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Review Article

Protracted inhibition of vascular endothelial growth factor signaling improves survival in metastatic colorectal cancer: A systematic review

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ABSTRACT

Clinical data suggest that beyond-progression, the blockade of angiogenesis is associated with improved survivals in colorectal cancer. We conducted a systematic review to investigate the therapeutic effects of antiangiogenic drugs administered as later lines of treatment in patients already progressed to a previous anti-VEGF based treatment. An extensive literature search was conducted. Hazard ratios (HR) for progression (PFS) and death (OS) were extracted. An inverse-variance meta-analysis model was implemented. 6 randomized controlled trials were retrieved, including 3407 patients, treated with different antiangiogenic drugs. All of them had progressed during or after a previous line of treatment with bevacizumab. Overall, both PFS (HR=0.63, *P* <0.001) and OS (HR=0.81 , *P* < 0.001) were significantly increased with the use of antiangiogenic drug. No heterogeneity was observed despite different drugs. Protracted inhibition of the VEGF pathway is associated with a significant improvement of both PFS and OS, independently from the antiangiogenic agent used.

Key words: colorectal cancer, angiogenesis, beyond-progression, systematic review

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INTRODUCTION

Angiogenesis is a critical step in colorectal cancer growth, progression and metastasization. The process of blood vessels formation involves many different molecules and pathways. Among these, the vascular endothelial growth factors (VEGFs) driven pathway is one of the most powerful and better studied.[1] VEGFs comprises a family of multiple growth factors that act through the activation of at least three different receptors.[2] In a landmark trial, the anti-VEGF-A monoclonal antibody bevacizumab improved progression-free survival (PFS) and overall survival (OS) when added to IFL chemotherapy for the treatment of metastatic colorectal cancer patients.[3] Since then, many studies confirmed the benefit of bevacizumab when added to both first- and second-line chemotherapy.[4,5] More recently, other drugs able to inhibit the VEGFR signaling showed efficacy, like the VEGF-trap Aflibercept, the anti VEGFR-2 Ramucirumab, and the tyrosine kinase receptor inhibitor (TKI) Regorafenib.[6-8] There are uncertainties regarding the best duration of an antiangiogenic treatment. Resistance to antiangiogenic agents can develop, mainly through the activation of other pathways like fibroblast growth factor (FGF) and platelet derived growth factor (PDGF).[9] Some authors have argued that, since resistance is established, the sudden suspension of the antiangiogenic drug can rapidly increase blood vessels formation, with more pronounced angiogenesis and faster progression, suggesting possible benefits from longer treatment durations.[10] Recently, two randomized trials investigated the administration of

bevacizumab beyond progression.[11,12] In these studies, patients progressed after the failure of a bevacizumab-based first line chemotherapy were randomized to continuation or suspension of bevacizumab. The chemotherapy backbone was changed. They both showed that continuation of bevacizumab can effectively improve survival, even if to a small amount. In order to verify if this strategy could be generalized to all the VEGF-targeting drugs, we conducted a systematic review of all the literature available regarding the administration of antiangiogenic drugs targeting VEGF pathway after failure of a previous antiangiogenic therapy and assess if, and to what extent, a survival benefit is present.

METHODS

PubMED and EMBASE have been searched for randomized controlled trials and meta-analysis using different combinations of the following terms, with no search filter: "metastatic", "colon", "angiogenesis", "colorectal", "vascular endothelial growth factor", "beyond progression"; "Bevacizumab", "Regorafenib", "Aflibercept" and "Ramucirumab". Meta-analysis and previous systematic reviews were also searched using the same combinations with filters for "review", "meta-analysis" or "systematic review". References of the retrieved publications were screened. Abstract and poster presented at the American Society of Clinical Oncology (ASCO) annual meetings, ASCO gastrointestinal symposium, European Society of Medical Oncology (ESMO) annual meetings, and World Gastroenterology Organization (WGO) annual meetings were searched, starting from 2008, using the same combinations as above. We included prospective randomized studies investigating the administration of antiangiogenic drugs targeting the VEGF pathway, either by blocking growth factors or their receptors, irrespectively from their mechanisms of action and administered in patients progressed during or after the treatment with an anti-VEGF drug for metastatic disease. The objective of the analysis was to assess differences in PFS and in OS between patients treated with anti-VEGF therapies versus the untreated controls. PFS was defined as the time since randomization or start of the treatment to clinical evidence of progression, radiological evidence of progression or death, whichever came first. OS was defined as time since randomization or start of the treatment to death from any cause. The retrieved publications were screened by two authors at a title or abstract level. Full publications were obtained for relevant papers. Hazard ratios (HRs) for PFS and OS and their 95% confidence intervals (95% CI) were extracted from the publications. If they were not reported, they were estimated using the Parmar method.[13] The data collection form is given in appendix material. In each randomized study, only the patients previously treated with antiangiogenic agents were included. The risk of bias was evaluated by two different authors using the Cochrane Collaboration's tool.[14] Natural logarithms of the hazard ratios were used as point estimates and standard errors were calculated with the normal approximation. We used inverse variance and random effect model. Between study heterogeneity was tested with Cochran's Q test and I^2. Sensitivity analyses were performed by repeating the analysis excluding one or more studies each time. If no heterogeneity was found, the analyses were also repeated with fixed effect model. The software used was RevMan v 5.2. PRISMA guidelines were followed to report the results.[15]

