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Systematic or Meta-analysis Studies

Bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: A meta-analysis of individual patients' data from 3 phase III studies

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ABSTRACT

Background: The real impact of bevacizumab maintenance as single agent in metastatic colorectal cancer (mCRC) remains unclear. SAKK-41/06 and PRODIGE-9 failed to demonstrate the non-inferiority and superiority of bevacizumab versus no maintenance, respectively, while AIO-KRK-0207 showed the non-inferiority of maintenance bevacizumab versus bevacizumab and fluoropyrimidines for time to strategy failure.

Methods: Bibliography electronic databases (PubMed, MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials) were searched for English published clinical trials prospectively randomizing mCRC patients to receive bevacizumab maintenance or not after first-line chemotherapy plus bevacizumab. Individual patients' data (IPD) were provided by investigators for all included trials. Primary endpoints were progression-free survival (PFS) and overall survival (OS), both from the start of induction and maintenance. Univariate and multivariate analyses for PFS and OS were performed.

Results: Three phase III studies - PRODIGE-9, AIO-KRK-0207 and SAKK-41/06 – were included. Considering the different timing of randomization, IPD of patients not progressed during induction and starting maintenance phase entered the analysis. 909 patients were included, 457 (50%) received bevacizumab maintenance. Median PFS from induction start was 9.6 and 8.9 months in bevacizumab group versus no maintenance group, respectively (HR 0.78; 95%CI: 0.68–0.89; $p < 0.0001$). Subgroups analysis for PFS showed a significant interaction according for *RAS* status ($p = 0.048$), with a maintenance benefit limited to *RAS* wild-type patients. No difference in terms of OS was observed.

Conclusions: Despite the statistically significant PFS improvement for bevacizumab maintenance, the absolute benefit appears limited. Subgroup analysis shows a differential effect of bevacizumab maintenance in favor of *RAS* wild-type patients. Considering these results, maintenance therapy with fluoropyrimidine with or without bevacizumab remains the first option. Single agent bevacizumab maintenance can be considered in selected cases, such as cumulative toxicity or patient's refusal, in particular for *RAS* wild-type patients.

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Introduction

CRC is the 3rd most commonly occurring cancer and the second cause of cancer-related death in the worldwide overall population ([1] https://www.who.int/news-room/fact-sheets/detail/cancer). In the last decade the management of mCRC patients has notably improved. Optimizing molecular and clinical selection of mCRC patients, maximizing medical treatments (both chemotherapy, biological drugs and immunotherapy) and their combination with locoregional approaches (surgery, radiotherapy, radiofrequency etc.) has allowed to achieve median survivals of more than 30 months [2,3]. First-line irinotecan- or oxaliplatin-based chemotherapy plus bevacizumab represents one of the standard treatment options for non resectable mCRC patients [4,5]. The optimal duration of chemotherapy is still debated, even if there is a general consensus on considering 4–6 months of induction treatment as an adequate timing in order to achieve the maximum benefit in terms of tumour shrinkage, and to avoid unnecessary (cumulative) toxicities, such as oxaliplatin-related neurotoxicity [6].

Four phase III randomized studies investigated the role of maintenance treatment with bevacizumab as single agent or in combination with flouropyrimidines versus observation after a first-line induction phase with doublet chemotherapy plus bevacizumab [7–10]. In particular, CAIRO3 [7] (phase III trial comparing maintenance with capecitabine plus bevacizumab versus observation) and AIO-KRK-0207 [8] (phase III non-inferiority trial investigating maintenance with bevacizumab single agent versus bevacizumab in combination with fluoropyrimidine versus observation) demonstrated the benefit of an active combination treatment (bevacizumab plus fluoropyrimidine) in terms of PFS and PFS2/time to strategy failure, in comparison to a complete discontinuation of treatment ("observation"). On the contrary, the role of bevacizumab as single agent is less clear: SAKK-41/06 [9] and PRODIGE-9 [10] trials failed to demonstrate the non-inferiority and superiority of bevacizumab single agent in comparison to no maintenance, respectively, whereas AIO-KRK-0207 [8] showed the non-inferiority of bevacizumab single agent versus the combination of bevacizumab plus fluoropyrimidine only in terms of time to strategy failure (primary end-point). With respect to PFS (secondary end-point), AIO-KRK-0207 [8] showed that bevacizumab was significantly inferior to fluoropyrimidine plus bevacizumab.

