



Effect of Application and Intensity of Bevacizumab-based Maintenance After Induction Chemotherapy With Bevacizumab for Metastatic Colorectal Cancer: A Meta-analysis

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Abstract

The role of bevacizumab-based maintenance after first-line bevacizumab-based induction treatment of metastatic colorectal cancer was evaluated in a meta-analysis of 3 randomized trials. Maintenance treatment with bevacizumab with or without fluoropyrimidines improved progression-free survival and showed a trend toward improved overall survival.

Background: The administration and intensity of bevacizumab-based maintenance therapy after induction treatment with bevacizumab is still a matter of debate. Thus, the present meta-analysis and an indirect comparison were performed to clarify these issues. **Patients and Methods:** Trials evaluating a separately defined “maintenance phase,” with randomization after the induction phase, were selected. Three trials of maintenance with bevacizumab with or without a fluoropyrimidine (CAIRO3, SAKK 41/06, and AIO KRK 0207) were analyzed regarding the effect on progression-free survival (PFS) and overall survival (OS) of any maintenance therapy compared with observation alone and different maintenance intensities (bevacizumab with or without fluoropyrimidine) compared with observation alone and between each other. **Results:** Maintenance with bevacizumab with or without fluoropyrimidine after bevacizumab-based induction treatment for 4 to 6 months significantly improved PFS (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.43-0.75; $P = .0004$) and showed a trend toward prolonged OS (HR, 0.89; 95% CI, 0.78-1.02; $P = .09$) compared with observation alone. The effect on PFS increased with the intensity of the maintenance regimen (HR, 0.72; 95% CI, 0.60-0.85 for single-agent bevacizumab vs. HR, 0.45; 95% CI, 0.39-0.51 for combination therapy, both compared to observation alone). In contrast, the HRs for OS remained in the same range. A similarly improved PFS (HR, 0.63; 95% CI, 0.50-0.79) was shown for the more intensive maintenance therapy (bevacizumab and fluoropyrimidine) compared with bevacizumab alone. **Conclusion:** Bevacizumab-based maintenance therapy after induction chemotherapy with bevacizumab significantly improves PFS and showed a trend toward prolonged OS and should thus be considered, in particular, in patients with a response to induction treatment.

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Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies and one of the leading causes of cancer death.¹

Approximately one quarter of patients with CRC will present with metastatic disease (mCRC) at diagnosis (synchronous disease), and about 40% of patients will develop metachronous metastases

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after curative intent treatment, resulting in the relatively high overall mortality rate associated with CRC.²

Several drugs as single agents or in various combinations are available to treat mCRC, including fluoropyrimidines (5-fluorouracil [5-FU], capecitabine), irinotecan, oxaliplatin, the vascular endothelial growth factor (VEGF) antibody bevacizumab, the epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab for *RAS* wild-type mCRC, the VEGF receptors 1 and 2 fusion protein aflibercept, and the multitarget tyrosine kinase inhibitor regorafenib. The current standard first-line treatment is a combination of a chemotherapy doublet of a fluoropyrimidine with oxaliplatin and/or irinotecan (FOLFOX [folinic acid, 5-FU, oxaliplatin], CAPOX [capecitabine, oxaliplatin], FOLFIRI [folinic acid, 5-FU, irinotecan] regimens) plus bevacizumab or an EGFR antibody (cetuximab or panitumumab) for patients with *RAS* wild-type tumors. As a result of recent advances in treatment, median overall survival (OS) can now be as long as 30 months in selected patient groups.³⁻⁶

The first-line treatment will be the longest treatment phase and is thus of particular importance regarding the overall treatment strategy. The established standard for many years was continuation of the initial treatment until the occurrence of progression or unacceptable toxicity. Newer strategies, developed particularly for oxaliplatin-based regimen, have used a limited concept of “induction and maintenance,” with several strategies used in addition to the previous standard of continuation of full treatment until progression (Table 1). These strategies were initially triggered by the dose-cumulative neurotoxicity associated with oxaliplatin. In addition to the sparing of cumulative side effects (and thus improving patient quality of life), continuation of induction treatment beyond 3 to 6 months in a palliative situation without a chance for secondary local ablation does not seem to be beneficial. Therefore, induction/maintenance strategies to date have used a 3- to 6-month duration of induction chemotherapy, including other regimen than only FOLFOX. Although intermittent treatment with preplanned maintenance or full-stop intervals was evaluated in several trials, this approach has not been widely adopted.⁷⁻⁹ Recent trials allocated

patients after 3 to 6 months of induction treatment to different maintenance strategies and/or observation alone.¹⁰⁻¹⁶ These trials all showed an effect on progression-free survival (PFS) or the respective alternate endpoints eg, time to failure of strategy or time to second progression; however, the effect on OS has remained unclear. The current meta-analysis was performed to compare observation alone with bevacizumab or bevacizumab and chemotherapy maintenance after induction chemotherapy in terms of PFS and OS.

Patients and Methods

Definition of Analysis and Trial Selection

Pertinent data from published trials (PubMed) and abstracts presented at selected oncology association meetings (American Society of Clinical Oncology and European Society for Medical Oncology/European Cancer Organization) until June 2015 were systematically searched using MeSH and full-text search terms for “metastatic colorectal cancer,” “first-line treatment,” or “maintenance treatment.” In addition, the references of all eligible studies were manually reviewed to find additional relevant studies.

