovorin[Title/Abstract] OR Camptothecin[MeSH Terms] OR Irinotecan[Title/Abstract]) AND (“Antineoplastic Combined Chemotherapy Protocols”[MeSH Terms] OR “Angiogenesis Inhibitors”[MeSH Terms] OR “Receptor, Epidermal Growth Factor”[MeSH Terms] OR “Antibodies, Monoclonal”[MeSH Terms] OR “Antibodies, Monoclonal, Humanized”[MeSH Terms] OR “Proto-Oncogene Proteins”[MeSH Terms] OR “Antibodies, Monoclonal, Murine-Derived”[MeSH Terms] OR “Molecular Targeted Therapy”[MeSH Terms] OR Infliximab[Title/Abstract] OR bevacizumab[Title/Abstract] OR cetuximab[Title/Abstract] OR panitumumab[Title/Abstract] OR ramucirumab[Title/Abstract] OR matuzumab[Title/Abstract] OR aflibercept[Title/Abstract]) AND (“Follow-Up Studies”[MeSH Terms] OR Prognosis[MeSH Terms] OR “Disease-Free Survival”[MeSH Terms] OR “Treatment Outcome”[MeSH Terms] OR “Survival Rate”[MeSH Terms] OR “Response Evaluation Criteria in Solid Tumors”[MeSH Terms])) AND (((“Clinical Trial as topic”[Mesh]) NOT (“Clinical Trial, Phase I”[Mesh] OR “Observational Study as topic”[Mesh])) OR (“Clinical Trial”[Publication Type]) NOT (“Clinical Trial, Phase I”[Publication Type] OR “Observational Study”[Publication Type])) OR Random*).

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American Society of Clinical Oncology database of abstracts. Metastatic colorectal cancer (<http://meetinglibrary.asco.org/abstracts>).

ClinicalTrials.gov. Category: "Carcinoma, Colorectal" (<http://clinicaltrials.gov/>).

Data extraction and assessment for risk of bias

The full manuscripts of eligible studies were reviewed independently by two investigators (Z-MY, Y-P). Information was extracted and inserted into an electronic database, including patient characteristics, inclusion and exclusion criteria, treatment protocols, and outcomes. Any disagreement between reviewers was discussed with other coauthors and corresponding author until a consensus was reached.

Data synthesis and analysis

The outcomes analyzed in this network meta-analysis included progression-free survival (PFS) and OS. Random-effects models were used to account for the heterogeneity among studies.

Traditional meta-analysis was performed using Stata 12.1 (StataCorp, College Station, TX, USA). Network meta-analysis was performed using a netmeta package developed according to the theories of a classical frequentist setting under R language framework.

Results

The title and abstract of 168 studies were reviewed. After the initial screening, we performed a detailed assessment of potentially eligible papers. Finally, 10 papers reporting six RCTs were included (Fig. 1). Table 1 showed the characteristics of these six RCTs. A total of 1,465 patients with mCRC and RAS mutations, receiving first-line treatment, were enrolled and randomized into two groups (treatment vs control), respectively (Table 1). Methodological quality assessment was performed according to the latest guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. The quality of the included studies was high (Table 2).

The network of all the comparisons analyzed is shown in Fig. 2. A total of three regimens from six trials were included in the network. Three studies compared anti-EGFR + chemotherapy and chemotherapy alone. Two studies compared anti-EGFR + chemotherapy and bevacizumab + chemotherapy. One study compared bevacizumab + chemotherapy and chemotherapy alone.

In three studies, PFS was reported as the primary end point (PRIME, CRYSTAL, PEAK) [3, 4, 8, 10, 12], and in three other studies, as the secondary end point (FIRE3, OPUS, AVF2107) [2, 7, 9, 11, 13]. In all included studies, OS was reported as the secondary end point [2-4, 7-13]. The results of direct comparisons are shown

Fig. 1. Literature search and selection of studies. Abbreviation: RCT (randomized controlled trial).

Table 1. Characteristics of the included randomized control trials. Abbreviations: wt (wild type); mt (mutations); Q2W (every 2 weeks); IV (intravenous)