RESULTS

Six studies including 3407 patients were included. The trial flow chart is shown in Figure 1. All patients had been previously administered bevacizumab. Except for CORRECT and CONCUR studies, which account for 964 patients, all patients had received only one previous line of treatment. Median age ranged from 55 to 62 years. All the studies carried a low risk of bias for overall survival analysis (Table 2). With respect to progression-free survival, all studies were scored as low risk, with the exceptions of Bebyp and TML; both were scored as intermediate risk because of the absence of blinding. The analysis for progression free survival showed a significant difference in favor of the anti-VEGF arm with an HR of 0.63 (0.60 – 0.66, $P < 0.001$) (Figure 2). Significant heterogeneity was present, and it was mainly attributable to the CORRECT study, in which a greater benefit could be observed. Regorafenib is a TKI that is able to block multiple targets, aside from VEGFRs. We conducted a separate analysis, removing CORRECT and CONCUR, and observed the results (HR 0.71 ,0.65 – 0.78, $P < 0.001$). Heterogeneity decreased to a non-significant level (Cochran P value = 0.12, $I^2 = 48\%$). The removal of one study at a time also changed the results, and very similar values of HR were obtained (data not shown). The main analysis for OS showed a significant increase in the overall survival (HR= 0.81 , 0.76 – 0.87, $P < 0.001$) (Figure 2), with no significant heterogeneity. The exclusion or regorafenib studies or the exclusion of one study at a time did not alter the results (HR = 0.83, 0.76 – 0.89, $P < 0.001$). Small study bias and publication bias have been assessed by visual inspection of funnel plot, constructed using the log-transformed HRs for progression free survival Figure 3).

DISCUSSION

Angiogenesis is a key step for cancer growth and progression. Bevacizumab, an anti-VEGF-A human

Table 1: Patient characteristics.

Study	Line	Treatments	*n*	ECOG			Sex		N° of sites of metastases			Kras		
				0	1	2	M	F	≤ 1	>1	n.r.	WT	MT	n.r.
TML	2°	CHT + Bevacizumab	409	179 (43.8)	209 (51.2)	19 (5)	267 (65.3)	142 (34.7)	148 (36.2)	261 (63.8)	0 (0)	151 (36.9)	164 (40.1)	94 (23)
		CHT	411	178 (43.5)	212 (51.8)	19 (4.7)	259 (62.9)	152 (37.1)	160 (39)	250 (60.8)	1 (0.2)	165 (40.1)	136 (33.1)	110 (26.8)
CORRECT	≥ 3°	Regorafenib	505	265 (52.5)	240 (47.5)	0 (0)	311 (61.6)	194 (38.4)	n.r.	n.r.	505 (100)	205 (40.6)	273 (54)	27 (5.4)
		Placebo	255	146 (57.3)	109 (42.7)	0 (0)	153 (60)	102 (40)	n.r.	n.r.	255 (100)	94 (36.9)	157 (61.5)	4 (1.6)
CONCUR	≥ 3°	Regorafenib	136	35 (25.7)	101 (74.3)	0 (0)	85 (62.5)	51 (37.5)	28 (20.6)	108 (79.4)	0 (0)	50 (36.7)	46 (33.8)	40 (29.5)
		Placebo	68	15 (22.1)	53 (77.9)	0 (0)	33 (48.5)	35 (51.5)	15 (22.1)	53 (77.9)	0 (0)	29 (42.7)	18 (26.4)	21 (30.9
Bebyp	2°	CHT + Bevacizumab	92	74 (80.4)	17 (18.5)	1 (1.1)	57 (62)	35 (38)	24 (26.1)	68 (73.9)	0 (0)	32 (34.8)	40 (43.5)	20 (21.7)
		CHT	92	74 (80.4)	16 (17.4)	2 (2.2)	75 (81.5)	17 (18.5)	24 (26.1)	68 (73.9)	0 (0)	36 (39.1)	32 (34.8)	24 (26.1)
VELOUR	2°	FOLFIRI + Aflibercept	187	107 (57.2)	74 (39.6)	6 (3.2)	105 (56.1)	82 (43.9)	87 (46.5)	100 (53.5)	0 (0)	n.r.	n.r.	187 (100)
		FOLFIRI + Placebo	186	107 (57.5)	74 (39.8)	5 (2.7)	110 (59.1)	76 (40.9)	81 (43.5)	105 (56.5)	0 (0)	n.r.	n.r.	186 (100)
RAISE	2°	FOLFIRI + Ramucirumab	532	263 (49.5)	268 (50.3)	1 (0.2)	289 (54.3)	243 (45.7)	171 (32.1)	361 (67.9)	0 (0)	265 (49.8)	267 (50.2)	0 (0)
		FOLFIRI + Placebo	534	259 (48.5)	273 (51.1)	2 (0.4)	326 (61)	208 (39)	158 (29.6)	376 (70.4)	0 (0)	274 (51.3)	260 (48.7)	0 (0)

