

WITHDRAWN ARTICLE

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Efficacy and toxicities of combination maintenance therapy in the treatment of advanced colorectal cancer: a meta-analysis of randomized controlled trials

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Li H. and Lin F. were responsible for study design. Wang J. and Wang F. were responsible for literature search. Li H. and Wang J. were responsible for data extraction. Lin F., Li H. and Wang F. were responsible for data analysis. Li H. were

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Conflicts of interest statement

All authors declare that they have no potential conflicts of interests.

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Abstract:

Purpose:

We performed a systematic review and meta-analysis to investigate the efficacy and toxicities of combination maintenance therapy for the treatment of advanced colorectal cancer (CRC).

Methods:

Relevant trials were identified by searching electronic databases and conference meetings. Prospective randomized controlled trials (RCTs) assessing combination maintenance therapy in advanced CRC patients were included. Outcomes of interest included overall survival (OS), progression-free survival (PFS) and grade 3-4 toxicities.

Results

A total of 3,174 advanced CRC patients received combination maintenance treatment from 6 RCTs were included for analysis. The use of combination maintenance therapy did not significantly improved PFS (HR 0.95, 95%CI: 0.75-1.20, $p=0.67$) and OS (HR 1.05, 95%CI: 0.93-1.17, $p=0.45$) in comparison with single bevacizumab maintenance therapy for the treatment of advanced CRC, similar results were observed in sub-group analysis according to treatment regimens. In addition, combination maintenance therapy significantly improved PFS (HR 0.57, 95%CI: 0.41-0.80, $p=0.001$), but not for OS (HR 0.93, 95%CI: 0.76-1.14, $p=0.47$) in comparison with

observation. Additionally, more incidences of any grade 3-4 toxicities (diarrhea, fatigue and hand-foot skin reaction) were observed in the combination maintenance therapy.

Conclusions:

The findings of this study show that the efficacy of combination maintenance therapy is comparable to that of bevacizumab alone in terms of PFS and OS for advanced CRC patients, but at the cost of increased grade 3-4 toxicities. Thus single agent bevacizumab remains the recommended maintenance treatment for advanced CRC patients.

Keywords: colorectal cancer; maintenance therapy; randomized controlled trials; meta-analysis;

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer worldwide , with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred annually[1]. Nearly one fourth of patients are diagnosed with advanced/metastatic disease, with a 5-year survival of less than 10%[2]. For patients with advanced/metastatic CRC, the treatment goal is to prolong survival and improve quality of life. For patients with advanced CRC, chemotherapy alone yields median survival durations of approximately 20 months [3, 4]. During the past decades, the introduction of novel targeted agents, such as bevacizumab, aflibercept and cetuximab, has modestly improved outcomes in treatment-naïve patients [5-7]. However, additional therapeutic options are needed.

In order to sustain a reduced tumor size and relieve tumor-related symptoms, maintenance therapy has emerged as a novel therapeutic strategy for advanced CRC[8]. Maintenance therapy can be classified into two types: switch maintenance therapy and continuous maintenance therapy. Continuation maintenance is defined as keeping ongoing administration one or more drugs (combination maintenance) used in first-line regimen; while switch maintenance generally introduces an additional agent immediately after completion of four to six cycles of first-line chemotherapy. A previously published meta-analysis has demonstrated that maintenance therapy with

either a continuation or a switch strategy significantly increased progression free survival (PFS, HR 0.56; CI 95% 0.44-0.71, $p<0.00001$) and time to failure strategies (TFS, HR 0.79; CI 95% 0.7-0.9, $p=0.0005$) in comparison to observation. Thus, the authors concluded that maintenance therapy should be considered the standard regimen in patients with stage IV colorectal cancer after first line induction therapy. However, to our best knowledge, the role of combination maintenance therapy in the treatment of advanced CRC remains undetermined. As a result, we conduct this systematic review and meta-analysis to assess the overall efficacy and toxicities of combined maintenance therapy in advanced CRC patients.

Materials and Methods

Study Design

We performed this systematic review and meta-analysis according to the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines 2009[9].

Search strategy

We conducted a comprehensive literature search of public databases including PubMed, EMBASE, Web of Science and the Cochrane library (up to April 30, 2017). Relevant search keywords including the followings: “colorectal cancer,” “maintenance therapy,” and “randomized controlled trials.” No language restriction was administered. An up-to-date search for relevant trials was performed on August 30, 2017. We also conducted a manual search of conference proceedings. All results were input into Endnote X7 reference software (Thomson Reuters, Stamford, CT, US) for duplication exclusion and further reference management.