Study	Study design (number of patients)	Treatment schedule	KRAS test	NRAS test
OPUS 2011 [11], 2015 [2]	FOLFOX4+Cetux. (<i>KRAS</i> exon 2-mt: 77; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 15)	Cetux.: initial dose 400 mg/m ² and 250 mg/m ² /week thereafter, Q2W. FOLFOX4: oxaliplatin 85 mg/m ² ; folinic acid 200 mg/m ² ; 5-FU 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 12, 13, 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
	FOLFOX4 (<i>KRAS</i> exon 2-mt: 59; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 16)	FOLFOX4: oxaliplatin 85 mg/m ² ; folinic acid 200 mg/m ² ; 5-FU 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 12, 13, 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
CRYSTAL 2011 [12], 2015 [3]	FOLFIRI+Cetux. (<i>KRAS</i> exon 2-mt: 214; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 32)	Cetux.: initial dose 400 mg/m ² and 250 mg/m ² /week thereafter, followed after 1 hour by FOLFIRI, Q2W. FOLFIRI: irinotecan 180 mg/m ² , day 1, infused over 30–90 minutes; leucovorin 200 mg/m ² L-form, or 400 mg/m ² racemic, infused over 2 hours; fluorouracil 400 mg/m ² IV bolus and 2400 mg/m ² 46-hour continuous infusion, Q2W.	codons 12, 13, 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
	FOLFIRI (<i>KRAS</i> exon 2-mt: 183; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 31)	FOLFIRI: irinotecan 180 mg/m ² , on day 1, infused over 30–90 minutes; leucovorin 200 mg/m ² L-form, or 400 mg/m ² racemic, infused over 2 hours; fluorouracil 400 mg/m ² IV bolus and 2400 mg/m ² 46-hour continuous infusion, Q2W.	codons 12, 13, 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
PRIME 2010 [10], 2013 [4]	FOLFOX4+Panit. (<i>KRAS</i> exon 2-mt: 221; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 51)	Panit.: IV over 1 hour, 6 mg/kg on day 1 before FOLFOX4, Q2W FOLFOX4: oxaliplatin 85 mg/m ² IV infusion on day 1; leucovorin 200 mg/m ² IV infusion; fluorouracil 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 12, 13, 61, 117, 146	codon 12, 13, 61, 117, 146
	FOLFOX4 (<i>KRAS</i> exon 2-mt: 219; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 57)	FOLFOX4: oxaliplatin 85 mg/m ² IV infusion on day 1; leucovorin 200 mg/m ² IV infusion; fluorouracil 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 12, 13, 61, 117, 146	codon 12, 13, 61, 117, 146
FIRE3 2012 [13], 2014 [6]	FOLFIRI+Cetux. (<i>KRAS</i> exon 2-mt: 50; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 34)	Cetux.: initial dose 400 mg/m ² and 250 mg/m ² /week thereafter, Q2W. FOLFIRI: irinotecan 180 mg/m ² , on day 1, infused over 30–90 minutes; leucovorin 200 mg/m ² L-form, or 400 mg/m ² racemic, infused over 2 hours; fluorouracil 400 mg/m ² IV bolus and 2400 mg/m ² 46-hour continuous infusion, Q2W.	codons 12, 13, 61, 146	codons 12, 13, 59, 61, 117, 146
	FOLFIRI+bevacizumab. (<i>KRAS</i> exon 2-mt: 46; <i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 31)	Bevacizumab: 5 mg/kg, Q2W. FOLFIRI: irinotecan 180 mg/m ² , on day 1, infused over 30–90 minutes; leucovorin 200 mg/m ² L-form, or 400 mg/m ² racemic, infused over 2 hours; fluorouracil 400 mg/m ² IV bolus and 2400 mg/m ² 46-hour continuous infusion, Q2W.	codons 12, 13, 61, 146	codons 12, 13, 59, 61, 117, 146
PEAK 2014 [8]	FOLFOX6+Panit (<i>KRAS</i> exon2-wt but other <i>RAS</i> -mt: 24)	Cetux.: initial dose 400 mg/m ² and 250 mg/m ² /week thereafter, Q2W. FOLFOX4: oxaliplatin 85 mg/m ² IV infusion on day 1; leucovorin 200 mg/m ² IV infusion; fluorouracil 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
	FOLFOX6+bevacizumab. (<i>KRAS</i> exon 2-wt but other <i>RAS</i> -mt: 27)	Bevacizumab: 5 mg/kg, Q2W. FOLFOX4: oxaliplatin 85 mg/m ² IV infusion on day 1; leucovorin 200 mg/m ² IV infusion; fluorouracil 400 mg/m ² IV bolus and 600 mg/m ² 22-hour continuous infusion on days 1 and 2, Q2W.	codons 59, 61, 117, 146	codons 12, 13, 59, 61, 117, 146
AVF 2107 [9]	IFL+bevacizumab. (<i>KRAS</i> exon 2-mt: 44)	Bevacizumab IFL: irinotecan, leucovorin, and leucovorin	codons 12, 13	-
	IFL+placebo. (<i>KRAS</i> exon 2-mt: 34)	Placebo IFL: irinotecan, leucovorin, and leucovorin	codons 12, 13	-

in Fig. 3. Only comparison of PFS and OS in patients with *RAS* mutations between anti-EGFR + chemotherapy and chemotherapy showed significance (Fig. 3).

