



Original Research

Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis



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KEYWORDS

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Abstract Background: This systematic review and meta-analysis aims to evaluate the additive effect of bevacizumab when combined with first-line chemotherapy in metastatic colorectal cancer (mCRC).

Methods: We searched EMBASE, MEDLINE, the Cochrane Library in April 2018. When possible, data were pooled to estimate summary effects. The present analysis evaluated treatment related efficacy based on progression-free survival (PFS) and overall survival (OS). The analysis was performed to define the overall effect and the effect observed in currently used chemotherapy regimens.

Results: Seven randomised studies were included. In the analysis of the overall effect, PFS (hazard ratio [HR] 0.71, $p < 0.00001$) and OS (HR 0.85, $p = 0.0008$) clearly favoured bevacizumab plus chemotherapy versus chemotherapy alone. When the analysis was focused on currently used chemotherapy excluding 5-FU bolus regimens and including only infusional 5-FU plus irinotecan or oxaliplatin, the addition of bevacizumab prolonged PFS (HR 0.79, $p < 0.0001$) but not OS (HR 0.92, $p = 0.18$). However, addition of bevacizumab to

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fluoropyrimidine monotherapy lead to a significant prolongation of PFS (HR 0.57, $p < 0.00001$) and OS (HR 0.83, $p = 0.03$).

Conclusion: The present meta-analysis demonstrates that the effect of bevacizumab on survival is not consistent throughout the included regimens. Considering only presently used regimens, a significant effect on PFS and OS was only observed when bevacizumab was added to fluoropyrimidine monotherapy.

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1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer worldwide with 1.36 million people affected globally, accounting for nearly 10% of cancers [1,2]. Nearly 20% of patients present with de novo metastatic disease, and 25%–30% of patients with stage II/III disease have a recurrence within five years of a curative intent surgery [3].

Metastatic CRC (mCRC) requires systemic treatment in the majority of patients. Over the past 10 years, various combinations of chemotherapies have been studied for treatment of mCRC, and the availability of combination chemotherapy and targeted agents has markedly improved overall survival (OS) of mCRC patients. Current treatment typically consists of a fluoropyrimidine-based doublet (FOLFOX/CAPOX or FOLFIRI/CAPIRI) or fluoropyrimidine monotherapy (5-FU/folinic acid or capecitabine) combined with a biological agent targeting either the vascular endothelial growth factor (VEGF) in an unselected population or the epidermal growth factor receptor (EGFR) in patients with *RAS* wild-type tumours [4,5].

The presently available evidence suggests that FOLFIRI and FOLFOX are comparable with regard to efficacy but differ with regard to toxicity [4,5].

In the continuum of care, first-line (compared with later line) treatment is typically associated with the greatest effect on tumour response (ORR) and progression-free survival (PFS). Accordingly, first-line treatment expectably has the greatest impact on OS [6]. Optimal choice of first-line treatment is important because it affects the tumour in its most sensitive phase. As a result, treatment effects that are missed in the first line cannot be induced at the same level in the second line. It is now common sense that outcome can be optimised by the choice of first-line targeted therapy which also determines the sequence of targeted therapies in later treatment lines. By contrast, the choice of the chemotherapy backbone (FOLFOX versus FOLFIRI) seems to have little effect on the outcome [7].

The present meta-analysis focusses on the effect of bevacizumab on the outcome when added to first-line chemotherapy. This agent is currently the most frequently used VEGF-directed monoclonal antibody (mAb), and it is the only one approved for first-line treatment of mCRC [8]. As per its approved indication,

bevacizumab can be used independent of the *RAS* mutation status or primary tumour sidedness. The present meta-analysis asks the question if the presently published evidence is sufficient to provide the basis for default use of bevacizumab in combination first-line chemotherapy. To this end, the randomised studies investigating the benefit from bevacizumab were categorised based on three different strata: (I) all evaluable studies, (II) studies combining bevacizumab with a fluoropyrimidine (5-FU/folinic acid, capecitabine) and (III) studies combining bevacizumab with standard infusional 5-FU-based combination chemotherapy (FOLFOX or FOLFIRI). Stratum III thus explicitly excludes regimens based on bolus 5-FU application such as the IFL (irinotecan/bolus 5-FU/LV) regimen that is not any more recommended by presently active guidelines (Fig. 1).