Overall, 9 trials were identified that had compared any maintenance strategy until progression with observation alone or the continuation of full treatment (Figure 1; Table 2).^{10-12,14,15,17-19} Of these, 5 trials were selected for additional analysis, because these trials evaluated a separately defined “maintenance phase,” with randomization after the induction phase (OPTIMOX 3/DREAM [Optimized Leucovorin Fluorouracil Oxaliplatin/Double Inhibition Reintroduction Erlotinib Avastin Metastatic Colorectal Cancer], Nordic ACT [Chemotherapy and Avastin Followed by Maintenance Treatment With Avastin +/- Tarceva], CAIRO 3 [Capecitabine, Irinotecan and Oxaliplatin], SAKK 41/07 [Swiss Group for Clinical Cancer Research], AIO KRK 0207 [Workinggroup Medical Oncology Colorectal Cancer]). The selected studies were assessed for potential bias with regard to the randomization approach, timely parallel enrollment, similarity of treatment groups, data-driven reporting, analysis population (intent-to-treat [ITT] vs. other), and other aspects. The OPTIMOX 3/DREAM and Nordic ACT trials evaluated the addition of erlotinib to bevacizumab maintenance.^{10,19} However, erlotinib has not been licensed for mCRC treatment, and approval, considering the data obtained, seems unlikely.

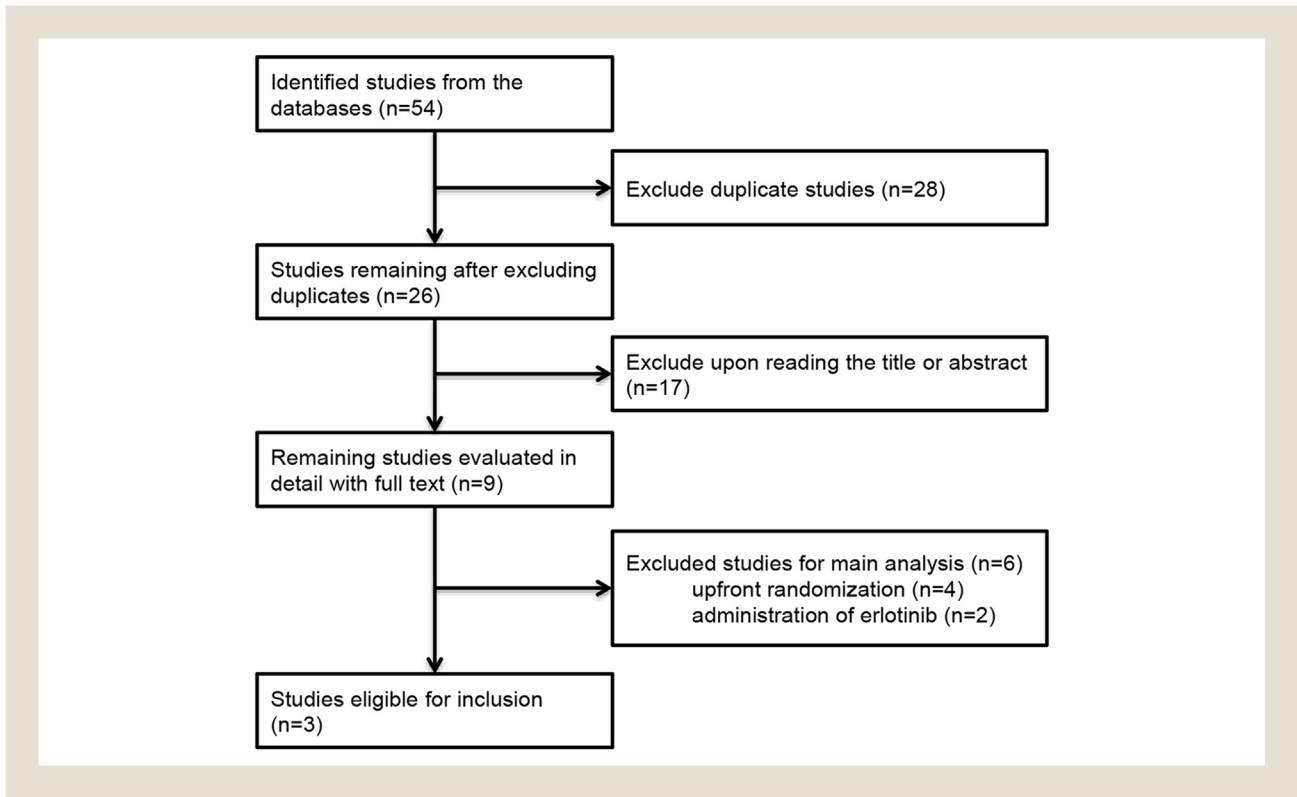
To clarify the most relevant issues to date, the 3 trials evaluating bevacizumab with or without fluoropyrimidine maintenance (CAIRO 3, SAKK 41/06, and AIO KRK 0207) were selected for the main analysis because of their similar design (comparison of bevacizumab-based maintenance with observation alone; Figure 2).¹³⁻¹⁵ The combined analysis of these data was performed to evaluate the following questions:

1. Effect of any bevacizumab-based (with or without chemotherapy) maintenance compared with observation alone
2. Effect of bevacizumab maintenance compared with observation alone
3. Effect of fluoropyrimidine and bevacizumab maintenance compared with observation alone
4. Indirect comparison of different maintenance intensities (fluoropyrimidine and bevacizumab compared with bevacizumab alone)

Table 1 Currently Available Maintenance Strategies and Respective Randomized Trials

Strategy	Trials
Partial stop and go with maintenance	
Stop most toxic drug (eg, oxaliplatin), apply maintenance (single-agent 5-fluorouracil, bevacizumab, or cetuximab or 5-fluorouracil plus bevacizumab); if feasible, restart induction treatment at progression	OPTIMOX 2, COIN-B, CAIRO3, SAKK 41/06, MACRO, Turkish Oncology Group - Stop and Go - Trial, AIO KRK 0207
Stop/restart toxic drug (eg, oxaliplatin) in preplanned intervals	OPTIMOX 1, CONcept
Complete stop and go	
Stop all drugs after 3 mo, restart at progression, and stop again after another 3 mo	COIN
Stop/restart all drugs in preplanned intervals	GISCAD
Switch maintenance	
Introduce new drug into maintenance strategy (adding erlotinib to bevacizumab maintenance)	DREAM, Nordic ACT

Figure 1 Flowchart of Study Selection



To answer the fourth question regarding the different maintenance intensities, the 2 single-agent bevacizumab arms (SAKK 41/06 and AIO KRK 0207) were compared with the 2 fluoropyrimidine and

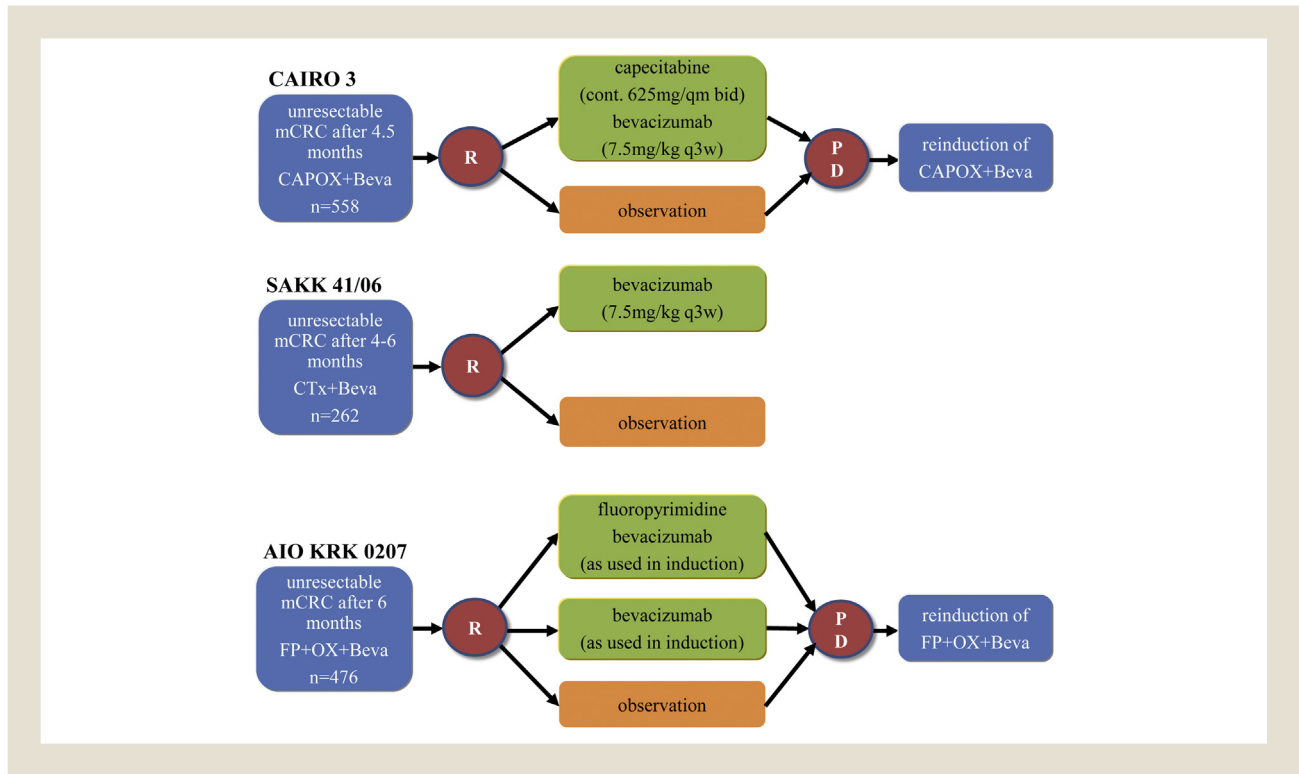
bevacizumab arms (AIO KRK 0207 and CAIRO 3). The meta-analysis of these 3 similarly performed trials was performed to combine the currently available data and provide a clinically relevant

Table 2 Currently Available Randomized Clinical Trials Evaluating Different Maintenance Strategies