A meta-analysis conducted by Stein et al. [11], including CAIRO3, AIO-KRK-0207 and SAKK-41/06 trials, showed a significant improvement in terms of PFS (HR 0.57; 95% CI: 0.43–0.75; $p = 0.0004$) and a positive trend in terms of OS (HR 0.89; 95% CI: 0.78–1.02; p 0.09), in favor of *any* bevacizumab-based maintenance versus no maintenance. An indirect comparison of bevacizumab plus fluoropyrimidine versus bevacizumab single agent showed an improved PFS for the combination and no difference in terms of OS. No indirect comparison between bevacizumab single agent and no maintenance was performed.

Of note, the main limitations for the overall evaluation of those findings are that all these randomized phase III trials, comparing bevacizumab as single agent versus observation, assumed a different definition of primary end-point (time to strategy failure for AIO-KRK-0207; time to progression for SAKK-41/06 and tumor control duration for PRODIGE-9), a different statistical design (AIO-KRK-0207 and SAKK-41/06 are non-inferiority trials, while PRODIGE-9 is a superiority trial) and a different randomization timing (at the start of maintenance for AIO-KRK-0207 and SAKK-41/06 and at the start of induction for PRODIGE-9).

Thus, in order to overcome these conceptual differences and to evaluate the magnitude of the eventual benefit of maintenance with bevacizumab single agent in comparison to no maintenance, an IPD meta-analysis of randomized trials prospectively investigating such research question was performed.

Methods

Search strategy and selection criteria

A systematic literature search was performed for full-text articles from electronic databases such as PubMed, MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. Only articles in English language were considered eligible. Clinical trials published as abstracts or congress proceedings were excluded. Search terms were "metastatic colorectal cancer", "bevacizumab",

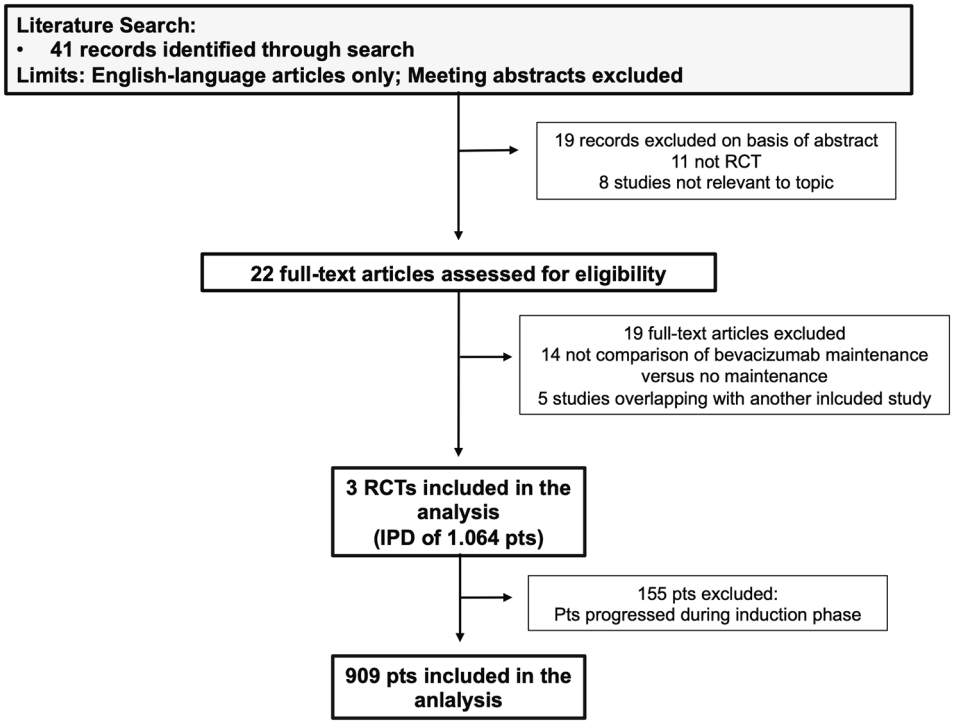

Fig. 1. Flow diagram of study selection. IPD: individual patient data; pts: patients; RCTs: randomized clinical trials.