Study Selection

Clinical trials that met the following criteria were included: (1) prospective phase II or III trials involving colorectal patients; (2) trials comparing combination maintenance therapy versus single agent maintenance therapy or observation; and (3) available survival data regarding advanced CRC patients. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

Data Extraction

Two independent investigators conducted the data abstraction, and any discrepancy between the reviewers was resolved by consensus. The following information was extracted for each study: first author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, median age, median progression-free survival, and overall survival.

Outcome measures

A formal meta-analysis was conducted using Comprehensive Meta Analysis software (Version 2.0). The outcome data were pooled and reported as hazard ratio (HR). The primary outcome of interest was OS and secondary outcomes PFS and any grade 3-4 toxicities in advanced CRC patients.

Statistical Analysis

All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ). Between-study heterogeneity was estimated using the χ^2 -based Q statistic[10]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. A statistical test with a *p*-value less than 0.05 was considered significant. Study quality was assessed by using the Jadad scale based on the reporting of the studies' methods and results[11].

Results:

Search results:

We initially found 160 relevant citations of maintenance therapy in CRC patients. After excluding review articles, phase I studies, case reports, editorial, letters, commentaries, meta-analyses and systematic review (figure 1), we selected 6 randomized controlled trials for analysis [12-17]. Table 1 listed the baseline characteristics of patients and studies. The quality of each included study was roughly assessed according to Jadad scale, and all of the included randomized controlled trials were open-label controlled trials, thus had Jadad score of 3.

Combination versus single agent maintenance therapy

Five randomized controlled trials with six comparisons reported PFS data of

combination versus single agent maintenance therapy in advanced CRC patients [12-15, 17]. The pooled hazard ratio for PFS demonstrated that the combination maintenance therapy in advanced CRC patients did not significantly improved PFS giving HR 0.95 (95%CI: 0.75-1.20, $p=0.67$, figure 2), in comparison with single bevacizumab maintenance therapy. There was significant heterogeneity between trials ($I^2=80.3\%$, $p=0.001$), and the pooled HR for PFS was performed by using random-effects model. We the performed sub-group analysis according to treatment regimens, and found that both chemotherapy plus bevacizumab (HR 0.911, 95%CI: 0.63-1.32, $p=0.62$) or EGFR tyrosine kinase inhibitors plus bevacizumab (HR 0.98, 95%CI: 0.72-1.32, $p=0.88$) did not significantly improved PFS in comparison with bevacizumab alone.

Five randomized controlled trials with six comparisons reported OS data of combination versus single agent maintenance therapy in advanced CRC patients [12-15, 17]. The pooled hazard ratio for OS demonstrated that the combination maintenance therapy in advanced CRC patients did not improved OS giving HR 1.05 (95%CI: 0.93-1.17, $p=0.45$, figure 3), in comparison with single bevacizumab maintenance therapy. There was moderate heterogeneity between trials ($I^2=78.1\%$, $p=0.003$), and the pooled HR for OS was performed by using random-effects model. We the performed sub-group analysis according to treatment regimens, and found that both chemotherapy plus bevacizumab (HR 1.04, 95%CI: 0.92-1.18, $p=0.49$) or EGFR tyrosine kinase inhibitors plus bevacizumab (HR 1.06, 95%CI: 0.75-1.20, $p=0.74$) did not improved OS in comparison with bevacizumab alone.

Combination maintenance therapy versus observation

Two included trials comparing combination maintenance therapy versus observation reported survival data [15, 16]. The pooled hazard ratio for PFS demonstrated that combination maintenance therapy in advanced CRC patients significantly improved PFS giving HR 0.57 (95%CI: 0.41-0.80, $p=0.001$, figure 4), in comparison with observation. However, no survival benefit was observed in combination maintenance in advanced CRC patients (HR0.93, 95%CI: 0.76-1.14, $p=0.47$).

Toxicities of combination versus single agent maintenance therapy

Toxicity was particularly relevant in maintenance treatment for advanced CRC, given the potential negative impact on benefit ratio and quality of life. As a result, pooled analysis of reported grades 3 and 4 adverse events (AEs) of interest was performed. There was a significantly increased risk of developing severe non-hematologic toxicities (diarrhea, fatigue, and hand-foot reaction), but not for hypertension, bleeding and thrombosis (table 2).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Begg's funnel plots did not reveal any evidence of obvious asymmetry (PFS, $p=0.85$; OS, $p=0.57$, figure 5). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for PFS ($p=0.74$) and OS ($p=0.77$).