2. Materials and methods

This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (www.prisma-statement.org) [9].

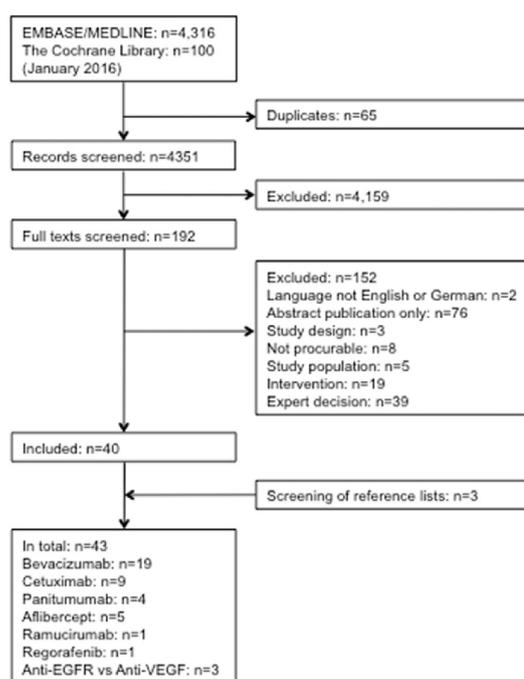


Fig. 1. A flowchart of the literature search and study selection procedure.

2.1. Data sources and searches

MEDLINE and EMBASE were searched via Elsevier and the Cochrane Library in January 2016. Searches were updated in May 2018. Owing to the fact that this systematic meta-analysis was performed in the course of the preparation of an evidence-based national clinical guideline, the searches included several antibody-based and multikinase inhibitor-based therapies: bevacizumab, aflibercept, cetuximab, panitumumab and regorafenib (Fig. 1). A highly sensitive search strategy was used that included both medical subject headings and free-text terms (e.g. ‘colorectal cancer’, ‘colorectal neoplasms’, ‘bevacizumab’, ‘metast*’, ‘randomised controlled trial’ and so on.) (see [Supplementary Table S1](#) for complete search strategy). The searches were limited to publications in German and English.

2.2. Study selection

Two reviewers independently screened titles, abstracts and full-texts and decided on the eligibility of publications. Any disagreements were resolved by discussion. We considered randomised controlled trials (RCTs) comparing chemotherapy plus bevacizumab with chemotherapy alone or plus bevacizumab. Patients had to be ≥ 18 years old with cytological or histological diagnosis of mCRC without prior chemotherapy (only in first-line treatment); non-randomised studies, cohort studies, case-control studies, cross-sectional studies, abstract publications and unpublished studies were excluded. The main outcomes of interest were symptoms of depression and anxiety and associations with diabetes management and glycaemic control. A complete list of included and excluded articles is available by request from the corresponding author.

2.3. Objectives

The primary objective of this meta-analysis was to estimate the relative impact of bevacizumab on survival parameters when added to first-line chemotherapy in patients with mCRC from RCTs.

2.4. Data extraction and risk of bias assessment

We extracted the following data: first author, year of publication, sample size, primary endpoint and results on OS and PFS. We assessed the risk of bias using the Cochrane Collaboration’s ‘Risk of Bias’ tool for RCTs using the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [10]. Based on the information given by the journal publications, we judged each domain in each study as low risk of bias, high risk of bias or unclear risk of bias.

The primary endpoints were PFS (defined as time from randomisation to either death or disease progression, whichever occurred first) or OS. If data on PFS were not available, data on time to progression or event-free survival were assessed.

2.5. Data synthesis and analysis

Dichotomous clinical outcomes are reported as risk ratio (RR) and survival data as hazard ratio (HR) [11].

We performed pooled analyses by using indirect methods as described by Parmar *et al.*, Tierney *et al.* and Williamson *et al.* leading to fixed-effects meta-analyses which may be less prone to bias than random-effects models in estimates of natural logarithm of the hazard ratio (lnHRs) [11–14]. If the variance was not reported, confidence intervals (CIs) were used to approximate the variance of the reported lnHR (V^* = variance of the ln(HR)).

$$V^* = \frac{\ln(\text{upper CI}) - \ln(\text{lower CI})}{[2 \times z \text{ score for upper CI boundary}]^2}$$

The reciprocal of the variance of the lnHR (estimated variance, V) was then used to obtain the $O - E$ ($\ln(\text{HR}) \times V = O - E$) [12].