Strategy	Randomization	Clinical Trial	Induction Regimen	Maintenance Regimen	Patients (n)	Comment
Maintenance vs. observation	Upfront	OPTIMOX 2	FOLFOX	5-FU/LV vs. observation	202	Excluded owing to different maintenance regimen
		COIN-B	FOLFOX + cetuximab	Cetuximab vs. observation	169	Excluded because no formal comparison
	After induction	CAIRO3	CAPOX + bevacizumab	Capecitabine + bevacizumab vs. observation	558	Included
		SAKK 41/06	Chemotherapy + bevacizumab (32% 5-FU + Iri; 62% 5-FU + Oxa)	Bevacizumab vs. observation	262	Included
Different maintenance regimen	After induction	AIO KRK 0207	5-FU + Oxa + bevacizumab	Bevacizumab ± 5-FU/LV or capecitabine vs. observation	472	Included
		OPTIMOX 3/DREAM	Chemotherapy + bevacizumab (90% 5-FU + Oxa; 10% FOLFIRI)	Bevacizumab vs. bevacizumab + erlotinib	452	Excluded owing to use of bevacizumab in both arms
	Upfront	Nordic ACT	Chemotherapy + bevacizumab	Bevacizumab vs. bevacizumab + erlotinib	159	
		MACRO	CAPOX + bevacizumab	Bevacizumab vs. CAPOX + bevacizumab	470	Comparison of full treatment continuation vs. maintenance
Maintenance vs. continuation of full treatment		Turkish Oncology Group - Stop and Go - Trial	CAPOX + bevacizumab	Capecitabine + bevacizumab vs. CAPOX + bevacizumab	123	

Abbreviations: 5-FU = 5-fluorouracil; CAPOX = capecitabine, oxaliplatin; FOLFIRI = folinic acid, 5-FU, irinotecan; FOLFOX = folinic acid, 5-FU, oxaliplatin; Iri = irinotecan; LV = leucovorin; Oxa = oxaliplatin.

Figure 2 Overview of Maintenance Trials Evaluating Bevacizumab With or Without Fluoropyrimidine (FP) Maintenance



Abbreviations: Beva = bevacizumab; cont. = continuous; CTx = cetuximab; mCRC = metastatic colorectal cancer; OX = oxaliplatin; qm = every month.

conclusion regarding the use of bevacizumab-based maintenance therapy after induction treatment with bevacizumab and chemotherapy.

The 4 remaining trials had randomized patients upfront (before induction treatment) and thus could not be analyzed for the effect of different maintenance strategies, at least not regarding PFS during maintenance therapy.

Statistical Analysis

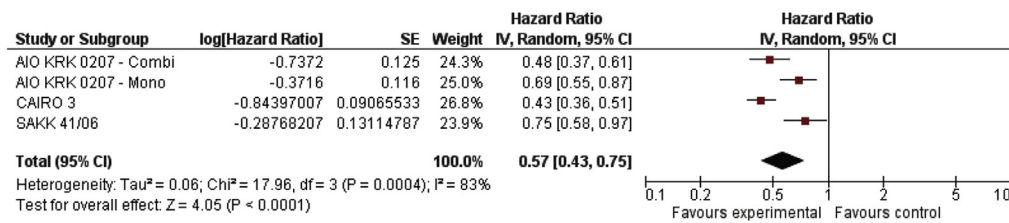
The PFS and OS were analyzed in meta-analyses and using an indirect comparison. All meta-analyses were performed using the software Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), based on the reported hazard ratios (HRs) and 95% confidence intervals (CIs) from each study using random effects models.²⁰ A test for heterogeneity was performed to assess for deviations from homogeneity of the studies and to assess whether the studies could be summarized in a meta-analysis. If the *P* value for heterogeneity was $\geq .20$, no proof for heterogeneity was concluded, and a meta-analysis was performed. With proof of heterogeneity ($P < .20$), considerable heterogeneity was concluded, and the studies were not summarized in a meta-analysis. The cause of heterogeneity was assessed, and only those studies were combined that did not show considerable heterogeneity. In addition, an indirect comparison was performed to compare combination therapy against single-agent bevacizumab using “observation” as the bridge comparator. The approach by Bucher et al²¹ was used to perform the comparison

according to the meta-analytical results. A 95% CI for the HR < 1 would show statistically significant results in favor of combination therapy.²¹ The indirect comparison was performed using Statistical Analysis Systems, version 9.2 (SAS Institute Inc., Cary, NC).

Results

The 3 studies comparing observation alone with bevacizumab with or without fluoropyrimidine after induction treatment (Figure 1), which had been selected for the meta-analyses and indirect comparison, were assessed for their potential for bias. All 3 studies were fully published randomized controlled trials with an adequate randomization approach and timely parallel enrollment. All 3 studies were open-label studies, and no crossover was allowed. The reported analyses for the endpoints of PFS and OS were standard approaches based on the ITT population; thus, data-driven reporting could be excluded. In the absence of any other aspect, the potential for bias was assessed as low for the endpoint OS in all 3 studies. Owing to the open-label design of the studies and the reading of the radiologic images at the study sites and not centrally, the endpoint PFS was suggested to have a high potential for bias. Therefore, the PFS results should be interpreted cautiously.