Discussion

Due to the addition of novel biological agents to first-line chemotherapy in advanced colorectal cancer patients, the prognosis of advanced CRC patients has been significantly improved [18-20]. However, the optimal duration of first-line treatment remains a controversial issue [21]. Continuous long-term chemotherapy would inevitably increase the side effects associated with chemotherapy and potentially induce the development of drug resistance. On the other hand, intermittent treatment is likely to adversely impact the chemotherapeutic efficacy and treatment outcomes. Two previously meta-analyses have found that maintenance therapy in advanced CRC patients significantly improved PFS and OS in comparison with observation [22, 23]. Before the present study, Dr. Xu et al [24] performed a meta-analysis of three randomized controlled trials to assess the overall efficacy and toxicities of bevacizumab in combination with erlotinib as maintenance therapy in advanced CRC patients, and found that the addition of erlotinib to bevacizumab as maintenance therapy significantly increased overall survival and progression-free survival with an increased but manageable toxicity in CRC patients. However, there is a major error in the meta-analysis analysis, thus the pooled results could be wrong. In fact, the trial

conducted by Hagman et al [25] found that bevacizumab plus erlotinib decreased OS in comparison with bevacizumab alone (median OS, 20.6 versus 30.7; HR 0.58, 95%CI: 0.34-1.01, $p=0.051$), and the authors should recalculate the HR values for meta-analysis. In addition, there would be a significant heterogeneity among included trials, and the pooled results should be performed by random effect model. As a result, the role of combination maintenance therapy in advanced CRC patients remains unknown.

A total of 3,174 advanced CRC patients received combination maintenance treatment from 6 RCTs were included for analysis. The use of combination maintenance therapy did not significantly improve PFS (HR 0.95, 95%CI: 0.75-1.20, $p=0.67$) and OS (HR 1.05, 95%CI: 0.93-1.17, $p=0.45$) in comparison with single bevacizumab maintenance therapy for the treatment of advanced CRC, similar results were observed in sub-group analysis according to treatment regimens. In addition, combination maintenance therapy significantly improved PFS (HR 0.57, 95%CI: 0.41-0.80, $p=0.001$), but it does not translate into survival benefits (HR 0.93, 95%CI: 0.76-1.14, $p=0.47$) in comparison with observation. Additionally, more incidences of any grade 3-4 toxicities (diarrhea, fatigue and hand-foot skin reaction) were observed in the combination maintenance therapy, although no significant risk difference of hypertension, bleeding and thrombosis was found between the two groups. Based on our findings, the efficacy of combination maintenance therapy is comparable to that of bevacizumab alone in terms of PFS and OS for advanced CRC patients, but at the cost of increased grade 3-4 toxicities. Thus single agent bevacizumab remains the recommended maintenance treatment for advanced CRC patients.

Given only modest improvement in PFS or OS obtained from maintenance therapy, quality of life (QOL) is another issue needed to be concerned for patients and physicians. Quidde J. et al [26] reported the quality of life assessment in CRC patients receiving maintenance therapy by using EORTC QLQ-C30 and found that continuation of an active maintenance treatment with combination maintenance therapy after induction treatment was neither associated with a detrimental effect on general health status and quality-of-life score (GHS/QoL) scores when compared with

both, less active treatment with Bev alone or no active treatment. In addition, Hegewisch-Becker S. et al [15] also reported that no significant differences in the mean value of GHS/QoL) score between combination and single agent maintenance therapy.

Several limitations are needed to be concerned in the present analysis. First of all, this is a meta-analysis at study level. We could not obtain individual patient data from the publication, thus we could not incorporate patients variables into the analysis. For instance, advanced CRC patients are more likely to have received biological agents, and we are unable to investigate whether the survival benefit is similar in advanced CRC patients with or without previously biological agents. Second, there is moderate heterogeneity among the included studies, because different treatment regimens are included for analysis, although we perform sub-group analysis according to treatment regimens. Thirdly, switch and continuous maintenance therapies are combined in the meta-analysis, which might increase the heterogeneity among included trials. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects no publication bias using Begg's and Egger's tests for OS and PFS.