Meta-analyses were performed using Review Manager software (version 5.3) calculating heterogeneity by χ^2 and I^2 statistics. Differences with a p value < 0.05 were considered relevant.

3. Results

3.1. Literature review

Our search identified 4316 citations of which nine studies compared OS and PFS in patients with mCRC receiving either chemotherapy alone or chemotherapy with bevacizumab in the first line, five studies in the second line and five studies in the maintenance therapy (Fig. 1). Finally, seven studies exploring the first-line efficacy of bevacizumab in combination with chemotherapy compared with chemotherapy alone were included into the analysis [15–21] (Table 1). Studies by Kabbavinar *et al.* and Stathopoulos *et al.* were excluded from the meta-analysis because of missing information about the HR, the number of events and exact p-values [22,23].

3.2. Risk of bias assessment

Four of seven publications did not describe randomisation sequence generation leading to an unclear risk of bias (Fig. 2) [15,16,20,21]. Allocation concealment was reported by Cunningham *et al.*, Guan *et al.*, Kabbavinar *et al.* and Saltz *et al.* in an adequate manner [15–17,20]. Owing to lack of information, the assessment for the remaining studies was ‘unclear risk of bias’. We

Table 1
Characteristics of randomised studies evaluating bevacizumab plus chemotherapy in patients with mCRC in first-line chemotherapy.

Publication	Cunningham et al 2013	Guan et al 2011	Hurwitz et al 2004	Kabbinavar et al 2005	Passardi et al 2015	Saltz et al 2008	Tebbutt et al 2010
Study type	Phase III	Phase III	Phase III	Phase III	Phase III	Phase III	Phase III
Number of patients	280	203	813	209	370	1400	313
Control	Cape	IFL	IFL	5-FU/LV	FOLFOX or FOLFIRI	XELOX or FOLFOX	Cape
Experimental	Cape/Bev	IFL/Bev	IFL/Bev	5-FU/LV/Bev	FOLFOX or FOLFIRI/Bev	XELOX or FOLFOX/Bev	Cape/Bev
Primary endpoint	PFS	PFS	OS	OS	PFS	PFS	PFS
PFS	5.1 vs. 9.1	4.2 vs. 8.3	6.2 vs. 10.6	5.5 vs. 9.2	8.4 vs 9.6	8 vs. 9.4	5.7 vs. 8.5
HR for PFS	0.53 (0.41–0.69)	0.44 (0.31–0.63)	0.54 (0.37–0.78)	0.50 (0.35–0.73)	0.86 (0.70–1.07)	0.83 (0.72–0.95)	0.63 (0.50–0.69)
OS	20.7 vs. 16.8	13.4 vs. 18.7	15.3 vs. 20.6	12.9 vs. 16.6	20.8 vs. 21.3	19.9 vs. 21.3	
HR for OS	0.79 (0.57–1.09)	0.62 (0.41–0.95)	0.66 (0.52–0.85)	0.79 (0.56–1.10)	1.13 (0.89–1.43)	0.89 (0.76–1.03)	0.88 (0.68–1.13)

HR: hazard ratio; OS: overall survival; PFS: progression-free survival; Bev: bevacizumab.

	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)	Selective reporting (reporting bias)	Other bias
Cunningham et al. 2013	?	+	+	+	+	+	+
Guan et al. 2011	?	+	+	+	+	+	+
Hurwitz et al. 2004	+	?	?	+	+	+	+
Kabbinavar et al. 2005	+	+	?	+	+	+	+
Passardi et al. 2015	+	?	+	+	+	+	+
Saltz et al. 2008	?	+	?	+	+	+	+
Tebbutt et al. 2010	?	?	+	+	+	+	+

Fig. 2. A summary of risk of bias for each randomised trial assessed by the Cochrane Collaboration's tool.

judged four studies as being at high risk of performance bias because of lack of blinding of participating patient and personnel [15,16,18,21], and three studies at unclear risk in this regard [19,17,20] (Fig. 2). Focussing on OS and PFS, we considered risk of detection bias as being low for all studies. With the exception of the studies by Guan *et al.* [16], Kabbinavar *et al.* [17] and Tebbutt *et al.* [21], who did not report data handling of patients dropping out or being lost to follow-up, the study authors described an intention-to-treat analysis minimising attrition bias and leading to a 'low risk of bias' judgement [16,17,21]. In general, there was low risk of bias due to selective reporting. All studies were affected by high risk of bias due to other potential sources. The main reason was funding or honoraria by pharmaceutical companies, and authors being employed by or holding stock in pharmaceutical companies.