"maintenance", and "randomized clinical trials", and synonyms.

Eligible studies were trials that prospectively randomized mCRC patients to receive bevacizumab maintenance or not, after a first-line induction chemotherapy containing oxaliplatin or irinotecan plus bevacizumab. We included trials that randomized patients both at the start of maintenance and the induction treatment. Considering the different timing of randomization, in case of randomization at the start of the induction treatment, we considered eligible for the analysis only those patients with controlled disease during induction treatment and that started the maintenance phase.

For each patient we collected the following available variables: baseline ECOG performance status (PS), gender, age, *RAS* and *BRAF* status, CEA baseline level, response (partial or complete response vs stable disease) during induction treatment, duration of induction treatment ($\leq$4 months vs $>$ 4 months), induction chemotherapy regimen (oxaliplatin- vs irinotecan-based regimen), resected primary tumor (yes vs no), primary tumor side (right vs left), synchronous vs metachronous disease, previous adjuvant treatment (yes vs no), and number of metastatic sites (single vs multiple).

Outcomes

The primary end-points of this IPD meta-analysis were PFS and OS. PFS was measured both from the start of induction therapy and maintenance until the first observation of disease progression or death due to any cause. The determination of disease progression was based on investigator-reported measurements. Patients who were alive without having one of the above events at the end of the study were censored at their last radiological assessment. Disease status was evaluated according to RECIST criteria. OS was measured both from the start of induction and maintenance until death due to any cause.

Statistical analysis

Descriptive statistics was used to determine the patients' characteristics. Survival curves were estimated by the Kaplan-Meier product-limit method from the date of treatment start (both from induction and maintenance start) until event (progression or death for PFS and OS, respectively). The log-rank test was to assess differences between subgroups. Significance was defined at the $p \leq 0.05$ level. The HR and the 95% CI were estimated using a univariate model; a multivariate Cox proportional hazard model was developed using stepwise regression (forward selection) to compare the prognostic power of different factors. Enter limit and remove limit were $p = 0.05$ and $p = 0.10$, respectively. The assessment of interactions between significant investigation variables was considered as well. The SPSS® (21.0) and Comprehensive Meta-Analysis (2.2.064) were used for all analyses.

Results

On the basis of the entry criteria, three studies resulted eligible (Fig. 1): the PRODIGE-9, AIO-KRK-0207 and SAKK-41/06 trials, that randomized patients to receive or not a maintenance treatment with bevacizumab single agent after an induction chemotherapy plus bevacizumab [8–10].

We collected IPD of 1064 patients. Considering the different timing of randomization in the three trials, that was at the start of the induction phase in the PRODIGE-9 and at the start of the maintenance phase in the AIO-KRK-0207 and SAKK-41/06 trials, we considered eligible for the analysis only those patients with controlled disease during induction treatment and that started the maintenance phase. A total of 909 patients were included, 457 patients received maintenance with bevacizumab single agent and 452 patients did not receive any maintenance. 68% of patients were male in both groups, the median age was 64 years (range 26–88) in bevacizumab group and 65 years (range 22–85) in no maintenance group and patients with good clinical conditions (ECOG PS 0) were 57% in bevacizumab group and 53% in no maintenance group. The presentation of metastases was synchronous in 61–60% of cases and the number of metastatic sites was $>$ 1 in 58% and 63% in bevacizumab and in no maintenance group, respectively. In the overall population, the rate of proven *RAS* mutation was 25% and 27% in bevacizumab and in no maintenance group, respectively, with a high rate of not available data (62% and 60.5%). 44% and 56% of patients received an oxaliplatin- and irinotecan-based induction regimen, respectively. During the induction phase, complete or partial response was achieved in 61% of patients in bevacizumab group and in 65% of patients in no maintenance group. Patients' characteristics are summarized in Table 1.