The studies with any active maintenance (bevacizumab with or without fluoropyrimidine), after bevacizumab-based induction treatment for 4 to 6 months, showed improved PFS (Figure 3). However, a meta-analysis showed considerable heterogeneity ($P = .0004$). Thus, the 3 studies were not combined but were separated into single-agent bevacizumab and combination bevacizumab and

Figure 3 Progression-free Survival of Maintenance With Bevacizumab With or Without Fluoropyrimidine Versus Observation

Abbreviations: CI = confidence interval; Combi = combination therapy; Mono = monotherapy; SE = standard error.

fluoropyrimidine. In contrast, with regard to mortality, the studies were not heterogeneous ($P = .89$). In the meta-analysis, active maintenance showed a trend toward prolonged OS (HR, 0.89; 95% CI, 0.78-1.02; $P = .09$; Figure 4) compared with observation alone (CAIRO3, SAKK 41/06, and AIO KRK 0207). Maintenance with single-agent bevacizumab significantly increased PFS (HR, 0.72; 95% CI, 0.60-0.85; $P = .0001$) and showed a trend toward prolonged OS (HR, 0.85; 95% CI, 0.69-1.05; $P = .14$) compared with observation alone (see Supplemental Figures 1 and 3 in the online version). The more intensive maintenance strategy with bevacizumab and fluoropyrimidine compared with observation alone seemed to have a stronger effect on PFS (HR, 0.45; 95% CI, 0.39-0.51; $P < .0001$). In contrast, the HRs for OS remained similar to single agent bevacizumab (HR, 0.92; 95% CI, 0.77-1.09; $P = .31$; see Supplemental Figures 2 and 4 in the online version).

Finally, the indirect comparison showed improved PFS (HR, 0.63; 95% CI, 0.50-0.79) for the more intensive maintenance regimen (bevacizumab and fluoropyrimidine) compared with bevacizumab alone. In line with the homogenous results across all therapy strategies, no effect on OS was found in favor of 1 of these 2 maintenance strategies (HR, 1.08; 95% CI, 0.82-1.42; Figure 5).

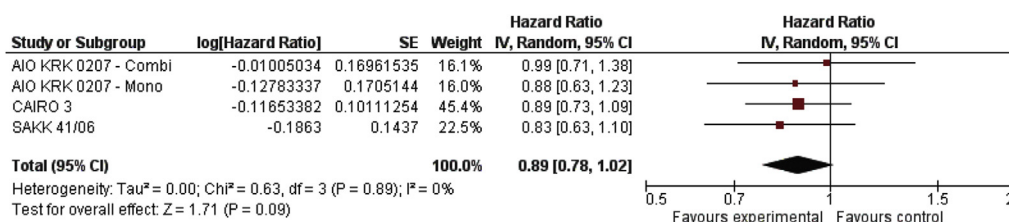
The consistency of direct and indirect evidence was assessed using direct evidence from AIO 0207 and indirect evidence from SAKK 41/06 and CAIRO3. For PFS, heterogeneity was found for the 2 treatment arms ($P = .03$), suggesting a treatment effect with regard to the HRs for the combination and mono-strategy (HR combination, 0.48; 95% CI, 0.37-0.61) versus (HR monotherapy, 0.69; 95% CI, 0.55-0.87; HR combination/HR mono, 0.70; 95% CI,

0.49-0.98). These results are in line with the advantage of the combination strategy in the indirect comparison of the data from CAIRO3 and SAKK 41/06 (HR, 0.57; 95% CI, 0.42-0.78). For OS, no deviance from homogeneity was found between the 2 treatment arms compared with observation ($P = .62$) within the AIO 0207 study (HR combination, 0.99; 95% CI, 0.71-1.38; vs. HR monotherapy, 0.88; 95% CI, 0.63-1.23) with a ratio of the HRs of 1.13 (95% CI, 0.70-1.80). This is in line with the findings from the indirect comparison of CAIRO3 and SAKK 41/06 (HR, 1.07; 95% CI, 0.76-1.51). Overall, a consistency of the direct and indirect evidence can be concluded for both endpoints evaluated.

For the combined switch maintenance with erlotinib and bevacizumab, a favorable outcome in terms of PFS (HR, 0.77; 95% CI, 0.64-0.93; $P = .006$) and a trend toward a prolonged OS (HR, 0.89; 95% CI, 0.73-1.08; $P = .24$) was noted (see Supplemental Figures 5 and 6 in the online version).