3.3. Characteristics and results of included studies

3.3.1. Studies investigating the addition of bevacizumab to chemotherapy

The meta-analytical results of seven available studies (2040 patients) evaluating the combination of bevacizumab plus chemotherapy for first-line treatment of mCRC demonstrated that addition of bevacizumab to a

5-FU-containing chemotherapy (monotherapy or combination therapy) significantly increased PFS (HR, 0.71; 95%CI, 0.65–0.77; $p < 0.00001$) and OS (HR, 0.85; 95%CI, 0.78–0.94; $p = 0.0008$) [15–20] (Figs. 3I and 4I). The study of Hurwitz *et al.* was excluded from the calculation of PFS because of missing information on the HR and CIs [19].

When the analysis was confined to fluoropyrimidine monotherapy (5-FU bolus, infusional 5-FU or capecitabine), the addition of bevacizumab led to a significant prolongation of PFS (HR, 0.57; 95%CI, 0.48–0.66; $p < 0.00001$) and OS (HR, 0.83; 95%CI, 0.70–0.98; $p = 0.03$) [15,17,21] (Figs. 3II and 4II).

By contrast, when the analysis was focussed on currently used standard chemotherapy regimens based on infusional 5-FU in combination with irinotecan or oxaliplatin, and when 5-FU bolus regimens were excluded from the analyses, the addition of bevacizumab only induced a significant increase of PFS (HR, 0.79; 95%CI, 0.71–0.88; $p < 0.0001$), but not of OS (HR, 0.92; 95%CI 0.81–1.04; $p = 0.18$) [16,18,20] (Figs. 3III and 4III).

4. Discussion

Access to all active drugs has been demonstrated to be an optimal strategy to obtain optimised survival [24]. Present guidelines consider the combination of bevacizumab or cetuximab/panitumumab plus chemotherapy with 5-FU, oxaliplatin or irinotecan as a standard option for first-line treatment of mCRC [4,5]. For patients with *RAS*-mutant tumours and those with *RAS*-wild-type right-sided primaries, first-line therapy with bevacizumab plus chemotherapy gains even greater significance.

The efficacy of bevacizumab added to chemotherapy is well supported by multiple clinical studies and has previously been investigated by manifold reviews and meta-analytic studies [25–34]. Their overall statement was that bevacizumab increases PFS and OS in first-line chemotherapy of mCRC patients.

Our meta-analysis differs from previously published reports by the selection of studies and a strict focus on first-line therapy. Three of ten previous analyses incorporated both, adjuvant and second line, therapies and