Table 1
Patients' characteristics.

	BV M N = 457 (%)	**No M N = 452 (%)**
Gender		
Female	145 (32)	144 (32)
Male	312 (68)	308 (68)
Median Age (range)	64 (26–88)	65 (22–85)
Age at treatment start		
$\leq$ 65	253 (55)	239 (53)
$>$ 65	204 (45)	213 (47)
ECOG PS		
0	263 (57)	239 (53)
1–2	186 (41)	201 (44)
NA	8 (2)	12 (3)
Presentation of metastases		
Synchronous	278 (61)	273 (60)
Metachronous	179 (39)	179 (40)
Adjuvant chemotherapy		
Yes	49 (11)	47 (10.5)
No	295 (64)	290 (64)
NA	113 (25)	115 (25.5)
Primary tumor side		
Right	77 (17)	68 (15)
Left	204 (45)	195 (43)
NA	176 (38)	189 (42)
Resected primary tumor		
Yes	221 (48)	213 (47)
No	105 (23)	108 (24)
NA	131 (29)	131 (29)
Number of metastatic sites		
1	191 (42)	168 (37)
$>$1	266 (58)	284 (63)
CEA baseline level		
$\leq$20 ng/mL	105 (23)	103 (23)
$>$20 ng/mL	203 (44)	201(44)
NA	149 (33)	148 (33)
Induction chemotherapy		
Oxaliplatin-based	203 (44)	198 (44)
Irinotecan-based	254 (56)	254 (56)
Duration of induction chemotherapy		
$\leq$4 months	82 (18)	91 (20)
$>$4 months	375 (82)	361 (80)
RR during induction		
CR/PR	279 (61)	292 (65)
SD	178 (39)	160 (35)
***RAS* status**		
Wild-type	61 (13)	57 (12.5)
mutant	113 (25)	121 (27)
NA	283 (62)	274 (60.5)
***BRAF* status**		
Wild-type	183 (40)	184 (41)
mutant	17 (4)	10 (2)
NA	257 (56)	258 (57)

BV: bevacizumab; CR: complete response; M: maintenance; NA: not applicable; PR: partial response; RR: response rate; SD: stable disease.

For PFS from treatment start (beginning of induction treatment plus maintenance), the use of a maintenance with bevacizumab was associated with a statistically significant 22% reduced risk of progression as compared with no maintenance (HR 0.78; 95% CI: 0.68–0.89; $p < 0.0001$) (Fig. 2a). Median PFS was 9.6 months and 8.9 months,