ECOG: ECOG performance status; Line: line of treatment for metastatic disease; WT: wild-type; MT: mutant; n.r.: not reported; M: male; F: female; CHT: chemotherapy. Numbers in parenthesis indicate the percentage on total.

Table 2: Summary of risk of bias assessment.

	TML	Bebyp	RAISE	VELOUR	CORRECT	CONCUR
Sequence Generation	Low	Low	Low	Low	Low	Low
Allocation Concealment	Low	Low	Low	Low	Low	Low
Blinding of participants and outcome assessors	High	High	Low	Low	Low	Low
Selective outcome reporting	Low	Low	Low	Low	Low	Low
Other sources of bias	Low	Unclear	Unclear	Low	Low	Low
Overall	Low	Low	Low	Low	Low	Low

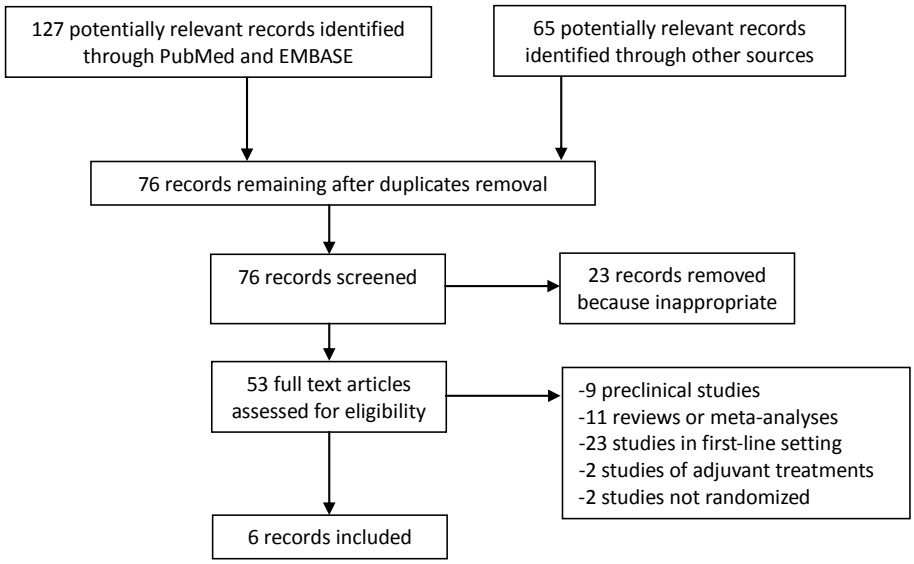

Figure 1: Trial flow chart of included studies

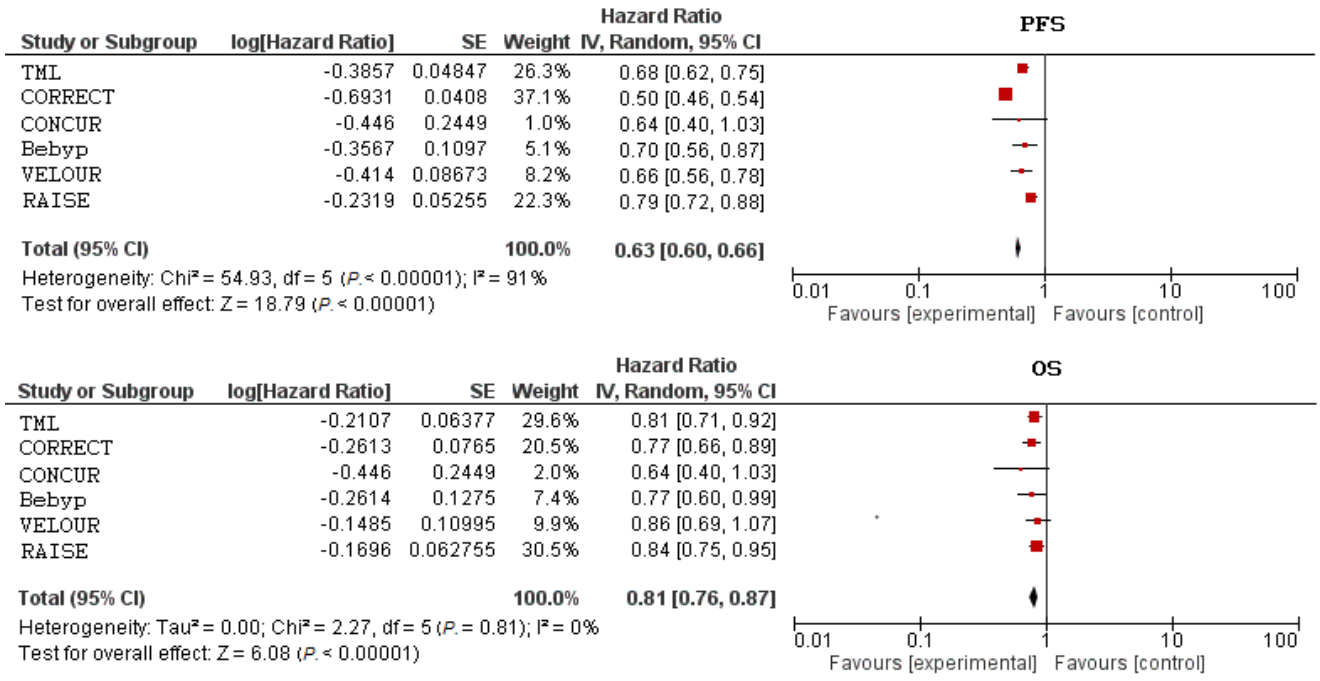

Figure 2: Progression-free survival. PFS: progression-free survival. OS: overall survival. SE: standard error.

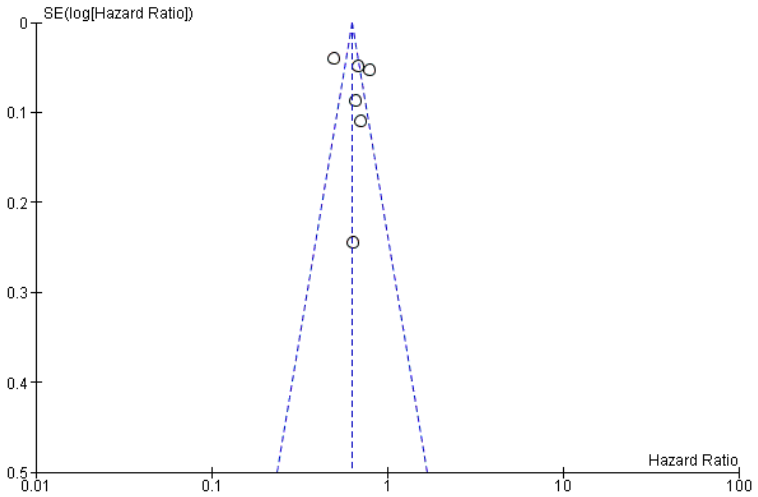

Figure 3: Small study bias and publication bias.