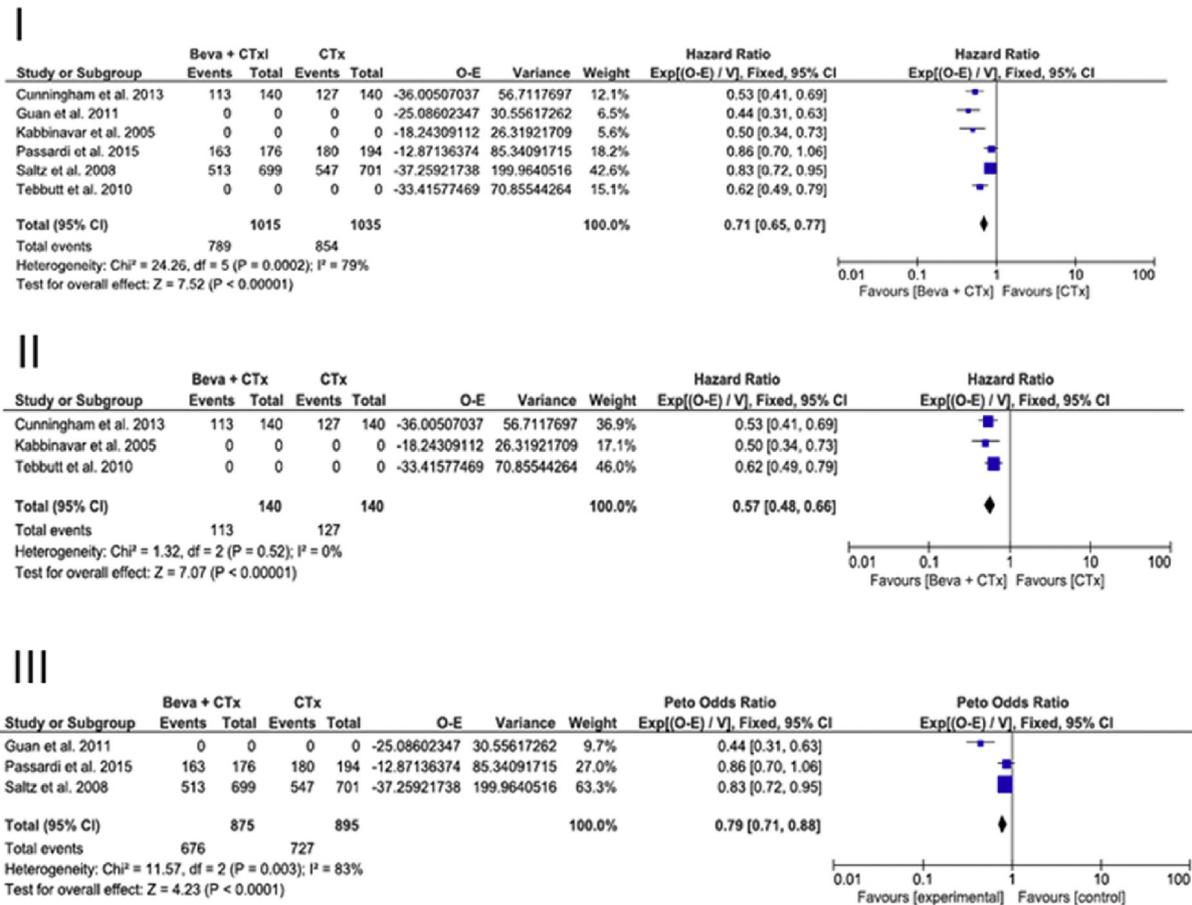


Fig. 3. Comparative effect on PFS of chemotherapy with bevacizumab versus chemotherapy alone. Stratum I: all includes studies with chemotherapy ± bevacizumab; stratum II: regimen with 5-FU monotherapy (bolus) or capecitabine monotherapy ± bevacizumab; stratum III: regimen with infusional 5-FU with irinotecan or oxaliplatin ± bevacizumab. SE: standard error; 95% CI: 95% confidence interval; Chi²: Chi-squared test; df: degree of freedom; Tau²: Tau-squared; I²: I-squared; P: Probability; 0: n.s.; Beva: bevacizumab; CTx: chemotherapy.