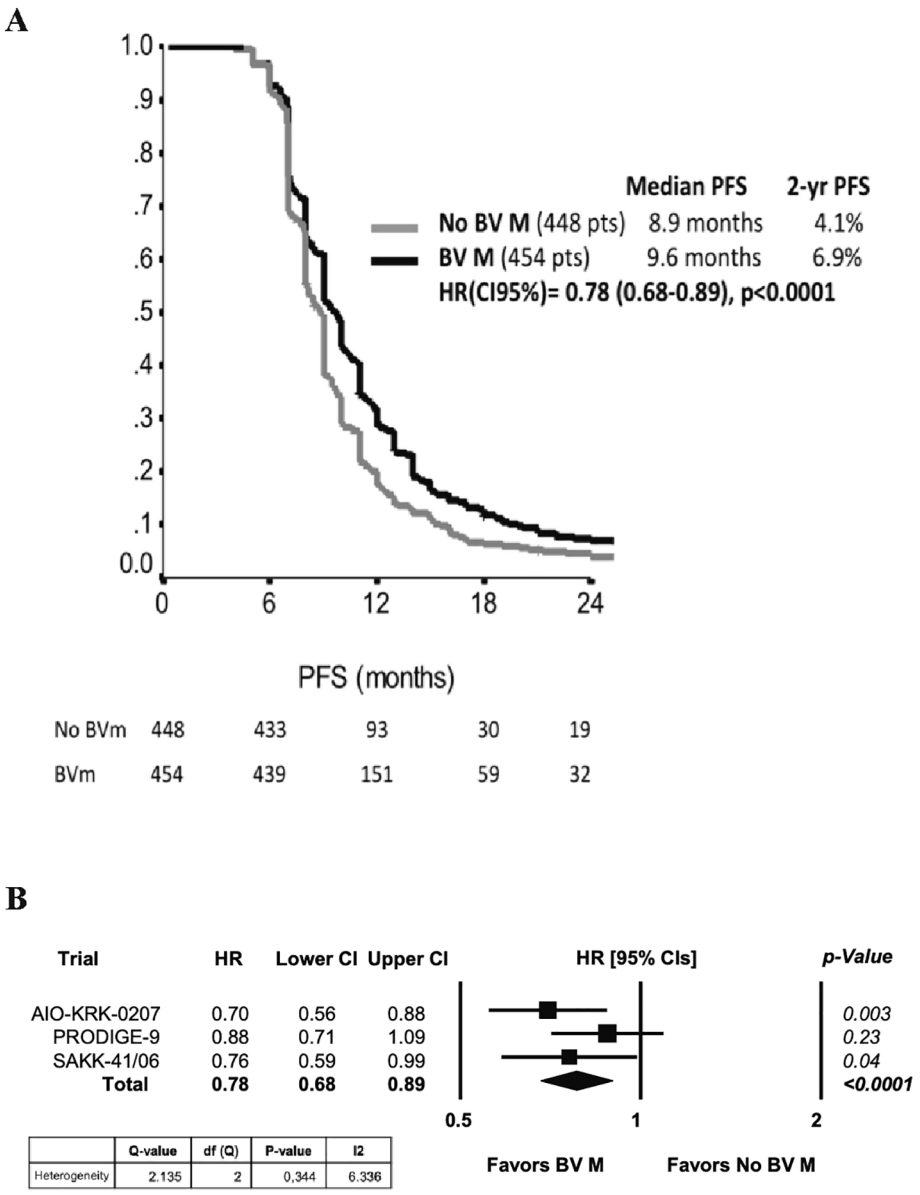

Fig. 2. A) Kaplan-Meier PFS (from induction) curve according to bevacizumab maintenance versus no maintenance. B) Forest plot of treatment effect on PFS (from induction).

respectively. No significant heterogeneity among the 3 trials (Q-value = 2.135; $p = 0.344$) was detected (Fig. 2b). The benefit from bevacizumab maintenance with respect to PFS was homogeneous in all clinical subgroups, with the exception of patients with *RAS* mutant disease (Fig. 3). At an exploratory analysis, *RAS* wild-type patients achieved a greater benefit from bevacizumab as single agent (HR 0.56; 95%CI: 0.37–0.83; log-rank $p < 0.0001$; median PFS 10.1 and 9.0 months, respectively; 2-year PFS rates of 19.7 and 0%) than patients with *RAS* mutant status (HR 0.91, 95% CI: 0.70–1.18; log-rank $p = 0.96$; mPFS 9.4 vs 9.0 months; 2-year PFS 6.5% vs 5.8%): a significant interaction according to *RAS* status and maintenance treatment ($p = 0.048$), with a benefit of maintenance limited to *RAS* wild type patients, was observed (Fig. 4).

At the multivariate analysis for PFS, the right side and the presence at diagnosis of primary tumor in site, the presence of multiple metastatic sites and no maintenance treatment were identified as poor prognostic factors (Appendix Table A1).

Median OS from induction start was 26.0 months in bevacizumab group and 25.2 months in no maintenance group, with a HR of 0.998 (95%CI: 0.858–1.162; $p = 0.982$) (Appendix Fig. A1). No significant heterogeneity among the 3 trials (Q-value = 1.739; $p = 0.419$) was detected (Appendix Fig. A.2). At the multivariate analysis for OS, age > 65 years, synchronous metastases, the presence of multiple metastatic sites and the stabilization of disease, instead of disease response, during the induction phase, were identified as poor prognostic factors (Appendix Table B1).