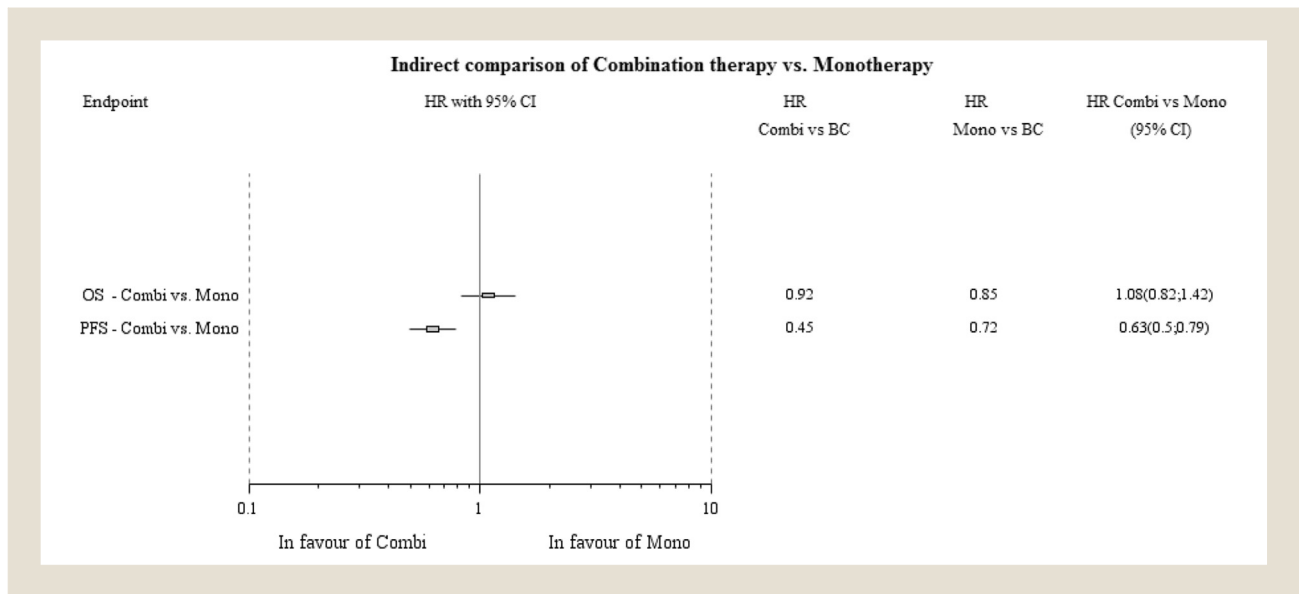
Discussion

The results from the current meta-analysis have clearly shown significant benefits in terms of PFS and a trend toward prolonged OS in favor of a bevacizumab-based maintenance compared with observation alone after 4 to 6 months of induction treatment. Although the intensity of maintenance bevacizumab and fluoropyrimidine versus single-agent bevacizumab showed an effect on PFS, no difference in OS was noted. Similar trends were found in the randomized AIO KRK 0207 trial comparing observation with single-agent bevacizumab and bevacizumab plus fluoropyrimidine.¹⁵ Thus, both options can be considered after 4 to 6

Figure 4 Overall Survival of Maintenance With Bevacizumab With or Without Fluoropyrimidine Versus Observation

Abbreviations: CI = confidence interval; Combi = combination therapy; Mono = monotherapy; SE = standard error.

Figure 5 Indirect Comparison of Bevacizumab (BC) and Fluoropyrimidine Versus Bevacizumab



Abbreviations: CI = confidence interval; Combi = combination therapy; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

months of bevacizumab-based induction treatment. Regarding the significant benefit in terms of PFS, the more intensive regimen might be chosen if durable disease control is of importance (eg, widespread and symptomatic disease at the initial presentation).

Because of the missing OS benefit, observation alone is a valid treatment approach, in particular in terms of the relevant treatment cost for bevacizumab-based maintenance therapy (estimated additional cost of approximately US\$30,000 in the SAKK 41/06 trial). Regarding the significant benefit for PFS and the noted trend for OS (HR, 0.89) with well-tolerated treatment administered for 5 to 6 months, maintenance therapy should still be considered. Both CAIRO3 and AIO KRK 0207 have consistently shown a significant benefit in terms of OS for those achieving an objective response (complete or partial response) during induction treatment. In addition, the RAS/BRAF subgroup analysis of the AIO KRK 0207 suggested that bevacizumab plus fluoropyrimidine maintenance might be better than single-agent bevacizumab in patients with mutations. Further research is needed to detect the subgroups that will benefit from maintenance therapy and to evaluate the cost-effectiveness of bevacizumab-based maintenance.

Although a significantly better PFS could be shown for the combination of erlotinib and bevacizumab compared with bevacizumab alone, the relatively modest efficacy seems to be outweighed by the significant toxicity, specifically rash, diarrhea, and fatigue.^{10,19} Therefore, the licensing and consecutive administration of erlotinib in mCRC maintenance seems unlikely.

The present meta-analysis had several limitations, including using the published HRs rather than individual patient data.¹³⁻¹⁵ Furthermore, the heterogeneities in the trial design (superiority in CAIRO3 and noninferiority in AIO KRK 0207 and SAKK 41/06), patient inclusion criteria (eg, exclusion of patients with toxic effects from induction treatment in CAIRO3), and the treatment applied (eg, differences in induction treatment and fluoropyrimidine maintenance schedule) should be considered as potential biases. The

induction treatment was heterogeneous among the trials in terms of duration, ranging from 4 to 6 months, the use of oxaliplatin (100% of patients in CAIRO3 and AIO KRK 0207, 62% in SAKK 41/06, with 31% receiving irinotecan), intensity (7% received induction treatment with fluoropyrimidine and bevacizumab in the SAKK 41/06), and the fluoropyrimidine backbone used (capecitabine/oxaliplatin at 100% in CAIRO3 and only 16% in AIO KRK 0207). The dosage of the fluoropyrimidine-based maintenance regimen differed between CAIRO3 (capecitabine with 625 mg/m² twice daily continuously) and AIO KRK 0207 (capecitabine with 1000 mg/m² twice daily for 2 weeks, followed by a 1-week break, or 5-FU/leucovorin [LV] at a full dosage ranging from 2400 to 3000 mg/m² continuous infusion for 2 days with or without a bolus every 2 weeks) thus potentially influencing the results of the pooled intensive maintenance arms.