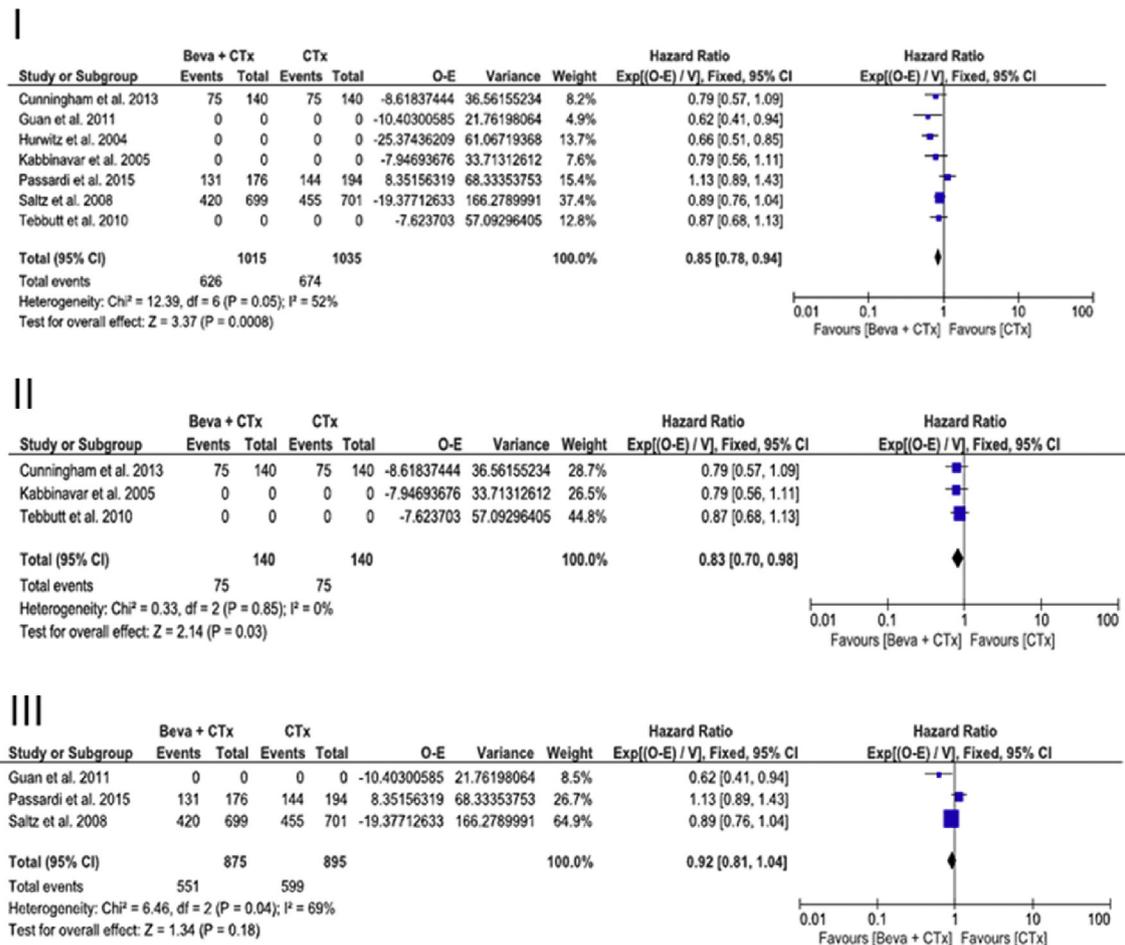


Fig. 4. Comparative effect on OS of chemotherapy with bevacizumab versus chemotherapy alone. Stratum I: all included studies with chemotherapy \pm bevacizumab; stratum II: regimen with 5-FU monotherapy (bolus) or capecitabine monotherapy \pm bevacizumab; stratum III: regimen with infusional 5-FU with irinotecan or oxaliplatin \pm bevacizumab. SE: standard error; 95% CI: 95% confidence interval; Chi^2 : Chi-squared test; df : degree of freedom; Tau^2 : Tau-squared; I^2 : I-squared; P : probability; 0: n.s.; Beva: bevacizumab; CTx: chemotherapy.

were not focused on first-line treatment [26,30,33]. Nine meta-analyses [25,27–34] included studies that did not provide complete information about the HR, the number of events or exact p-values. The present meta-analysis excluded the studies by Kabbinavar *et al.* [22] and Stathopoulos *et al.* [23] for that reason.

The present evaluation applies a more selective approach taking into consideration not only the available studies as a whole but also focussing on the presently recommended and used regimens. This critical view excludes those studies that investigated regimens presently regarded as obsolete because of toxicity. As a consequence, the present analysis was limited to studies using either fluoropyrimidine monotherapy or combination regimens based on infusional 5-FU (FOLFOX or FOLFIRI) as a chemotherapy backbone. Following this line of differentiated evaluation, we realise that the contribution of bevacizumab to the efficacy of the treatment clearly varies dependent on the chemotherapy regimen. The addition of bevacizumab to infusional 5-FU combined with irinotecan or oxaliplatin increases PFS but does not improve OS. By contrast, a

concordant increase of both, PFS and OS, was reached only by the addition of bevacizumab to single-agent fluoropyrimidines. This finding is consistent with a previous meta-analysis reported by Pinto *et al.* [35].