Conclusion

In conclusion, this is the most comprehensive meta-analysis specifically assessing the efficacy and toxicities of combination maintenance therapy in the treatment of advanced CRC patients. The results of our study suggest that efficacy of combination maintenance therapy is comparable to that of bevacizumab alone in advanced CRC patients who have not progressed after at least four cycles of platinum-based chemotherapy, but at the cost of increased grade 3-4 toxicities. Thus single agent bevacizumab remains the recommended maintenance treatment for advanced CRC patients.

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Figure legend:

Figure 1 Studies eligible for inclusion in the meta-analysis

Figure 2 Random-effect Model of hazard ratio (95%CI) of PFS in advanced CRC patients treated combined maintenance therapy versus single agent maintenance

Figure 3 Random-effect Model of hazard ratio (95%CI) of OS in advanced CRC patients treated combined maintenance therapy versus single agent maintenance

Figure 4 Fixed-effect Model of hazard ratio (95%CI) of OS and PFS in advanced CRC patients treated combined maintenance therapy versus observation

Figure 5 funnel plot for publication bias

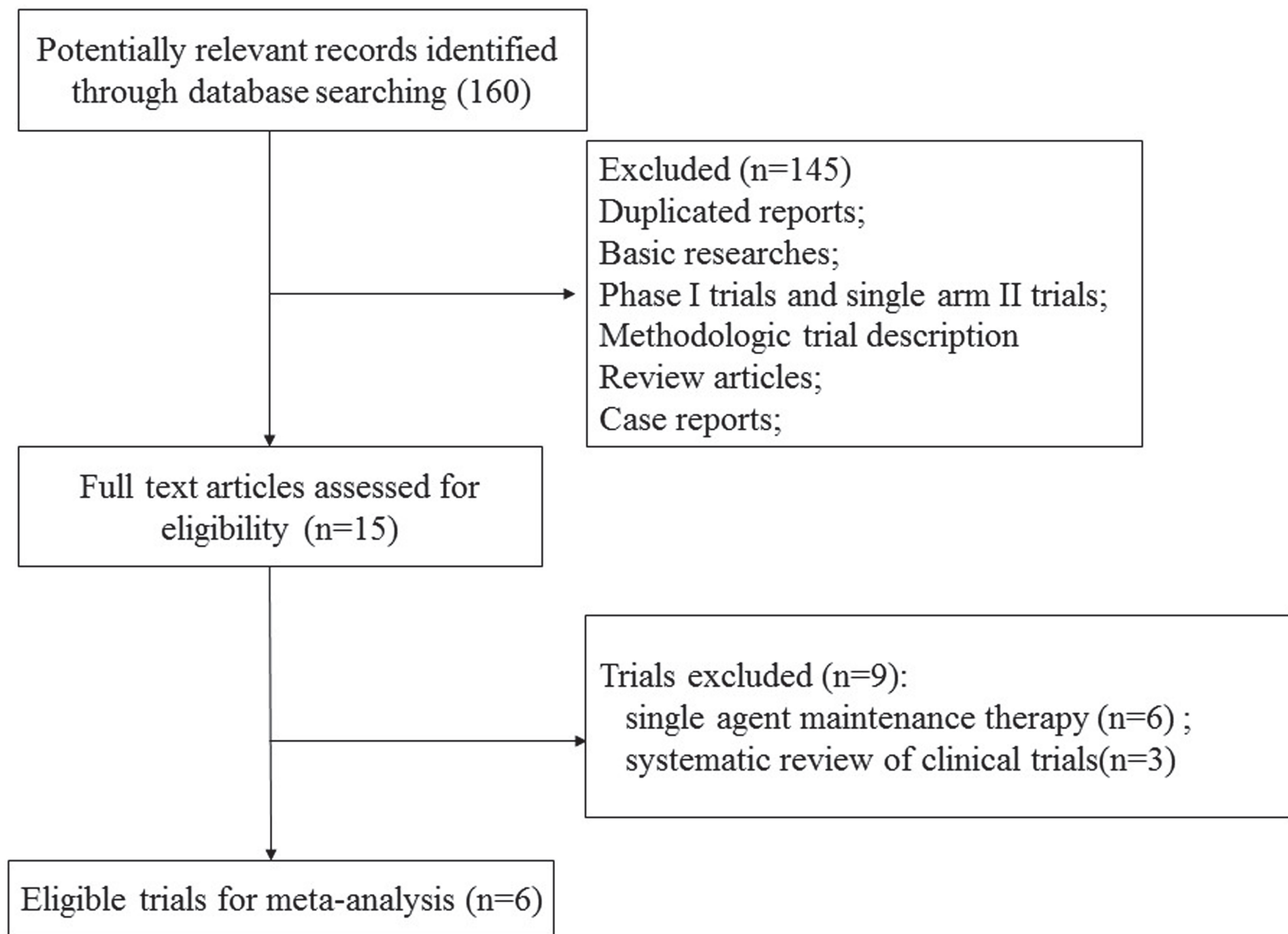
Table 1 baseline characteristics of six included trials