Additional maintenance strategies (eg, single-agent cetuximab or 5-FU/LV compared with observation alone or bevacizumab-based maintenance compared with full treatment continuation) could not be included owing to the upfront randomization.^{11,12,17,18} The results from the present analysis do not allow for conclusions regarding the comparative value of bevacizumab versus fluoropyrimidines or the effect of EGFR antibodies in this setting. The discussed maintenance approach has generally been limited to an oxaliplatin-based regimen, although a small number of patients receiving an irinotecan-based induction regimen were included in the SAKK 41/06 (about 30%) and the OPTIMOX 3/DREAM trials. In addition to the intermittent treatment approach applied in the GISCAD trial, the effect of a de-escalation strategy after an irinotecan-based first-line regimen combined with monoclonal antibodies compared with continuation of full-dose treatment remains unclear.⁷

In addition, the endpoint of PFS was considered to have a high potential for bias owing to the open-label design of all 3 studies and the assessment of the radiologic images at the study sites and not

centrally. Also, the indirect comparison had some limitations. The similarity of the studies was assessed, and no deviance was detected; however, hidden confounders could have introduced bias into the results. Owing to the limited number of studies, no sensitivity analyses were performed to assess any confounding. The high potential for bias for the PFS endpoint also led to relevant uncertainty; thus, the results should be interpreted with care. The consistency of the direct and indirect evidence was assessed using the indirect comparison and study AIO KRK 0207. No major deviances were found, suggesting a valid indirect comparison.

Regarding the remaining unresolved issues in maintenance (eg, patient or regimen selection), the evaluation of new treatment strategies or agents in the maintenance setting has gained widespread interest in the past years, with a variety of trials currently ongoing.²²

Conclusion

Bevacizumab-based maintenance after induction chemotherapy with bevacizumab significantly improves PFS and shows a favorable trend in prolonging OS. Regarding the lack of a significant OS benefit, bevacizumab-based maintenance therapy after induction treatment is not the standard approach for all patients with mCRC. However, patients achieving an objective response during bevacizumab-based induction treatment seem to derive a relevant OS benefit. The intensity of the maintenance therapy (single-agent bevacizumab or combined with a fluoropyrimidine) only affects PFS. Thus, the more intensive maintenance regimens may be limited to patients in need of durable disease control or those with worse prognostic features (eg, *RAS*/*BRAF* mutation). The decision regarding maintenance therapy warrants consideration in a shared decision-making process with the patient considering disease-specific factors (eg, the response to induction treatment).

Clinical Practice Points

- Regarding the recently achieved long-term survival of patients with mCRC, continuation of full-dose systemic treatment throughout the disease course is no longer feasible.
- Different treatment approaches are available after 3 to 6 months of induction treatment (treatment break, intermittent treatment, or maintenance).
- Recent data have shown the beneficial effect of bevacizumab-based maintenance treatment compared with observation alone in terms of PFS, although the effect on OS is unclear and the intensity of maintenance treatment remains a matter of debate.
- Bevacizumab-based maintenance therapy after 4 to 6 months of bevacizumab-based induction treatment significantly improved PFS (HR, 0.57; 95% CI, 0.43-0.75; $P = .0004$) and showed a trend toward prolonged OS (HR, 0.89; 95% CI, 0.78-1.02; $P = .09$).
- Improved PFS (HR, 0.63; 95% CI, 0.50-0.79) was shown for the more intensive maintenance regimen (bevacizumab and fluoropyrimidine) compared with bevacizumab alone, although OS remained unaffected (HR, 1.08; 95% CI, 0.82-1.42).
- Because of the limited effect on OS, bevacizumab-based maintenance therapy is not the standard treatment approach for all patients but should be considered for patients with a response to

induction or requiring durable disease control (significant PFS benefit).

- The addition of fluoropyrimidine to bevacizumab had no effect on OS; thus, both strategies can be considered if active maintenance therapy is chosen.

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Supplemental Data

The supplemental figures accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clcc.2015.12.005>.

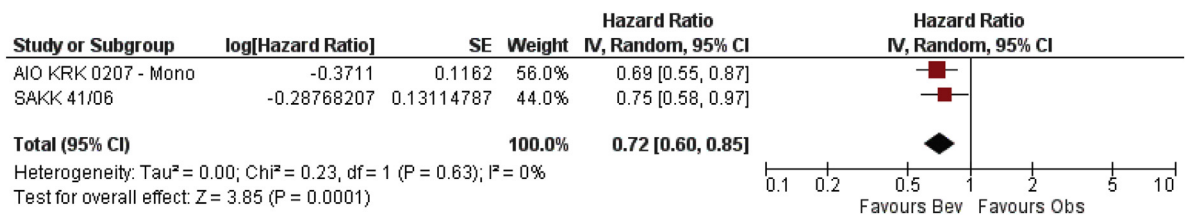
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Effect of Application and Intensity of Bevacizumab-based Maintenance Therapy

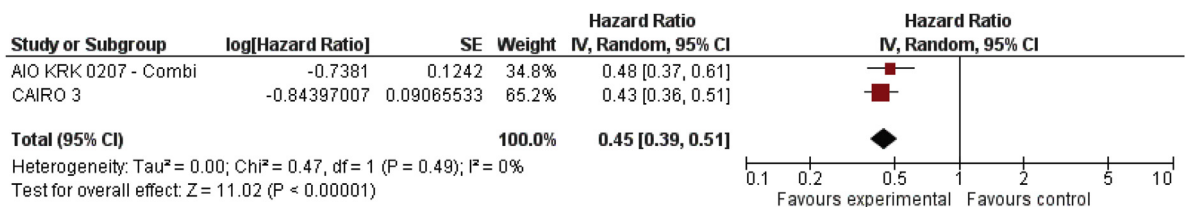
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Supplemental Figure 1 Progression-free Survival of Maintenance With Bevacizumab (Bev) Versus Observation (Obs)



Abbreviations: CI = confidence interval; Mono = monotherapy; SE = standard error.