It is certainly an unresolved challenge to define the true effect of first-line chemotherapy on OS. This is even more true with regard to the analysis of a single agent such as bevacizumab and its potentially complex interaction with chemotherapy. Relevant answers to this question can be expected only in the context of data from subsequent chemotherapy and interventions applied within the continuum of care. Unfortunately, data on sequences of therapy are incompletely collected and rarely described in the available studies.

With regard to an evaluation of the therapeutic efficacy of bevacizumab, it must also be taken into consideration, that OS was evaluated as a primary study endpoint in only two of seven studies [19,17]. In fact, PFS was the primary endpoint of most trials [15,16,18,20,21], limiting the possibility for identification of an OS improvement by bevacizumab-containing regimens. Furthermore, crossover to bevacizumab occurred in some trials [15,20] and

was not allowed in others [17,19]. Some trials have not reported the possible crossover [16,18,21].

Certainly, it must be considered that the present meta-analysis takes an exploratory approach that implies some potential biases; all trials were affected by methodological flaws leading to risk of bias. We found an unclear risk of selection bias because of a poor description of the process of allocation. We judged performance bias because of lack or unclear blinding of participants and personnel being of high risk because it can be assumed that additional therapies will affect patients and personnel in terms of hope and will to survive. We considered a high risk of bias because of funding or honoraria by pharmaceutical companies. More particularly, the potential for conflicts of interest increases in combination with substantial funding [36]. It is not without reason that highly ranked scientific journals require an appropriate and comprehensive disclosure of conflicts of interest and that the Committee on Publication Ethics was established in 1997. In addition, ‘publication bias’ may lead to an under-reporting of negative study results. In addition, a tendency for editors and reviewers could be found to preferably accept ‘positive-data’ [37]. On the other hand, the constantly rising flood of scientific publications may jeopardise the availability of top level peer-review because experts in their respective fields become rare. Thus, the capacities of excellent peer review should not be over-estimated, and the impact of pharmaceutical industry on published content should be monitored closely. A further basic limitation of our meta-analysis is the lack of individual patient data. Moreover, the literature search was limited to English and German language studies only.

In conclusion, the present meta-analysis of seven randomised clinical studies showed that the addition of bevacizumab induced a consistent prolongation of PFS in all studies. However, prolongation of OS was achieved only in combination with fluoropyrimidine monotherapy, whereas this was not the case when bevacizumab was added to infusional combination therapy regimens. Prospective examination of survival benefit from the addition of bevacizumab to standard chemotherapy in the first-line setting is clearly needed, not only with regard to the optimal sequence of targeted therapy but also with regard to the molecularly defined subgroups of mCRC where treatment is applied.

Author contribution statement

A.B., W.S., B.B., U.G. and C.P. designed the research. W.S., B.B., A.B., V.H., C.P., U.G. and J.H. analyzed the results. A.B., V.H., W.S. and B.B. wrote the paper.

Conflict of interest statement

A.B. has received honoraria for lectures from Amgen, Merck Serono, Roche and Servier. C.P. has received

honoraria for lectures from Falk, Hitachi, Immunodiagnosics and Roche. U.G. has consulted for Novartis, Merck KGaA, Amgen, Hexal and Bristol-Myers Squibb; has received honoraria from Servier, Boehringer Ingelheim, Sirtex and Daiichi Sankyo and has received travel support from Merck KGaA and Amgen. J.W.H. has received honoraria for advisory board and speaker from Roche and travel support from Novartis. W.S. consulted for AiCuris, Amgen, Apceh, AstraZeneca, Indivumed, Merck Serono, Roche and 4SC and received honoraria for lecture from Abbott, Falk Foundation, GSB GmbH, Lilly Deutschland GmbH, Merck Serono, Pfizer, Roche and Sanofi Aventis. V.H. consulted for Merck KGaA, Roche AG, Amgen, Sanofi, Lilly, SIRTEX, Boehringer Ingelheim, Taiho, Shire and Servier; he received honoraria for lectures from Merck KGaA, Roche AG, Amgen, Sanofi, SIRTEX, Shire, Servier, BMS and MSD and he received funding for research from Merck KGaA, Pfizer, AMGEN, Roche, Shire, Servier and SIRTEX. The remaining authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2018.10.009>.

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