monoclonal antibody, was the first antiangiogenic agent approved for the treatment of colorectal cancer given its survival benefits when combined with IFL chemotherapy.[3] Subsequent trials investigated the administration of bevacizumab in combination with different regimens of chemotherapy.[4,5] They consistently showed benefits in progression free-survival, and many of them also reported improvements in overall survival. In recent years, other antiangiogenic drugs have been developed and tested in colorectal cancer. Aflibercept is a molecular construct that is able to bind all the different isoforms of VEGF-A, as well as other members of the VEGF family. Ramucirumab is a monoclonal antibody that targets and inactivates the VEGFR-2. Both have been investigated in two large randomized controlled trials (i.e., the VELOUR and the RAISE), in combination with FOLFIRI chemotherapy in pretreated colorectal cancer patients. Both studies were positive with almost identical results. All patients enrolled in the RAISE and a significant proportion of those in the VELOUR had received prior bevacizumab. Regorafenib is a small molecule able to block multiple targets like VEGFR-1, -2 and -3, RAF, PDGFRb and kit. It was seen

that regorafenib helped to improve both PFS and OS in heavily pretreated patients[8] in majority of trials; the antiangiogenic agent were suspended after progression. However, the optimal duration is unclear and there is a biological rationale to hypothesize a survival benefit from post-progression administrations.[10] The TML and the Bebyp trials investigated protracted administration of bevacizumab after progression to a first-line chemotherapy. Both trials were positive, confirming that protracted administration of bevacizumab, beyond progression, leads to survival advantage. These trials suggest that once started, antiangiogenic agents should not be discontinued. One of the main goals of this paper is to assess if this statement is limited to bevacizumab or could conversely apply to all VEGF-targeting drugs. The analysis included all the studies which investigated the administration of anti-VEGF drugs, alone or combined with chemotherapy, in patients already progressed after a previous line of treatment including antiangiogenic agents. Our results confirmed a significant improvement of both progression free and overall survival. Most notably, the magnitude of benefit was almost identical, regardless of the drug used. All the drugs included had an exclusive activity against VEGFs or VEGFR-2, with the only exception of regorafenib. However, in the CORRECT and the CONCUR studies, a very similar amount of benefit was present and if these studies were removed, the results did not change significantly. We recognize some limitations to the present analysis. The number of studies is small, and for some molecules, only one trial was available. The time between the progression and the start of treatment were different, with some studies allowing only a very short time, unlike the Bebyp in which a longer period was allowed. Even if the results appear to be very similar, the timing of second-line antiangiogenic agents may not be negligible. Moreover, the absolute benefit in survival, although statistically significant, appears to be very small. Considering the high costs and the associated toxicities, a routine use is controversial and this strategy should be evaluated case by case, also considering patient and tumor characteristics like age, comorbidities and KRAS status. Despite these limitations, the body of evidence acquired in the last decades confirms that the inhibition of VEGF signaling can effectively improve the overall survival in metastatic colorectal cancer patients, and that a prolonged administration is associated with greater benefits. Future efforts should focus on better strategy to inhibit angiogenesis as well as preventing angiogenesis resistance. Concomitant blockage of other proangiogenic factors like FGF and PDGF could improve the effectiveness of this strategy. Many agents that can target these pathways have been developed, like sorafenib and sunitinib. Unfortunately, both failed to improve prognosis in phase III randomized trials, even if sorafenib still maintains promise for pretreated KRAS mutant patients.[16-18] Other antiangiogenic molecules able to target multiple pathways are under investigation. Among these, nintedanib (BIBF 1120), a multi target TKI able to efficiently block VEGFR, FGFR and PDGFR, is one of the most promising, as it has already shown to improve survival in lung adenocarcinoma.[19] Preliminary results showed clinical activity also in colorectal cancer and results of ongoing trials are awaited in the coming years (NCT02149108, NCT02393755, NCT00904839).[20]

Conflict of interest

None declared.

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APPENDIX

PRISMA CHECKLIST

Section/Topic	# Checklist Item	Reported on
TITLE		
Title	1. Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT		
Structured summary	2. Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION		
Rationale	3. Describe the rationale for the review in the context of what is already known.	Background
Objectives	4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Background
METHODS		
Protocol and registration	5. Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Protocol not registered
Eligibility criteria	6. Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Materials and Methods
Information sources	7. Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Materials and Methods
Search	8. Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Materials and Methods
Study selection	9. State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Materials and Methods
Data collection process	10. Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Materials and Methods
Data items	11. List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Materials and Methods – Table 1
Risk of bias in individual studies	12. Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Materials and Methods
Summary measures	13. State the principal summary measures (e.g., risk ratio, difference in means).	Materials and Methods
Synthesis of results	14. Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Materials and Methods
Risk of bias across studies	15. Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Materials and Methods
Additional analyses	16. Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Materials and Methods
RESULTS		
Study selection	17. Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results- Figure 1
Study characteristics	18. For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results – Table 1
Risk of bias within studies	19. Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Not applicable
Results of individual studies	20. For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Results – Figure 2-4
Synthesis of results	21. Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results
Risk of bias across studies	22. Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23. Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results
DISCUSSION		
Summary of evidence	24. Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	Discussion
Limitations	25. Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26. Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING		
Funding	27. Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Fundings