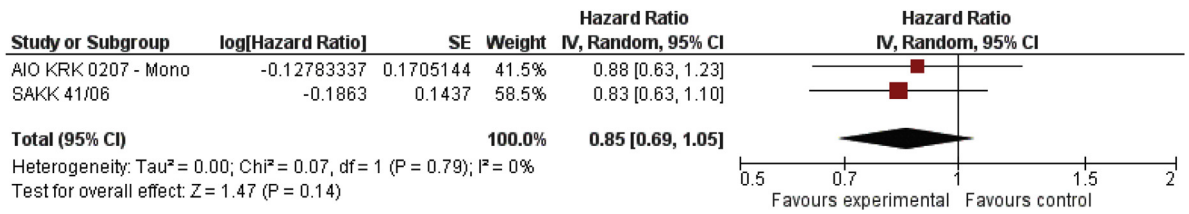
Supplemental Figure 2 Progression-free Survival of Maintenance With Bevacizumab and Fluoropyrimidine Versus Observation



Abbreviations: CI = confidence interval; Combi = combination therapy; SE = standard error.

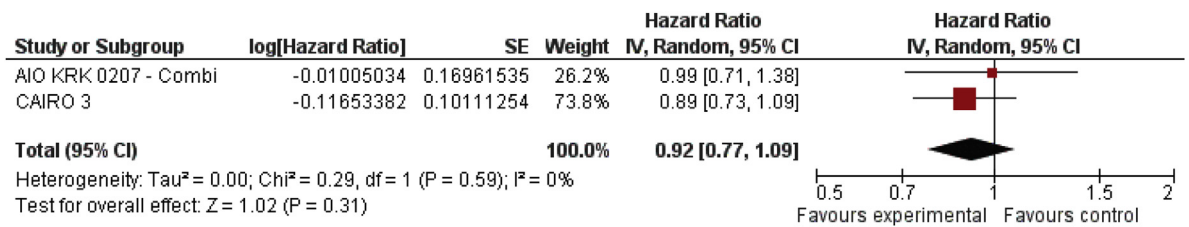
Effect of Application and Intensity of Bevacizumab-based Maintenance Therapy

Supplemental Figure 3 Overall Survival of Maintenance With Bevacizumab Versus Observation



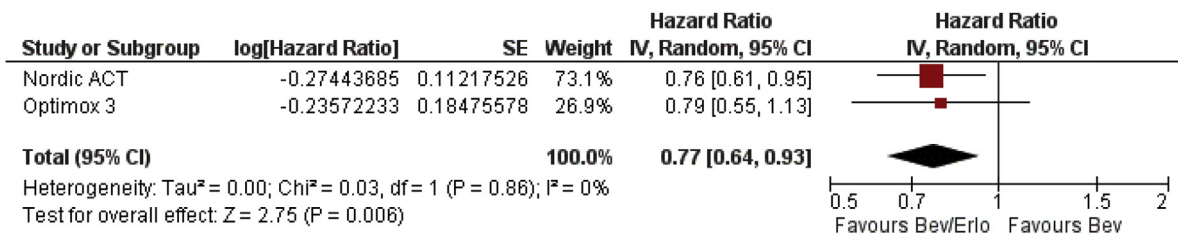
Abbreviations: CI = confidence interval; Mono = monotherapy; SE = standard error.

Supplemental Figure 4 Overall Survival of Maintenance With Bevacizumab and Fluoropyrimidine Versus Observation



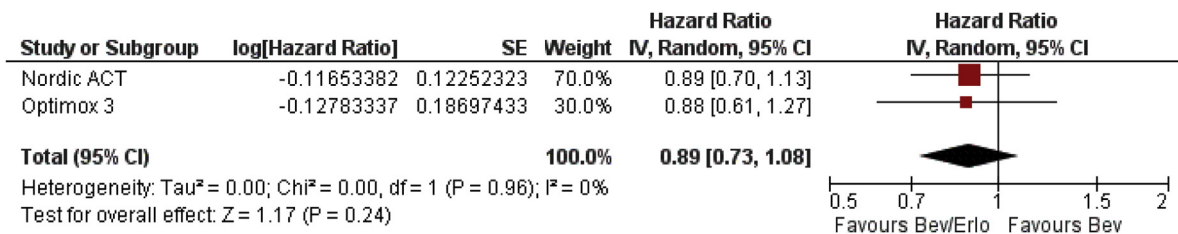
Abbreviations: CI = confidence interval; Combi = combination therapy; SE = standard error.

Supplemental Figure 5 Progression-free Survival of Bevacizumab (Bev) Versus Bevacizumab/Erlotinib (Bev/Erlo)



Abbreviations: CI = confidence interval; SE = standard error.

Supplemental Figure 6 Overall Survival of Bevacizumab (Bev) Versus Bevacizumab/Erlotinib (Bev/Erlo)



Abbreviations: CI = confidence interval; SE = standard error.