Pooled HRs of PFS of patients with *RAS* mutations for individual regimens compared with chemotherapy in the network meta-analysis showed an advantage for bevacizumab + chemotherapy (HR 0.75, 95% CI 0.51–1.10) and no benefit for anti-EGFR + chemotherapy (HR 1.19, 95% CI 0.94–1.51), but the difference was not statistically significant (Fig. 4A).

Table 2. Methodological quality of included RCTs. ITT (intention to treat). Unclear reporting of allocation was considered inadequate

study	Sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other risk of bias
OPUS 2011	adequate	adequate	Not report	yes	no	no	no
OPUS 2015	adequate	adequate	Not report	yes	no	no	no
CRYSTAL 2011	adequate	adequate	Not report	yes	no	no	no
CRYSTAL 2015	adequate	adequate	Not report	yes	no	no	no
PRIME 2010	adequate	adequate	Not report	yes	no	no	no
PRIME 2013	adequate	adequate	Not report	yes	no	no	no
FIRE3 2012	adequate	adequate	Not report	yes	no	no	no
FIRE3 2014	adequate	adequate	Not report	yes	no	no	no
PEAK 2014	adequate	adequate	Not report	yes	no	no	no
AVF2107	adequate	adequate	Not report	yes	no	no	no

Fig. 2. Network of the comparisons for the network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments.

Fig. 3. Pooled HRs by traditional meta-analysis. PFS (A) and OS (B) of patients with RAS mutations mCRC. Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal cancer.

Pooling of HRs of OS of patients with RAS mutations for individual regimens compared with chemotherapy in the network meta-analysis showed no benefit for bevacizumab + chemotherapy (HR 1.10, 95% CI 0.73-1.66) and anti-EGFR + chemotherapy (HR 1.11, 95% CI 0.86-1.42) (Fig. 4B).

Fig. 4. Pooled HRs by network meta-analysis. PFS (A) and OS (B) of patients with RAS mutations mCRC. Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal.

Fig. 5. Pooled HRs for PFS and OS. PFS (A) and OS (B) of patients with RAS mutations mCRC. The column treatment is compared with the row treatment. Numbers in parentheses indicate 95% credible intervals. HRs with p value less than 0.05 are in bold. Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal.

Results of random-effects network meta-analysis for PFS and OS are summarized in Fig. 5. For patients with RAS mutations, bevacizumab + chemotherapy significantly prolonged PFS compared to anti-EGFR + chemotherapy (HR 0.63, 95% CI 0.45-0.89) (Fig. 5).

Discussion

This network meta-analysis compared the efficacy of chemotherapy in combination with bevacizumab or anti-EGFR mAb to chemotherapy in patients with RAS mutations mCRC ($N = 1,465$). The present results suggest that evidence is insufficient to definitively state that bevacizumab + chemotherapy would not provide any advantage to patients with RAS mutations over anti-EGFR mAb or chemotherapy alone.

In the network meta-analysis of patients with RAS mutations, bevacizumab + chemotherapy prolonged PFS compared with chemotherapy alone and anti-EGFR + chemotherapy, but the difference was not statistically significant. Both bevacizumab + chemotherapy and anti-EGFR + chemotherapy experienced did not prolong OS of patients with RAS mutations compared with chemotherapy alone. Several reasons could explain the benefit of bevacizumab + chemotherapy in terms of PFS rather than OS. First, the primary end points of most involved RCTs included PFS rather than OS. Further, PFS reflects the effectiveness of the first-line therapy. Thus, PFS might be a more appropriate primary end point for the first-line treatment of mCRC. Second, OS was likely to be influenced by multiple factors, including subsequent treatments. Third, the sample size of patients with RAS mutations was still overly small for the difference to reach statistical significance.

Results of several clinical trials indicated that all patients without RAS status testing may benefit from the combination of bevacizumab and chemotherapy. The AVF2107 study