authors	phase	total	induction regimen	maintenance regimens	No. of patients	median age (years)	median PFS	median OS	Jadad Score
Hecht J.R. et al/2009	III	823	FOLFOX	Panitumumab +bevacizumab	413	61	10	19.4	3
				bevacizumab	410	62	11.4	24.5	
			FOLFIRI	Panitumumab +bevacizumab	115	60	10.1	20.7	
				bevacizumab	115	59	11.7	20.5	
Diaz-rubio E. et al/2012	III	480	Xelox+bevacizumab	Xelox+bevacizumab	239	63	10.41	23.2	3
				bevacizumab	241	64	9.66	19	
Johnsson A. et al/2013	III	159	Bevacizumab +chemotherapy	Bevacizumab +erlotinib	80	64	5.7	21.5	3
				bevacizumab	79	65	4.2	22.8	
Hegewisch-Becker S. et al/2015	III	472	Bevacizumab +chemotherapy	Fluoropyrimidine +bevacizumab	158	64	6.3	20.2	3
				Bevacizumab	156	65	4.6	21.9	
				No treatment	158	66	3.5	23.1	
Simkens L.H. et al/2015	III	558	Bevacizumab +chemotherapy	Bevacizumab +capecitabine	279	64	11.7	25.9	3
				observation	278	63	8.5	22.4	
Tournigand C. et al/2015	III	452	Bevacizumab +chemotherapy	Bevacizumab +erlotinib	224	63	5.4	22.1	3
				bevacizumab	228	63	4.9	24.9	

Abbreviation: PFS, progression-free survival; OS, overall survival; FOLFOX, Oxaliplatin+5-FU/LV; FOLFIRI, Irinotecan+5-FU/LV; Xelox, Oxaliplatin +capecitabine;

Table 2 Outcome of grade 3 or 4 toxicity comparing combination versus single agent maintenance therapy.

Toxicity	Trials	Combination therapy	Single agent	Heterogeneity		RR(95%CI)	<i>P</i> value
				<i>P</i> value	<i>I</i> ²		
Grade 3–4 hypertension	4	37/1071	51/1073	0.88	0	0.73(0.48-1.10)	0.13
Grade 3–4 diarrhea	5	182/1229	94/1229	0.001	75	2.44(1.24-4.78)	0.01
Grade 3-4 fatigue	3	36/701	13/701	0.38	0	2.45(1.31-4.57)	0.005
Grade 3–4 hand-foot reaction	3	35/701	18/704	0.65	0	1.91(1.11-3.29)	0.02
Grade 3-4 bleeding	3	1/701	4/704	0.72	0	0.40(0.08-2.03)	0.27
Grade 3–4 thrombosis	5	47/1229	41/1229	0.42	0	1.14(0.76-1.70)	0.53



Group by regimens	Study name	Statistics for each study				
		Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
CT+BEV	Diaz-rubio E. et al/2012	1.098	0.891	1.353	0.879	0.379
CT+BEV	Hegewisch-Becker S. et al/2015	0.750	0.594	0.947	-2.421	0.015
CT+BEV		0.911	0.627	1.323	-0.490	0.624
EGFR+BEV	Hecht J.R. et al/2009(FOLFOX)	1.270	1.061	1.521	2.599	0.009
EGFR+BEV	Hecht J.R. et al/2009(FOLFIRI)	1.190	0.791	1.791	0.834	0.404
EGFR+BEV	Johnsson A. et al/2013	0.790	0.554	1.127	-1.299	0.194
EGFR+BEV	Tournigand C. et al/2015	0.780	0.678	0.897	-3.475	0.001
EGFR+BEV		0.978	0.722	1.323	-0.146	0.884
Overall		0.951	0.751	1.203	-0.422	0.673