RISK OF BIAS ASSESSMENT

VELOUR

Domain	Description	Review authors' judgement
Sequence generation	Permuted-block randomization, stratified according to prior therapy with bevacizumab.	Low risk of bias
Allocation concealment	Concealment reported but not specified in details. Centralized interactive voice-response system.	Centralization minimize the risk to foresee the allocation. Low risk of bias
Blinding of participants, personnel and outcome assessors	As above. No mentions of masking breaks.	Low risk of bias.
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias.
Selective outcome reporting	No evidence of selective outcome reporting in the publication.	Low risk of bias
Other sources of bias	No evidence of other significant sources of bias.	Low risk of bias

RAISE

Domain	Description	Review authors' judgement
Sequence generation	computerized voice-response system.	Low risk of bias
Allocation concealment	Concealment reported but not specified in details. Centralized interactive voice-response system.	Centralization minimize the risk to foresee the allocation. Low risk of bias
Blinding of participants, personnel and outcome assessors	Double-blind, placebo-controlled. Masking break allowed for emergency. No mention of breaks.	Low risk of bias.
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias.
Selective outcome reporting	No evidence of selective outcome reporting in the publication.	Low risk of bias
Other sources of bias	10-20% of patients per arm discontinued treatment because of patients or investigator's decision.	Unclear risk of bias

Bebyp

Domain	Description	Review authors' judgement
Sequence generation	Centralized web-based system and a minimization algorithm.	Low risk of bias
Allocation concealment	Concealment reported but not specified in details. Centralized interactive voice-response system.	Centralization minimize the risk to foresee the allocation. Low risk of bias
Blinding of participants, personnel and outcome assessors	No blinding. No placebo-control.	High risk of bias
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias
Selective outcome reporting	No evidence of selective outcome reporting in the publication.	Low risk of bias
Other sources of bias	Trial flow chart not shown. Small difference in median number of cycles in favor of treatment arms (9 for experimental arm, 8 for controls).	Unclear risk of bias

TML

Domain	Description	Review authors' judgement
Sequence generation	Stratified permuted block design. Interactive voice-response system.	Low risk of bias
Allocation concealment	Centralized randomization for patients included in the AIO KRK 0504. Interactive voice response system for patients enrolled in TML. The patient's study identification number was uploaded automatically by the IVRS on the electronic case-report form.	Low risk of bias
Blinding of participants, personnel and outcome assessors	No blinding. No placebo-control.	High risk of bias.
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias.
Selective outcome reporting	No evidence of selective outcome reporting in the publication.	Low risk of bias
Other sources of bias	No evidence of other significant sources of bias.	Low risk of bias.

CONCUR

Domain	Description	Review authors' judgement
Sequence generation	Pre-allocated block design (block size of six) and stratified randomization by number of metastatic sites (single vs multiple organs) and time from diagnosis of metastatic disease (<18 months vs ≥18 months).	Low risk of bias
Allocation concealment	Each bottle of study drug was labelled with a unique number and assigned to patients through the IVRS. Booklet labels produced by the sponsor containing appropriate label. Packaging, labelling, and distribution was done centrally.	Low risk of bias
Blinding of participants, personnel and outcome assessors	No blinding. No placebo-control.	High risk of bias.
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias.
Selective outcome reporting	No evidence of selective outcome reporting in the publication.	Low risk of bias
Other sources of bias	No evidence of other significant sources of bias.	Low risk of bias.

CORRECT

Domain	Description	Review authors' judgement
Sequence generation	Pre-allocated block sizes (block size six) stratified by previous treatment with VEGF-targeting drugs, time from diagnosis of metastatic disease (≥18 months or <18 months), and geographical region.	Low risk of bias
Allocation concealment	Study medication labelled with a unique drug pack number preprinted on each bottle, assigned to the patient through the interactive voice response system.	Low risk of bias
Blinding of participants, personnel and outcome assessors	Double blind, placebo-controlled, masked to investigators, patients and sponsor.	Low risk of bias.
Incomplete outcome data	Complete reporting of primary and secondary outcomes.	Low risk of bias.
Selective outcome reporting	No evidence of selective outcome reporting in the publication	Low risk of bias
Other sources of bias	No evidence of other significant sources of bias.	Low risk of bias.