was the first phase III study to suggest that the efficacy of the anti-VEGF moAb bevacizumab in the first-line treatment of mCRC was independent of *KRAS* status, unlike anti-EGFR moAb [9]. In 2008, the No. 16966 trial, a randomized phase III study, evaluated the efficacy of bevacizumab in combination with oxaliplatin-based chemotherapy as first-line treatment for mCRC without previously testing for *RAS* status. The No. 16966 trial suggested that the addition of bevacizumab improved PFS of patients, but the difference did not reach statistical significance [15]. The FIRE3 study was the first head-to-head randomized phase III clinical trial to compare the efficacy of bevacizumab and anti-EGFR moAb in combination with an irinotecan-containing regimen for the first-line treatment of mCRC. The FIRE3 study suggested that there was no difference of efficacy between bevacizumab + chemotherapy and anti-EGFR moAb + chemotherapy for patients with *RAS* mutations [7]. These results were consistent with the result of our network meta-analysis. However, the results of the PEAK study were inconsistent with this trend. The PEAK study was the first head-to-head randomized phase II clinical trial to compare the efficacy of bevacizumab and anti-EGFR moAb in combination with an oxaliplatin-containing regimen for the first-line treatment of mCRC. The PEAK study suggested that the addition of bevacizumab in an oxaliplatin-containing regimen resulted in a better PFS but worse OS in patients with *RAS* mutations [8]. The resulting improved OS in the anti-EGFR moAb arm was explained by the high percentage of patients that received subsequent chemotherapy and anti-VEGF treatment in this arm. Because the OS curves in these studies separated after approximately 2 years, it seems that the following treatment contributed to the OS difference. Additionally, only 51 patients with other *RAS* mutations were enrolled in the PEAK study. Moreover, significant heterogeneity may exist between this phase II study and other phase III studies. The median OS of patients with *RAS* mutations that received anti-EGFR combined with chemotherapy was 27 months in the PEAK study, but it ranged from 13.5 to 20.3 months in other studies. Furthermore, the CALGB 80405 study was another head-to-head randomized phase III clinical trial that compared whether there was a clinical benefit of adding bevacizumab or anti-EGFR moAb to chemotherapy. However, the data for treatment outcomes of patients with *RAS* mutations in the CALGB 80405 study have not been published yet.

In 2010, Loupakakis et al. published a meta-analysis that included the AVF2107 and No.16966 trials, along with two other studies, and aimed to analyze the benefit of adding bevacizumab to chemotherapy as first-line treatment for mCRC [16]. They suggested that the addition of bevacizumab prolonged both PFS and OS by 17.1% and 8.6%, respectively. The studies involved in this meta-analysis included phase II and III clinical trials. Of note, *RAS* status was not evaluated in that meta-analysis. As far as we know, no previous meta-analyses aimed to compare the benefit of bevacizumab and anti-EGFR combined with chemotherapy as first-line treatment for mCRC. This network meta-analysis is the first to assess the clinical benefit of bevacizumab combined with chemotherapy, anti-EGFR combined with chemotherapy and chemotherapy alone for the first-line treatment of patients with *RAS* mutations mCRC.

Petrelli et al. published a meta-analysis in 2015 that aimed to find the predictors of clinical outcome of bevacizumab in combination with chemotherapy for the first-line treatment of mCRC [17]. They suggested that mCRC with *KRAS* mutations have high risk of death compared with patients with *KRAS* wild-type. This conclusion was drawn based on the pooled HRs of three studies. All patients in these three studies were treated with bevacizumab in combination with chemotherapy. Patients were stratified by *KRAS* status. Median OS was 17.98 months in patients with *KRAS* mutations and 26.73 months in patients without *KRAS* mutations.

Our network meta-analysis had several strengths. This study was the first comprehensive comparative study of all the present major strategies for the first-line treatment of patients with *RAS* mutations mCRC. Both PFS and OS were assessed in both a traditional meta-analysis and a network meta-analysis. The traditional meta-analysis performed a direct comparison between the two strategies, with little heterogeneity. However, only the AVF2107 study compared bevacizumab + chemotherapy with chemotherapy alone among the patients with

KRAS exon 2 mutations [9]. No previous studies compared bevacizumab + chemotherapy with chemotherapy alone in the patients with *KRAS* exon 2 wild-type but other *RAS* mutations and patients with any *RAS* mutations. This network meta-analysis provided an indirect comparison of bevacizumab + chemotherapy and chemotherapy alone when this direct comparison was not previously available. Additionally, bevacizumab + chemotherapy was suggested to prolong the PFS of patients with *RAS* mutations mCRC compared with chemotherapy alone.

Our network meta-analysis also had several limitations. First, the primary end points of all the RCTs did not include OS. The OS might be influenced by multiple factors. In this network meta-analysis, there was no difference between the OS achieved by treatment with bevacizumab + chemotherapy and chemotherapy alone for patients with *RAS* mutations mCRC. Thus, the OS of patients with *RAS* mutations mCRC treated with bevacizumab + chemotherapy should be further investigated. Second, because *RAS* testing was unnecessary for the recent application of bevacizumab, the sample size of patients with *RAS* mutations mCRC treated with bevacizumab was still small. In the future, the conduction of RCTs with large sample sizes is required. Third, indirect comparison in network meta-analysis would increase bias.

In conclusion, there was insufficient evidence to definitively state that patients with *RAS* mutations mCRC could benefit from bevacizumab combined with chemotherapy as first-line treatment.

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Disclosure Statement

There is no conflict of interest.

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