Median PFS from maintenance was 4.0 months in bevacizumab group and 3.1 months in no maintenance group (HR 0.77; 95% CI: 0.68–0.88; $p < 0.0001$); median OS from maintenance was 21.0 and 20.0 months in bevacizumab group and no maintenance group, respectively (HR 1.01; 95% CI: 0.87–1.17; $p = 0.92$) (Appendix Fig. B1). Univariate and multivariate analyses for PFS and OS, both from maintenance, are shown in Appendix Tables C1 and D1.

Discussion

To date, European and American guidelines [3,2,12] recommend a treatment de-escalation after 4–6 months of first-line induction chemotherapy plus bevacizumab, continuing a maintenance treatment

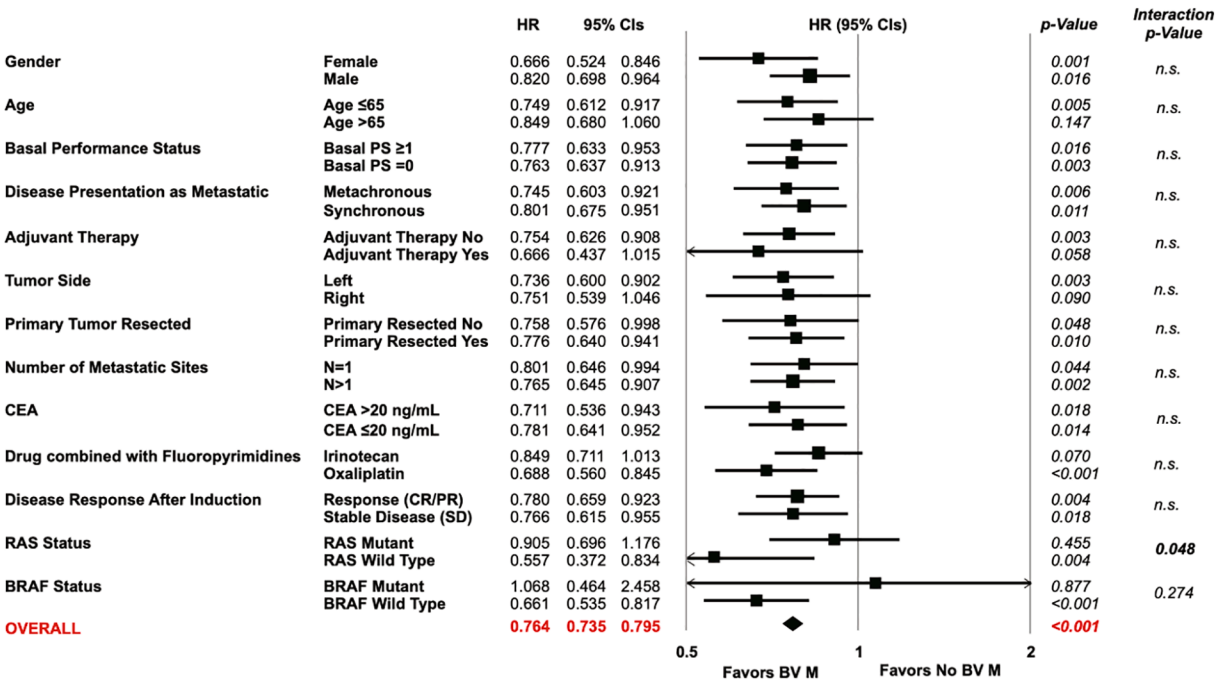

Fig. 3. Forest plot of the bevacizumab maintenance effect on PFS in subgroup analyses.

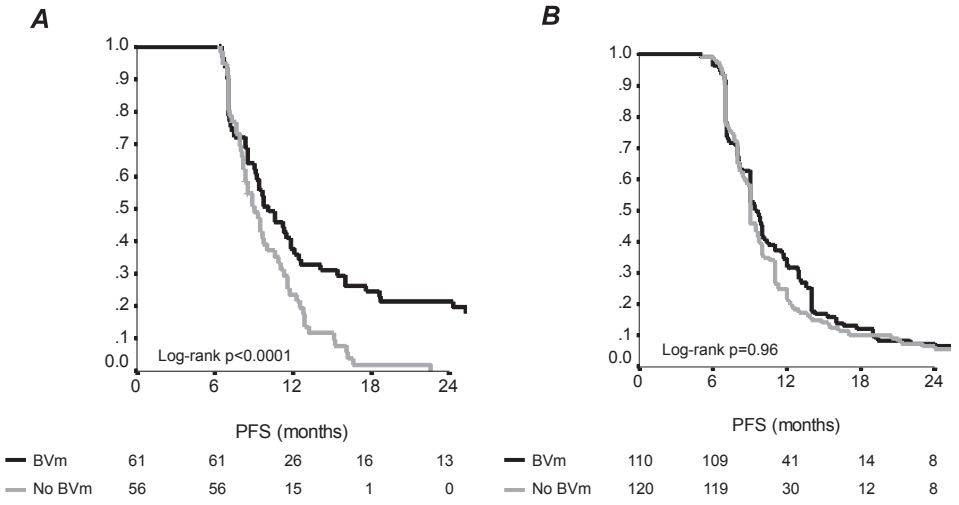

Fig. 4. Kaplan-Meier PFS curves according to bevacizumab maintenance versus no maintenance on the basis of *RAS* status: Panel A: RAS wt patients (117 patients); Panel B: RAS mutant (230 patients).

with a fluoropyrimidine with or without bevacizumab, after a careful evaluation of the risk/benefit ratio.

Such recommendation is mainly based on the results deriving from CAIRO3 [7] and AIO-KRK-0207 [8] phase III studies that demonstrated a significant improvement in PFS of the combination fluoropyrimidine/bevacizumab versus no maintenance. The recent metanalysis by Sonbol et al. [13], confirmed such recommendation as the preferred one, demonstrating a benefit in terms of PFS, even if not in OS, of maintenance with a fluoropyirimidine, with or without bevacizumab, versus observation. Actually, a direct comparison between fluoropyrimidine plus bevacizumab versus fluoropyrimidine alone has never been performed. A phase III randomized study, the BEVAMAINT-PRODIGE71 trial [14], comparing these two maintenance regimes, is ongoing. The role of bevacizumab as single agent is less clear: although the PRODIGE-9 and SAKK-41/06 trials showed no difference between bevacizumab single agent and no maintenance [9,10], the AIO-KRK-0207 trial demonstrated the non-inferiority of bevacizumab single agent in comparison to maintenance combination in terms of time to strategy failure (primary and-point), but not in terms of PFS (secondary end-point) [8].

Thus, the objective of our metanalysis was to evaluate the magnitude of the potential benefit of bevacizumab single agent versus no maintenance, collecting individual data of patients randomized to receive maintenance with bevacizumab or no maintenance in AIO-KRK-0207, PRODIGE-9 and SAKK-41/06 trials. Results have shown a significant improvement of PFS – from the start of induction treatment - in favor of bevacizumab maintenance, with a 22% reduction for risk of progression (HR 0.78; 95% CI: 0.68–0.89; $p < 0.0001$). However, the median difference is limited to only 0.7 months. Based on such results, we can conclude that the standard maintenance remains the combination of fluoropyrimidine and bevacizumab. Also, the difference in PFS did not translate into any difference in OS likelihood (HR 0.998; 95%CI: 0.858–1.162; $p = 0.982$).

For the evaluation of cost-effectiveness of such strategy, despite the lack of specific tools, it is essential to consider, beyond the limited, albeit significant, advantage in PFS and the manageble safety profile, also the availability of bevacizumb biosimilars that can reduce costs and expand access for patients [15].

The strength points of our metanalysis are the following: 1) this is the first metanalysis that aims to definitively clarify the role of bevacizumab single agent as maintenance therapy; 2) this is a metanalysis based on IPD and not on extracted data; 3) only patients without progression during induction and starting maintenance phase entered the analysis. However, this last point should be also considered as a selection bias, due to the exclusion of patients with worse prognosis showing progression during induction.

The main limit of the study is the high rate of missing data, in particular regarding *RAS* (61%) and *BRAF* (57%) status (at least partly explained with the accrual period - before *KRAS*-testing became standard of care in 2009) and the site of primary tumor (40%).

Considering the subgroup analysis, besides the high attrition, as an exploratory analysis, a differential effect of bevacizumab maintenance on the basis of *RAS* status seems to exist. Specifically, patients with *RAS* wild type mCRC significantly benefit from bevacizumab maintenance versus no maintenance, while no difference is shown in patients with *RAS* mutant tumors (interaction *p-value* = *0.048*). Such result strengthens the suggestions observed in each individual study. The subgroup analysis for PFS of AIO-KRK-0207 study showed a HR of 2.21 (95% CI 1.38–3.52; $p = 0.00067$) in patients with all wild type tumors in favor of bevacizumab maintenance versus no maintenance, while no difference was observed in patients with tumors harboring *RAS* or *BRAF* mutation (HR 1.19, 95% CI 0.84–1.70; $p = 0.33$). Conversely, the subgroup analysis for PFS of the same study, comparing combination maintenance versus bevacizumab single agent, showed no difference in all wild type patients (HR 1.07, 95% CI 0.69–1.67), whereas it showed a benefit in favor of fluoropyrimidine plus bevacizumab in patients with mutant tumors (HR 1.51, 95% CI 1.03–2.22), although the interaction test did not reach significance. Kaplan-Meier curves of time to first progression by maintenance group for *RAS/BRAF* status, showed that *RAS/BRAF* wild type patients presented longer time to first progression when treated with bevacizumab single agent (6.2 months) or in combination with fluoropyrimidine (8.0 months) versus no maintenance (3.9 months) (log-rank $p < 0.0001$), whereas mutant mCRC patients seemed to benefit only from combination maintenance (6.4 months) in comparison to bevacizumab single agent (4.1 months) or no maintenance (3.6 months) (log-rank $p = 0.0047$) [8]. The same suggestion was observed in the PRODIGE-9 study: the subgroup analysis for PFS, although the interaction test was not significant ($p = 0.079$), showed a HR of 0.72 (95% CI 0.54–0.95) in favor of bevacizumab single agent versus no maintenance in *KRAS* wild type patients, while a HR of 1.07 (95% CI 0.79–1.44) in *KRAS* mutant patients [10].

Therefore, these results contribute to the hypothesis that a differential effect of bevacizumab maintenance in favor of *RAS* wild type patients might exist. One possible explanation could be that *RAS* wild type patients, in comparison to *RAS* mutant ones, have a less aggressive disease with a better prognosis that can benefit also from a less intensive maintenance [16,17]. A further explanation could be related to the different expression of pro-angiogenic factors according to *(K)RAS* status. In particular the presence of *(K)RAS* mutation seems to be associated to an increased production of angiogenic factors, such as VEGF and IL-8, and an increased expression of HIF-1 [18], that seem to be related to bevacizumab resistance [19]. Obviously, the above considerations must be considered as hypothesis generating and should be further investigated.

On the basis of such results, we can conclude that while in *RAS* mutant patients the combination maintenance is still the preferred choice, in *RAS* wild type patients, a maintenance with bevacizumab single agent can be considered.

Conclusions

In conclusion, our metanalysis, focusing on the role of bevacizumab as single agent, confirms that fluoropyrimidine with or without bevacizumab remains the preferred option of maintenance. Bevacizumab single agent can be considered in selected cases, such as in case of cumulative toxicity to fluoropyrimidine or patient's refusal to continue maintenance combination, in particular for *RAS* wild type patients.

Author contributors

LS and EB were involved in the conception and design of the study. LS contributed to the literature search. LS, EB, AH, SHB, TA, KLM, VB, DK, DB, DD worked on data collection. LS, EB, GT and DA planned the analyses and IS performed the individual patient data *meta*-analysis. LS, EB, GT and DA interpreted the data. LS and EB wrote the manuscript drafts. All authors read and approved the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. B. received speakers' and travels' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. E.B received consultant's fee from Roche, Pfizer. E.B. received institutional research grants from Astra-Zeneca, Roche.T.A. received speakers' and travels' fee from Roche, Servier, Sanofi, Amgen and Astra-Zeneca. T.A. received consultants' fee from BIOVEN. D.K. received consultants'fees from Pierre Fabre, BMS and Roche. A.H. received honoraria for tutorials from Roche.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2021.102202.

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